CALCULATION OF ABRAHAM MODEL L-DESCRIPTOR AND STANDARD MOLAR ENTHALPIES OF VAPORIZATION AND SUBLIMATION FOR C_9 - C_{26} MONO-ALKYL ALKANES AND POLYMETHYL ALKANES

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Abraham model **L** solute descriptors have been determined for 127 additional mono-alkyl alkanes and polymethyl alkanes based on published gas chromatographic retention indices for solutes eluted from a fused-silica capillary column coated with a cross-lined methyl silicone stationary phase. Standard molar enthalpies of vaporization and sublimation at 298 K are calculated for the 127 mono-alkyl alkanes and polymethyl alkanes using the reported solute descriptors and our recently published Abraham model correlations. Calculated vaporization and sublimation enthalpies derived from the Abraham model compare very favourably with values based on a popular atom-group additivity model.

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INTRODUCTION

Physicochemical and thermodynamic properties are important input parameters in the design of efficient synthetic methods and purification processes for the commercial preparation of new chemical compounds. Standard molar enthalpies and Gibbs energies of formation can be used to select reaction conditions that optimize product yields, and determine the spontaneity of a chemical reaction at a given temperature and reactant concentrations. Enthalpic and kinetic considerations determine if the reaction mixture needs to be heated or cooled in order for the chemical synthesis to proceed at a controlled reaction rate. Solubility, partition coefficient, vapor pressure, activity coefficient and enthalpy of vaporization data suggest possible purification methods (recrystallization, solvent extraction, fractional distillation) for the chemical product once the synthesis is complete. These represent only a few of the physicochemical and thermodynamic properties needed by individuals working in the chemical manufacturing sector.

Experimental data is readily available for only a small fraction of the more than six billion known chemical compounds. Moreover, in designing industrial manufacturing processes one must consider the properties of liquid mixtures, as well as the properties of individual components that comprise the mixture. Mixture properties such as density, viscosity, surface tension, and vapor pressure depend on the actual concentration of the mixture components. Experimental measurements are both time-consuming and expensive, and it is highly unlikely that there will be a significant increase in the number of experimental values in the near future.

In the absence of actual experimental data, and when measurement is not a viable option, the chemical manufacturing sector has turned to predictive methods as a means to generate the needed input values in design calculations. Many of the current predictive approaches can be classified as either: (1) *Ab-initio* calculational methods; (2) Quantitative Structure Property Relationships (QSPR); or (3) Group Contribution methods. *Ab-initio* methods[1-8] have been successfully applied to compute enthalpies and Gibbs energies of formation, molar heat capacities, enthalpies of solvation, dipole moments, and other properties of molecules of reasonable molecular size. A single computation, however, can take several hours to complete. Various calculation schemes have been employed to reduce the computational time through parameter optimization that allows one to obtain the best possible result for a certain, rather finite, set of test molecules. *Ab-initio* methods are not widely used in process design applications where many computations may be required in order to complete the design of an industrial process.

QSPR relationships are based on finding a mathematical relationship:

$$\varphi = f(MD) \qquad (1)$$

where φ - a physicochemical or thermodynamic property and MD - molecular descriptors

between the desired physicochemical or thermodynamic property and molecular descriptors that describe (or based upon) the molecular characteristics of the molecule. Molecular descriptors can be based upon molecular size,

molecular shape, atom connectivity, atomic volumes and surface areas, components of the dipole and quadruple moment vectors, and calculable local quantities characterizing the reactivity and binding properties (such as atomic charges, atom–atom polarizabilities, molecular orbital energies, and frontier orbital densities). Molecular descriptors are discussed in greater detail elsewhere.[9-11] The mathematical relationship between the descriptors and each physicochemical/thermodynamic property of interest is obtained by curve-fitting the measured experimental data in accordance to Eqn. (1). Properties of any additional compounds are calculated by simply inserting the compound's molecular descriptors into the derived QSPR expression. QSPR expressions have been derived for a large range of physicochemical and thermodynamic properties, including vapor pressure,[12] flash point temperatures,[13,14] Gibbs energies of solvation and Ostwald solubility coefficients,[15,16] liquid viscosity,[17] enthalpies of solvation,[18,19] and liquid and gas molar heat capacities.[20,21]

Group contribution methods belong to a class of empirical property prediction methods that base calculations upon the functional groups or "molecular building blocks" contained within the chemical compound. The molecule is broken down into individual building blocks and the physicochemical and/or thermodynamic property is then estimated as:

$$\varphi = C + \sum_{i}^{groups} n_i G_i \qquad (2)$$

where a constant (C) plus the summation of the product of the number times each group appears in the molecule, n_i, multiplied by the respective group value, G_i. Second- and third-order group terms can be added if necessary to capture subtle structural features that might impact the given property. Such methods assume that the property value for a given function group has the same contribution in all compounds containing the functional group. In other words, the contribution of an ester group would be the same in ethyl acetate as in propyl decanoate. The physicochemical or thermodynamic property of a given chemical compound is thus a function of the contribution of all of the functional groups (or molecular building blocks) needed for the unique representation of the compound's molecular structure.

Molecules can be fragmented into basic organic functional groups (*e.g.*, esters, amides, primary amines, ethers, etc.) or into much smaller atom types and bonded atoms. The key is to find a fragmentation method that results in a general predictive expression for a wide range of chemical compounds or mixtures. Published functional group contribution and atom group additivity methods provide reasonably accurate predictions of enthalpies of combustion,[22] enthalpies of formation,[22-24] standard molar enthalpies of vaporization[25,26] and sublimation,[25,27] solid-liquid total phase entropies,[28,29] surface tensions,[25] isobaric molar heat capacities of liquid and solid organic and organometallic compounds.[30-33] Mathematical expressions for mixtures are more complex and include the mixture compositions as well as terms describing interactions between functional groups on neighboring molecules,[34-38]

The method that we have been promoting in recent years for predicting thermodynamic properties is based on the Abraham solvation parameter model[39-43] which was originally developed to describe solute transfer between two phases.

$$\log(P \text{ or } C_{S,organic}/C_{S,water}) = c_p + e_p \cdot \mathbf{E} + s_p \cdot \mathbf{S} + a_p \cdot \mathbf{A} + b_p \cdot \mathbf{B} + v_p \cdot \mathbf{V} \qquad (3)$$

$$\log(K \text{ or } C_{S,organic}/C_{S,gas}) = c_k + e_k \cdot \mathbf{E} + s_k \cdot \mathbf{S} + a_k \cdot \mathbf{A} + b_k \cdot \mathbf{B} + l_k \cdot \mathbf{L} \qquad (4)$$

Equation (3) describes solute transfer from one condensed phase to another, while Eqn. (4) describes solute transfer from the gas phase into a condensed phase. Solute transfer is described in terms of the logarithms of water-to-organic solvent and gas-to-organic solvent partition coefficients, log *P* and log *K*, or in terms of the logarithms of two molar solubility ratios, $C_{S,organic}/C_{S,water}$ and $C_{S,organic}/C_{S,gas}$. The first molar solubility ratio is calculated as the molar solubility of the solute in the organic solvent divided by its aqueous molar solubility, while the second ratio involves a molar gas phase concentration, $C_{s,gas}$. This latter quantity is calculable from the equilibrium vapor pressure of the solute at the system temperature, or can be determined by fitting experimental solubility data in accordance with Eqns. 3 and 4.

The right-hand side of both Abraham model expressions represents the different types of solute-solvent molecular interactions that govern solute transfer processes. Each solute-solvent interaction is quantified as the product of a solute property (**E, S, A, B, V** and **L**) multiplied by the complementary solvent property (c_p, e_p, s_p, a_p, b_p, v_p, c_k, e_k, s_k, a_k, b_k, and l_k). Solute descriptors are described as follows: **E** denotes the molar refraction of the given solute in excess of that of a linear alkane having a comparable molecular size; **S** is a combination of the electrostatic polarity and polarizability of the solute; **A** and **B** refer to the respective hydrogen-bond donating and accepting capacities of the dissolved solute; **V** corresponds to the McGowan molecular volume of the solute calculated from atomic sizes and chemical bond numbers; and **L** is the logarithm of the solute's gas-to-hexadecane partition coefficient measured at 298.15 K. The complimentary solvent properties are determined by multi-linear regression analysis of measured log (*P* or $C_{S,organic}/C_{S,water}$) and log (*K* or $C_{S,organic}/C_{S,gas}$) values for solutes of known descriptor values. Once the solvent coefficients are known they be used to predict the solubility of additional solutes in the given solvent or log *P* values for a given water-to-partitioning system. Solubility and partition coefficient data are used in the chemical manufacturing sector to design the chemical separation processes needed to purify the synthesized chemical product. Thus far we have determined solute descriptors for more than 8,000 different organic and organic compounds[44], and have reported Abraham model correlations for more than 130 different water-to-organic solvent and gas-to-organic solvent transfer processes.[39-43] The Gibbs energy of solvation, ΔG_{solv}, is related to the gas-to-liquid partition coefficient through Eqn. (5):

$$\Delta G_{solv} = - RT \ln K \qquad (5)$$

where *R* denotes the universal gas constant and *T* is the system temperature. Abraham model correlations are available for predicting the enthalpies of solvation of solutes in several common organic solvents as well.[45-55] Each of our published Abraham model correlations uses the same set of solute descriptors for a given compound, irrespective of the property being predicted.

Our recent modeling efforts have been devoted to developing Abraham model correlations that enable us to predict more physicochemical and thermodynamic properties of organic and organometallic compounds, such as vapor pressures,[56] and enthalpies of vaporization[57] and sublimation.[58] We have now decided to expand our efforts on determining solute descriptors for more chemical compounds. The current communication is devoted to obtaining a complete set of solute descriptors for both the larger $C_9 - C_{26}$ polyalkyl alkanes and polymethyl alkanes so that we can predict their vapor pressures, enthalpies of vaporization and enthalpies of sublimation.

Determination of the solute descriptors of alkane solutes is relatively simple as **E**=0, **S**=0, **A**=0 and **B**=0. Alkane solutes possess no excess molar refraction (**E**=0) or polarity/polarizability (**S**=0), and are not capable of hydrogen-bond formation (**A**=0 and **B**=0) with surrounding solvent molecules. The numerical value of the **V**-solute descriptor is calculable from the number of chemical bonds and the atomic sizes of the atoms contained in the molecular.[59] Only the **L** solute descriptor remains to be calculated. A recent paper[60] published in the *European Chemical Bulletin* illustrated the determination of the **L**-solute descriptor of large mono-methyl branched alkanes from measured gas chromatographic retention indices. The identical computational methodology will be followed in the current study using the gas chromatographic Kovats retention indices reported by Kissin and coworkers[61-63] for large alkane and alkene solutes on a fused-silica capillary column coated with a cross-lined methyl silicone stationary phase.

CALCULATION OF ABRAHAM MODEL SOLUTE DESCRIPTORS

The computational method that we will use to calculate the L-solute descriptor involves establishing an Abraham model relationship:

$$RI = c_{ri} + e_{ri} \cdot \mathbf{E} + s_{ri} \cdot \mathbf{S} + a_{ri} \cdot \mathbf{A} + b_{ri} \cdot \mathbf{B} + l_{ri} \cdot \mathbf{L} \qquad (6)$$

using the measured Kovats retention indices, *RI*, for those alkane solutes for which we already have a complete set of solute descriptors. Only two of the stationary phase coefficients, c_{ri} and l_{ri}, will need to be determined as the other four terms will not contribute to the computation. Remember that the **E, S, A** and **B** solute descriptors of alkane solutes are equal to zero.

The alkane solute that we have available for our linear regression analysis will include the C_5-C_{30} linear alkanes for which the Kovats retention indices are defined to be 100 times the number of carbon atoms, 3-ethyloctane, 4-ethyloctane, 2,3-dimethyloctane, 2,6-dimethyloctane, 2,7-dimethyloctane, 3,5-dimethyloctane, 3,6-dimethyloctane, 2,6-dimethylheptane, and the 2-methylalkanes for which we recently determined descriptor values.[60] In total we have both retention indices and solute descriptors for 188 different alkane solutes to use in our regression analyses. Analysis of the numerical values in columns 2 and 3 of Table 1 yielded Eqn. 7.

$$\mathbf{L} = 0.507(0.000)\cdot(RI/100) - 0.398(0.007) \qquad (7)$$

$$(N = 118,\ SD = 0.023,\ R^2 = 1.000,\ F = 1712340)$$

Standard errors in both equation coefficients are given in parenthesis immediately following the respective coefficient. The statistical information, namely the standard deviation (*SD*), squared correlations coefficient (R^2), and Fisher F-statistic (*F*) is provided below the derived correlation.

The derived mathematical relationship allows us to calculate the **L** solute descriptor of the remaining 127 polyalkyl alkane and polymethyl alkane molecules. These calculations are summarized in the last column of Table 1. Examination of the last two columns of numerical entries in Table 1 reveals that Eqn. (7) provides a very accurate back-calculation of the solute descriptor values used in the regression analysis. The average absolute difference and average difference betwen the experimental-based **L**-solute descriptor values and those back-calculated from Eqn. (7) were 0.013 and -0.006, respectively.

Table 1. Retention Indices, *RI*, and Abraham Model **L** Solute Descriptors for n-Alkanes, Polyalkyl Alkanes and Polymethyl Alkanes.

Compound	*RI*	L (database)	L Eqn.(7)
Hexane	600.0	2.668	2.644
Heptane	700.0	3.173	3.151
Octane	800.0	3.677	3.658
Nonane	900.0	4.182	4.165
Decane	1000.0	4.686	4.672
Undecane	1100.0	5.191	5.179
Dodecane	1200.0	5.696	5.686
Tridecane	1300.0	6.200	6.193
Tetradecane	1400.0	6.705	6.700
Pentadecane	1500.0	7.209	7.207
Hexadecane	1600.0	7.714	7.714
Heptadecane	1700.0	8.218	8.221
Octadecane	1800.0	8.722	8.728
Nonadecane	1900.0	9.226	9.235
Eicosane	2000.0	9.731	9.742
Heneicosane	2100.0	10.236	10.249
Docosane	2200.0	10.740	10.756
Tricosane	2300.0	11.252	11.263
Tetracosane	2400.0	11.758	11.770
Pentacosane	2500.0	12.264	12.277
Hexacosane	2600.0	12.770	12.784
Heptacosane	2700.0	13.276	13.291
Octacosane	2800.0	13.780	13.798
Nonacosane	2900.0	14.291	14.305
Triacontane	3000.0	14.794	14.812
2-Methyloctane	865.0	3.966	3.988

2-Methylnonane	964.0	4.453	4.489
2-Methyldecane	1065.0	4.981	5.002
2-Methylundecane	1164.5	5.516	5.506
2-Methyldodecane	1265.0	6.022	6.016
2-Methyltridecane	1364.5	6.528	6.520
2-Methyltetradecane	1465.0	7.034	7.030
2-Methylpentadecane	1564.0	7.539	7.531
2-Methylhexadecane	1664.5	8.046	8.041
2-Methylheptadecane	1764.0	8.551	8.545
2-Methyloctadecane	1864.5	9.057	9.055
2-Methylnonadecane	1964.0	9.563	9.559
2-Methyleicosane	2064.5	10.070	10.069
2-Methylheneicosane	2164.0	10.575	10.573
2-Methyldocosane	2263.5	11.080	11.078
2-Methyltricosane	2363.0	11.449	11.582
2-Methyltetracosane	2463.0	11.952	12.089
3-Methyloctane	872.0	3.998	4.023
3-Methylnonane	971.0	4.486	4.525
3-Methyldecane	1071.5	5.037	5.035
3-Methylundecane	1172.0	5.550	5.544
3-Methyldodecane	1272.0	6.056	6.051
3-Methyltridecane	1372.0	6.563	6.558
3-Methyltetradecane	1472.5	7.070	7.068
3-Methylpentadecane	1572.0	7.577	7.572
3-Methylhexadecane	1673.0	8.073	8.084
3-Methylheptadecane	1773.5	8.573	8.594
3-Methyloctadecane	1873.5	9.099	9.101
3-Methylnonadecane	1973.7	9.607	9.609
3-Methyleicosane	2074.0	10.114	10.117
3-Methylheneicosane	2174.0	10.621	10.624
3-Methyldocosane	2274.0	11.127	11.131
3-Methyltricosane	2373.7	11.635	11.637
3-Methyltetracosane	2473.7	12.142	12.144
4-Methylnonane	962.0	4.441	4.479
4-Methyldecane	1061.5	4.963	4.984
4-Methylundecane	1161.0	5.495	5.488
4-Methyldodecane	1261.0	5.998	5.995
4-Methyltridecane	1360.0	6.502	6.497
4-Methyltetradecane	1460.5	7.008	7.007
4-Methylpentadecane	1560.0	7.512	7.511
4-Methylhexadecane	1660.5	8.018	8.021
4-Methylheptadecane	1760.0	8.524	8.525
4-Methyloctadecane	1860.2	9.030	9.033
4-Methylnonadecane	1960.2	9.536	9.540
4-Methyleicosane	2060.5	10.043	10.049
4-Methylheneicosane	2160.0	10.549	10.553
4-Methyldocosane	2259.5	11.055	11.058
4-Methyltricosane	2359.0	11.561	11.562
4-Methyltetracosane	2458.5	12.067	12.067
5-Methylnonane	961.0	4.432	4.474
5-Methyldecane	1058.0	4.963	4.966
5-Methylundecane	1156.0	5.475	5.463
5-Methyldodecane	1255.0	5.975	5.965
5-Methyltridecane	1354.0	6.477	6.467
5-Methyltetradecane	1453.8	6.980	6.973
5-Methylpentadecane	1553.6	7.483	7.479
5-Methylhexadecane	1653.4	7.988	7.985
5-Methylheptadecane	1753.2	8.492	8.491
5-Methyloctadecane	1853.0	8.998	8.997
5-Methylnonadecane	1953.2	9.503	9.505
5-Methyleicosane	2053.0	10.009	10.011
5-Methylheneicosane	2153.0	10.514	10.518
5-Methyldocosane	2252.0	11.019	11.020
5-Methyltricosane	2352.5	11.525	11.529
5-Methyltetracosane	2453.0	12.031	12.039
6-Methyldodecane	1254.0	5.965	5.960
6-Methyltetradecane	1451.0	6.964	6.959
6-Methylhexadecane	1650.0	7.968	7.968
6-Methylheptadecane	1749.0	8.473	8.469
6-Methyloctadecane	1848.0	8.977	8.971
6-Methyleicosane	2048.0	9.986	9.985
6-Methylheneicosane	2147.5	10.490	10.490
6-Methyldocosane	2247.0	10.995	10.994
6-Methyltetracosane	2446.5	12.006	12.006
7-Methyltridecane	1351.0	6.460	6.452
7-Methyltetradecane	1450.0	6.957	6.954
7-Methylpentadecane	1548.0	7.456	7.450
7-Methylhexadecane	1646.0	7.956	7.947
7-Methylheptadecane	1745.0	8.458	8.449
7-Methylnonadecane	1944.0	9.465	9.458
7-Methylheneicosane	2143.0	10.473	10.467
7-Methyltricosane	2342.0	11.481	11.476
3-Ethyloctane	961.0	4.467	4.474
3-Ethyldecane	1157.0		5.468
3-Ethyldodecane	1355.0		6.472
3-Ethyltetradecane	1554.0		7.481
3-Ethylhexadecane	1753.0		8.490
3-Ethyloctadecane	1952.0		9.499
3-Ethyleicosane	2152.0		10.513
3-Ethyldocosane	2351.5		11.524
4-Ethyloctane	954.0	4.409	4.439
4-Ethyldecane	1152.0		5.443
4-Ethyldodecane	1348.0		6.436
4-Ethyltetradecane	1548.0		7.450
4-Ethylhexadecane	1747.0		8.459
4-Ethyloctadecane	1947.5		9.476
4-Ethyleicosane	2148.0		10.492
4-Ethyldocosane	2348.0		11.506
5-Ethyldecane	1146.0		5.412
5-Ethyldodecane	1341.0		6.401
5-Ethyltetradecane	1538.0		7.400
5-Ethylhexadecane	1736.0		8.404
5-Ethyloctadecane	1937.0		9.423
5-Ethyleicosane	2137.0		10.437
5-Ethyldocosane	2335.0		11.440
6-Ethyldodecane	1336.0		6.376
6-Ethyltetradecane	1533.0		7.374
6-Ethylhexadecane	1731.0		8.378
6-Ethyloctadecane	1929.0		9.382
6-Ethyleicosane	2129.0		10.396
6-Ethyldocosane	2327.0		11.400
7-Ethyltetradecane	1530.0		7.359
7-Ethylhexadecane	1727.0		8.358
7-Ethyloctadecane	1924.0		9.357
7-Ethyleicosane	2122.0		10.361
7-Ethyldocosane	2320.0		11.364
5-Propyltridecane	1516.0		7.288
5-Propylpentadecane	1712.0		8.282
5-Propylheptadecane	1910.0		9.286
5-Propylnonadecane	2108.0		10.290
7-Propyltridecane	1506.0		7.237
7-Propylpentadecane	1700.0		8.221
7-Propylheptadecane	1898.0		9.225
5-Butyldecane	1313.0		6.259
5-Butyldodecane	1505.0		7.232
5-Butyltetradecane	1699.0		8.216

5-Butylhexadecane	1896.0		9.215
6-Butyldodecane	1498.0		7.197
6-Butyltetradecane	1691.0		8.175
6-Butylhexadecane	1887.0		9.169
7-Butyltetradecane	1688.0		8.160
7-Butylhexadecane	1880.0		9.134
2,3-Dimethyloctane	956.9	4.401	4.453
2,4-Dimethyloctane	919.8		4.265
2,5-Dimethyloctane	926.6		4.300
2,6-Dimethyloctane	936.0	4.304	4.348
2,7-Dimethyloctane	930.6	4.282	4.320
3,5-Dimethyloctane	927.6	4.259	4.305
3,6-Dimethyloctane	942.3	4.331	4.379
4,5-Dimethyloctane	947.8		4.407
2,3-Dimethyldecane	1158.0		5.473
2,4-Dimethyldecane	1115.2		5.256
2,5-Dimethyldecane	1118.5		5.273
2,6-Dimethyldecane	1120.0		5.280
2,7-Dimethyldecane	1125.7		5.309
2,8-Dimethyldecane	1136.8		5.366
2,9-Dimethyldecane	1130.1		5.332
3,5-Dimethyldecane	1118.4		5.272
3,6-Dimethyldecane	1128.8		5.325
3,7-Dimethyldecane	1132.6		5.344
3,8-Dimethyldecane	1143.6		5.400
4,5-Dimethyldecane	1138.0		5.372
4,6-Dimethyldecane	1111.2		5.236
4,7-Dimethyldecane	1120.8		5.284
2,6,10-Trimethylundecane	1276.8		6.075
2,6,10-Trimethyldodecane	1380.6		6.602
2,6,10-Trimethyltridecane	1466.6		7.038
2,6,10-Trimethylpentadecane	1653.6		7.986
2,6,10,14-Tetramethylpentadecane	1711.7		8.280
2,6,10,14-Tetramethylhexadecane	1816.2		8.810
2,6-Dimethylheptane	830.0	3.780	3.810
2,6-Dimethylnonane	1025.3		4.800
3,7-Dimethylnonane	1042.2		4.886
2,6-Dimethylundecane	1216.7		5.771
3,7-Dimethyldodecane	1321.2		6.300
3,7,11-Trimethyltridecane	1485.0		7.131
2,6,10-Trimethyltetradecane	1557.0		7.496
2,6,10,15-Tetramethylhexadecane	1806.0		8.758
2,6,10,15-Tetramethylheptadecane	1913.8		9.305
2,6,10,15-Tetramethyloctadecane	1989.8		9.690
2,6,10,15-Tetramethylnonadecane	2088.5		10.191
2,6,10,15-Tetramethyleicocane	2165.5		10.581
2,6,10,15-Tetramethylheneicosane	2268.0		11.101
2,6,10,15-Tetramethyldocosane	2354.5		11.539
8-Ethylhexadecane	1726.6		8.356
4-Ethylheptadecane	1846.9		8.966
4-Propylhexadecane	1823.4		8.847
5-Propylhexadecane	1808.9		8.773
6-Propylhexadecane	1804.3		8.750
7-Propylhexadecane	1800.0		8.728
8-Propylhexadecane	1798.6		8.721
5-Butylhexadecane	1897.4		9.222
6-Butylhexadecane	1889.7		9.183
7-Butylhexadecane	1884.6		9.157
9-Butylhexadecane	1883.1		9.149
6-Ethylnonadecane	2028.3		9.885
6-Propyloctadecane	2000.0		9.742
6-Butylheptadecane	1987.7		9.680
6-Pentylhexadecane	1979.6		9.639
7-Pentylhexadecane	1972.8		9.604
8-Pentylhexadecane	1971.3		9.596
7-Propylnonadecane	2094.7		10.222
7-Butyloctadecane	2080.5		10.150
7-Pentylheptadecane	2071.7		10.106
7-Hexylhexadecane	2066.0		10.077
8-Hexylhexadecane	2064.2		10.067
8-Methyldocosane	2241.5	11.019	10.966
8-Ethylheneicosane	2218.4		10.849
8-Propyleicosane	2189.5		10.703
8-Butylnonadecane	2174.8		10.628
8-Pentyloctadecane	2166.0		10.584
8-Hexylheptadecane	2160.1		10.554
8-Heptylhexadecane	2158.5		10.546
9-Methyltricosane	2339.4	11.459	11.463
9-Ethyldocosane	2314.9		11.339
9-Propylheneicosane	2285.4		11.189
9-Butyleicosane	2270.4		11.113
9-Pentylnonadecane	2261.2		11.066
9-Hexyloctadecane	2253.4		11.027
9-Heptylheptadecane	2251.7		11.018
10-Methyltetracosane	2436.6	11.957	11.956

PREDICTION OF MOLAR ENTHALPIES OF VAPORIZATION AND MOLAR ENTHALPIES OF SUBLIMATION

A complete set of solute descriptors enables one to estimate a large number of physicochemical and thermodynamic properties using published Abraham model correlations. To date we have reported mathematical expressions for predicting log *K* and log *P* values for solutes dissolved in both traditional molecular organic solvents[39-43] and ionic liquid solvents,[64-73] molar solubility ratios,[39-43] blood-to-body tissue/fluid partition coefficients,[74-78] Draize scores and eye irritation thresholds,[79-81] enthalpies of solvation,[45-55] lethal median concentrations of organic compounds towards fish and other aquatic organisms,[82-85] nasal pungency,[79,86-88] vapor pressures,[56] enthalpies of vaporization[57] and sublimation,[58] isobaric molar heat capacities of crystalline, liquid and gaseous organic and organometallic compounds,[89] and many other solute properties.[90-95]

To illustrate the importance of determining solute descriptors for additional compounds, we want to predict a couple of properties that can be used by the scientific community and manufacturing sector. Of the properties for which we have developed Abraham model correlations enthalpies of vaporization and enthalpies of sublimation seem the most logical choice. Large alkanes are not very

soluble in water so the likelihood for the scientific community needing to know the compounds' water-to-organic solvents partition coefficients and lethal molar concentrations towards aquatic organisms is small. Even if large alkanes were to be accidentally released in the environment their aqueous molar concentration would be too small to do significant harm to fish and other aquatic organisms. Also, large alkanes are not pharmaceutical compounds and there is little demand to estimate their distribution in the body. Knowledge of their enthalpies of vaporization and enthalpies of sublimation might be needed, however, in the design of high temperature industrial processes.

Our published Abraham model correlations:[57,58]

$$\Delta H_{vap,298K}\ (kJ\ mol^{-1}) = 6.100 - 7.363\ \mathbf{E} + 9.733\ \mathbf{S} + 4.025\mathbf{A} + 2.123\mathbf{B} + 9.537\mathbf{L} - 1.180\ \mathbf{S{\cdot}S} + 77.871\ \mathbf{A{\cdot}B} - 5.781\ \mathbf{I_{amine}} - 14.783\ \mathbf{I_{non\text{-}\alpha,\omega\text{-}diol}} - 17.873\ \mathbf{I_{\alpha,\omega\text{-}diol}} \quad (8)$$

(N = 703, SD = 2.09, R^2 = 0.986, F = 4925.6)

and

$$\Delta H_{sub,298K}\ (kJ\ mol^{-1}) = 13.93 - 16.90\ \mathbf{E} + 9.66\ \mathbf{S} + 10.02\ \mathbf{A} + 1.82\ \mathbf{B} + 13.57\ \mathbf{L} - 0.30\ \mathbf{S{\cdot}S} + 35.43\ \mathbf{A{\cdot}B} - 0.05\ \mathbf{L{\cdot}L} - 9.09\ \mathbf{I_{OH,adj}} + 17.26\ \mathbf{I_{OH,non}} + 7.37\ \mathbf{I_{NH}} \quad (9)$$

(N = 864, SD = 9.94, R^2 = 0.867, F = 503.2)

provide reasonably accurate predictions the standard molar enthalpies of vaporization, $\Delta H_{vap,298K}$, and standard molar enthalpies of sublimation, $\Delta H_{sub,298K}$, as evidence by the correlations' respective standard deviations of SD = 2.09 kJ mol^{-1} and SD = 9.94 kJ mol^{-1}, respectively. The larger standard deviations for $\Delta H_{sub,298K}$ result from the difficulty in measuring the low vapor pressures, and from the fact that the measurements were performed at high temperatures and extrapolated back to 298 K.

For the polyalkyl alkanes and polymethyl alkanes considered in the present study only the terms containing the **L** descriptor contribute to the $\Delta H_{vap,298K}$ and $\Delta H_{sub,298K}$. For the convenience of the reader we have simplified the predictive expressions:

$$\Delta H_{vap,298K}\ (kJ\ mol^{-1}) = 6.100 + 9.537\ \mathbf{L} \quad (10)$$

$$\Delta H_{sub,298K}\ (kJ\ mol^{-1}) = 13.93 + 13.57\ \mathbf{L} - 0.05\ \mathbf{L{\cdot}L} \quad (11)$$

to contain only the non-zero terms. Enthalpy of sublimation predictions given in Table 2 start with the C_{20}-compounds as most of the smaller compounds are liquid at 298 K. Predicted values of $\Delta H_{vap,298K}$ are given in Table 3 for all compounds as vaporization enthalpies of compounds that are crystalline at 298 K can be easily determined using the method of correlation gas chromatography[96-100]. Calculated values are given only for those polyalkyl alkanes and polymethyl alkanes for which we just calculated L-descriptor values. Calculated $\Delta H_{vap,298K}$ and $\Delta H_{sub,298K}$ values for the 2-methyl branched alkanes were reported elsewhere.[60]

Table 2. Comparison of the Enthalpies of Sublimation, $\Delta H_{sub,298K}$ (kJ mol^{-1}), Predicted by the Abraham Model, Eqn. (11), and the Group-Additivity Method of Naef and Acree, Eqn. (14)

Compound	ΔH_{sub} **Eqn. (11)**	ΔH_{sub} **Eqn. (14)**
3-Ethyloctadecane	138.32	140.76
3-Ethyleicosane	151.06	153.46
3-Ethyldocosane	163.67	166.16
4-Ethyloctadecane	138.03	140.76
4-Ethyleicosane	150.81	153.46
4-Ethyldocosane	163.45	166.16
5-Ethyloctadecane	137.36	140.76
5-Ethyleicosane	150.11	153.46
5-Ethyldocosane	162.63	166.16
6-Ethyloctadecane	136.84	140.76
6-Ethyleicosane	149.60	153.46
6-Ethyldocosane	162.13	166.16
7-Ethyltetradecane	111.09	115.36
7-Ethylhexadecane	123.85	128.06
7-Ethyloctadecane	136.52	140.76
7-Ethyleicosane	149.16	153.46
7-Ethyldocosane	161.69	166.16
5-Propylheptadecane	135.63	140.76
5-Propylnonadecane	148.27	153.46
7-Propylheptadecane	134.86	140.76
5-Butylhexadecane	134.73	140.76
6-Butylhexadecane	134.15	140.76
7-Butyltetradecane	121.33	128.06
7-Butylhexadecane	133.70	140.76
2,6,10,14-Tetramethylhexadecane	129.60	124.29
2,6,10,15-Tetramethylhexadecane	128.95	124.29
2,6,10,15-Tetramethylheptadecane	135.87	130.64
2,6,10,15-Tetramethyloctadecane	140.73	136.99
2,6,10,15-Tetramethylnonadecane	147.03	143.34
2,6,10,15-Tetramethyleicocane	151.92	149.69
2,6,10,15-Tetramethylheneicosane	158.41	156.04
2,6,10,15-Tetramethyldocosane	163.86	162.39
5-Butylhexadecane	134.82	140.76
6-Butylhexadecane	134.32	140.76
7-Butylhexadecane	134.00	140.76
9-Butylhexadecane	133.90	140.76
6-Ethylnonadecane	143.19	147.11
6-Propyloctadecane	141.38	147.11
6-Butylheptadecane	140.60	147.11
6-Pentylhexadecane	140.08	147.11
7-Pentylhexadecane	139.65	147.11
8-Pentylhexadecane	139.55	147.11
7-Propylnonadecane	147.42	153.46
7-Butyloctadecane	146.52	153.46
7-Pentylheptadecane	145.96	153.46
7-Hexylhexadecane	145.59	153.46

8-Hexylhexadecane	145.48	153.46
8-Ethylheneicosane	155.27	159.81
8-Propyleicosane	153.44	159.81
8-Butylnonadecane	152.51	159.81
8-Pentyloctadecane	151.95	159.81
8-Hexylheptadecane	151.57	159.81
8-Heptylhexadecane	151.47	159.81
9-Ethyldocosane	161.37	166.16
9-Propylheneicosane	159.50	166.16
9-Butyleicosane	158.56	166.16
9-Pentylnonadecane	157.98	166.16
9-Hexyloctadecane	157.48	166.16
9-Heptylheptadecane	157.38	166.16

Table 3. Comparison of the Enthalpies of Vaporization, $\Delta H_{vap,298K}$ (kJ mol^{-1}), Predicted by the Abraham Model, Eqn. (10), and the Group-Additivity Method of Naef and Acree, Eqn. (13)

Compound	ΔH_{vap} **Eqn. (10)**	ΔH_{vap} **Eqn. (13)**
3-Ethyldecane	58.25	59.83
3-Ethyldodecane	67.82	69.35
3-Ethyltetradecane	77.44	78.87
3-Ethylhexadecane	87.07	88.39
3-Ethyloctadecane	96.69	97.91
3-Ethyleicosane	106.36	107.43
3-Ethyldocosane	116.01	116.95
4-Ethyldecane	58.01	59.83
4-Ethyldodecane	67.48	69.35
4-Ethyltetradecane	77.15	78.87
4-Ethylhexadecane	86.78	88.39
4-Ethyloctadecane	96.47	97.91
4-Ethyleicosane	106.17	107.43
4-Ethyldocosane	115.84	116.95
5-Ethyldecane	57.72	59.83
5-Ethyldodecane	67.15	69.35
5-Ethyltetradecane	76.67	78.87
5-Ethylhexadecane	86.24	88.39
5-Ethyloctadecane	95.96	97.91
5-Ethyleicosane	105.63	107.43
5-Ethyldocosane	115.21	116.95
6-Ethyldodecane	66.90	69.35
6-Ethyltetradecane	76.43	78.87
6-Ethylhexadecane	86.00	88.39
6-Ethyloctadecane	95.58	97.91
6-Ethyleicosane	105.25	107.43
6-Ethyldocosane	114.82	116.95
7-Ethyltetradecane	76.28	78.87
7-Ethylhexadecane	85.81	88.39
7-Ethyloctadecane	95.33	97.91
7-Ethyleicosane	104.91	107.43
7-Ethyldocosane	114.48	116.95
5-Propyltridecane	75.61	78.87
5-Propylpentadecane	85.08	88.39
5-Propylheptadecane	94.66	97.91
5-Propylnonadecane	104.23	107.43
7-Propyltridecane	75.12	78.87
7-Propylpentadecane	84.50	88.39
7-Propylheptadecane	94.08	97.91
5-Butyldecane	65.79	69.35
5-Butyldodecane	75.07	78.87
5-Butyltetradecane	84.46	88.39
5-Butylhexadecane	93.98	97.91
6-Butyldodecane	74.74	78.87
6-Butyltetradecane	84.07	88.39
6-Butylhexadecane	93.55	97.91
7-Butyltetradecane	83.92	88.39
7-Butylhexadecane	93.21	97.91
2,4-Dimethyloctane	46.78	47.61
2,5-Dimethyloctane	47.11	47.61
4,5-Dimethyloctane	48.13	47.61
2,3-Dimethyldecane	58.30	57.13
2,4-Dimethyldecane	56.23	57.13
2,5-Dimethyldecane	56.39	57.13
2,6-Dimethyldecane	56.46	57.13
2,7-Dimethyldecane	56.73	57.13
2,8-Dimethyldecane	57.27	57.13
2,9-Dimethyldecane	56.95	57.13
3,5-Dimethyldecane	56.38	57.13
3,6-Dimethyldecane	56.88	57.13
3,7-Dimethyldecane	57.07	57.13
3,8-Dimethyldecane	57.60	57.13
4,5-Dimethyldecane	57.33	57.13
4,6-Dimethyldecane	56.03	57.13
4,7-Dimethyldecane	56.50	55.53
2,6,10-Trimethylundecane	64.04	63.95
2,6,10-Trimethyldodecane	69.06	68.71
2,6,10-Trimethyltridecane	73.22	73.47
2,6,10-Trimethylpentadecane	82.26	82.99
2,6,10,14-Tetramethylpentadecane	85.07	85.05
2,6,10,14-Tetramethylhexadecane	90.12	89.81
2,6-Dimethylnonane	51.88	52.37
3,7-Dimethylnonane	52.70	52.37
2,6-Dimethylundecane	61.13	61.89
3,7-Dimethyldodecane	66.19	66.65
3,7,11-Trimethyltridecane	74.11	73.47
2,6,10-Trimethyltetradecane	77.59	78.23
2,6,10,15-Tetramethylhexadecane	89.63	89.81
2,6,10,15-Tetramethylheptadecane	94.84	94.57
2,6,10,15-Tetramethyloctadecane	98.52	99.33
2,6,10,15-Tetramethylnonadecane	103.29	104.09
2,6,10,15-Tetramethyleicocane	107.01	108.85
2,6,10,15-Tetramethylheneicosane	111.97	113.61
2,6,10,15-Tetramethyldocosane	116.15	118.37
8-Ethylhexadecane	85.79	88.39
4-Ethylheptadecane	91.61	93.15
4-Propylhexadecane	90.47	93.15
5-Propylhexadecane	89.77	93.15
6-Propylhexadecane	89.55	93.15
7-Propylhexadecane	89.34	93.15
8-Propylhexadecane	89.27	93.15
5-Butylhexadecane	94.05	97.91
6-Butylhexadecane	93.68	97.91
7-Butylhexadecane	93.43	97.91
9-Butylhexadecane	93.36	97.91
6-Ethylnonadecane	100.38	102.67
6-Propyloctadecane	99.01	102.67
6-Butylheptadecane	98.41	102.67
6-Pentylhexadecane	98.02	102.67
7-Pentylhexadecane	97.69	102.67
8-Pentylhexadecane	97.62	102.67
7-Propylnonadecane	103.59	107.43
7-Butyloctadecane	102.90	107.43
7-Pentylheptadecane	102.48	107.43
7-Hexylhexadecane	102.20	107.43
8-Hexylhexadecane	102.11	107.43

8-Ethylheneicosane	109.57	112.19
8-Propyleicosane	108.17	112.19
8-Butylnonadecane	107.46	112.19
8-Pentyloctadecane	107.04	112.19
8-Hexylheptadecane	106.75	112.19
8-Heptylhexadecane	106.67	112.19
9-Ethyldocosane	114.24	116.95
9-Propylheneicosane	112.81	116.95
9-Butyleicosane	112.08	116.95
9-Pentylnonadecane	111.64	116.95
9-Hexyloctadecane	111.26	116.95
9-Heptylheptadecane	111.18	116.95

We were unable to find experimental $\Delta H_{vap,298K}$ and $\Delta H_{sub,298K}$ data in the published chemical literature to compare our calculated values against. What we offer in the way of a comparison is to compare our calculated values against the calculated values of a popular group-additivity method proposed by Naef and Acree[25] that has been shown to predict $\Delta H_{vap,298K}$ and $\Delta H_{sub,298K}$ values for a wide range of organic and organometallic compounds to within standard deviations of SD = 4.30 kJ mol^{-1} (N=3,460 compounds) and SD = 10.33 kJ mol^{-1} (N = 1,866 compounds), respectively. The basic method sums the contributions that each atomic group makes to the given thermodynamic or physical property:

$$\varphi = \sum_i A_i a_i + \sum_j B_j b_j + C \qquad (12)$$

where A_i is the number of occurrences of the ith atom group, B_j is the number of times each special group occurs, a_i and b_j are the numerical values of each atom group and special group, and C is a constant.

The atom group-additivity method proposed by Naef and Acree[25] fragments branched alkane molecules into three types of sp^3 hybridized carbon atoms based on the number of each type of atoms bonded to the carbon atom. One of the carbon atom-groups will be bonded to three hydrogen atoms and one carbon atom (CH_3 group), a second carbon atom type is bonded to two hydrogen atoms and two carbon atoms (CH_2 group), and the third carbon atom type is bonded to one hydrogen atom and three carbon atoms (CH group). There is also one special group that is defined as the number of carbon atoms in the alkane molecule.

In Eqns. (13) and (14) below we have filled in the numerical group values and constants for predicting $\Delta H_{vap,298K}$ and $\Delta H_{sub,298K}$ of C_nH_{2n+2} polyalkyl alkanes and polymethyl alkanes:

$$\Delta H_{vap,298K}\ (\text{kJ mol}^{-1}) = 3.07\ n_{CH3} + 4.67\ n_{CH2} + 3.57\ n_{CH} + 0.09\ n_{carbons} + 8.61 \qquad (13)$$

and

$$\Delta H_{sub,298K}\ (\text{kJ mol}^{-1}) = 5.99\ n_{CH3} + 6.88\ n_{CH2} + 2.28\ n_{CH} - 0.53\ n_{carbons} + 21.03 \qquad (14)$$

Examination of the numerical entries in Tables 2 and 3 reveals that the predictions based on the Abraham model are similar to predictions based on the group-additivity model of Naef and Acree[73]. The group-additivity method though is not able to distinguish between the placement of the alkyl-substituted group attached to large carbon atom chain, and gives the same predicted values for a given molecular formula. In other words, the predicted values of all mono-propylhexadecane molecules are the same. This limitation is a common feature of most group-additivity and group contribution methods. The Abraham model, on the other hand, would provide different predicted values for the different propylhexadecane isomers, and does not require fragmentation of the molecule into atom groups or functional groups. Fragmentation of molecules into functional groups can be difficult at times, particularly in the case of more complex molecules having many different functional groups.

As stated in the Introduction we have elected to promote the Abraham solvation parameter model for the correlation and estimation of physicochemical and thermodynamic properties over the many other QSAR and group contribution methods that have been proposed over the years. Abraham model correlations have been developed for a large number of solute transfer process having chemical, biological, pharmaceutical, and environmental significance. The published QSAR and group contribution methods are applicable to a much smaller number of chemical and biological processes. Moreover, the Abraham model solute descriptors for a given molecule can be used to predict many other properties such as vapor pressure, water-to-organic solvent partition coefficients, gas-to-water partition coefficients, solubility ratios, enthalpies of solvation, molar heat capacities of hydration[101], and the infinite dilution activity coefficients of the compound in water[102,103]. There is no need to calculate a different set of descriptor values for each property that one wishes to predict.

SUMMARY

Abraham model **L**-descriptors have been determined for 127 additional mono-alkyl alkanes and polymethyl alkanes from the published gas chromatographic retention indices for solutes eluted from a fused-silica capillary column coated with a cross-lined methyl silicone stationary phase. The computation is based on establishing a mathematical Abraham model correlation using the measured Kovats retention indices, *RI*, for those alkane solutes for which we already have a complete set of solute descriptors. In total experimental values for 118 different alkanes were used to establish the Abraham model correlation.

Calculated **L**-descriptor values were used to predict the standard molar enthalpies of vaporization and standard molar enthalpies of sublimation of 127 mono-alkyl alkanes and polyalkyl alkanes at 298 K based on recently published Abraham model correlations[57,58]. The predicted values compare very favorably with calculated values based on an atom-group additivity model[25].

Unlike simple atom-additivity and group contribution methods, the Abraham model is able to capture the effect that subtle structural features have on the physicochemical and thermodynamic properties of the molecule.

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DFT STUDY ON THE RELATIVE STABILITY OF ISOMERIC MACROCYCLIC METAL CHELATES OF DIVALENT 4*d*-ELEMENT IONS WITH TETRADENTATE (NSSN)- AND (NNNN)-"TEMPLATE" LIGANDS

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Keywords: 4*d*-element ion, 2,7-dithio-3,6-diazaoctadien-3,5-dithioamide-1,8, metal chelate, DFT method.

Using the density functional method (DFT) in the OPBE/TZVP//QZP approximation and the Gaussian09 program, geometric parameters and total energies of molecular structures of the Mo(II), Tc(II), Ru(II), Rh(II), Pd(II), Ag(II) and Cd(II) macrotricyclic complexes with (NSSN)- and (NNNN)-coordinations of the ligand donor centers to the complex, arising as a result of complexing between M(II) indicated above, dithiooxamide $H_2N–C(=S)–C(=S)–NH_2$ and glyoxal HC(=O)–CH (=O), were calculated. Based on the data of this calculation, it is shown that in the case of Mo(II), Tc(II), Ru(II), Rh(II) and Pd (II) complexes with (NSSN)-coordination of ligand are more stable, whereas in the case of Ag(II) and Cd(II), with (NNNN)-coordination; in addition, for the Mo(II) and Ru(II) complexes, a pseudo-tetrahedral environment of the central metal ion takes place by donor atoms, while for the complexes Tc(II), Rh(II), Pd(II), Ag(II), and Cd(II) are planar ones. The bond lengths and bond angles in the indicated coordination compounds are given and it is noted that the Ag(II) and Cd(II) complexes are almost flat, the Tc(II), Rh(II), and Pd(II) complexes are small, while the Ru(II), a fairly significant deviation from coplanarity. The five-membered metal chelate cycles formed as a result of complexing, in most of these complexes are either practically flat, or exhibit a slight (within 5°) deviation from coplanarity; the only exceptions are the Mo(II) and Ru(II) complexes.

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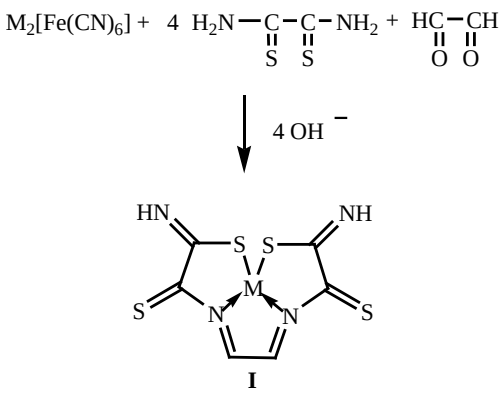
INTRODUCTION

We experimentally recorded template synthesis of (555)macrotricyclic metal complexes (**I**) in the ternary systems M(II)-dithiooxamide [$H_2N–C(=S)–C(=S)–NH_2$] and glyoxal [CH(=O)–CH(=O)] (M=Co, Ni, Cu), proceeding according to Scheme 1 in the $Co_2[Fe(CN)_6]^-$, $Ni_2[Fe(CN)_6]^-$ and $Cu_2[Fe(CN)_6]^-$gelatin-immobilized matrix implants.[1-5]



Scheme 1. Formation of "template" complex of type **I.**

Based on the data of various physicochemical methods, it was also shown that the ligand contained in each of these complexes namely, 2,7-dithio-3,6-diazaoctadiene-3,5-dithioamide-1,8, is tetradentate and coordinated to any of the above M(II) through two donor nitrogen atoms and two donor sulfur atoms. It should be noted in this connection that such a tetradentate ligand is in principle capable of coordinating to M(II) in a slightly different way, namely, through four donor nitrogen atoms and, together with the type **I** complexes where (NSSN)-coordination of 2,7-dithio-3,6-diazaoctadiene-3,5-dithioamide-1,8 to M(II) ion takes place, also forms complexes of type **II** isomeric to complexes of type **I** (Figure 1) in which, (NNNN)-coordination of the ligand indicated above, occurs.

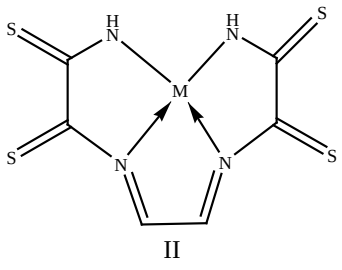


Figure 1. Structure of "template" complex of type **II**.

A quantum chemical calculation of the molecular structures of complexes of type **I** with 2,7-dithio-3,6-diazaoctadiene-3,5-dithioamide-1.8 and (NSSN)-coordination of chelate ligand was carried out using the DFT method as the above-mentioned M(II) ions, as well as three other M(II) of 3*d* elements, namely Mn(II), Fe(II) and Zn(II).[6,7] In subsequent works,[8,9] the fundamental possibility of the existence of complexes **I** and **II** of similar

composition containing M(II) ions of 4*d* elements, Mo(II), Tc(II), Ru(II), Rh(II), Pd(II), Ag(II), and Cd(II) was shown. However, in these works, the question of that which of these isomeric macrocyclic metal chelates – with (NSSN) or with (NNNN) coordination is more energetically favorable in the case of 4*d* element M(II) complexes, as well as the extent to which this depends on the nature of M(II) and the interpretation of this dependence, remained outside the scope of consideration. In this connection, the given article will be devoted to the consideration of namely these questions.

CALCULATION METHOD

To carry out quantum-chemical calculations, we in this work used the DFT method using the non-hybrid OPBE functional described in[10,11] with the basis set TZVP for H, C, N, O, and S atoms and the basis set QZP for the corresponding atom 4*d*-element M.[12-14] The calculations were performed by using the Gaussian09 program.[15] As in our earlier works,[7-9,16-21] the correspondence of the found stationary points to energy minima in all cases was proved by calculating the second derivatives of energy with respect to atomic coordinates; besides, all equilibrium structures corresponding to minimum points on the potential energy surfaces, had only positive values of frequencies. For Mo(II) complexes having $4d^4$ electron configuration, multiplicities 1, 3, 5 and 7, for Tc(II) complexes ($4d^5$), 2, 4 and 6, for Ru(II) ones ($4d^6$), 1, 3 and 5, for Rh(II) ones ($4d^7$), 2, 4 and 6, for Pd(II) ones ($4d^8$), 1, 3 and 5, for Ag(II) ones ($4d^9$), 2, 4 and 6, and for Cd(II) ones ($4d^{10}$), 1 and 3, were considered. Of the structures optimized for the indicated multiplicities, the structure having the lowest energy, was chosen for each of these complexes. The calculation of the parameters of molecular structures with multiplicities other than 1 was always carried out by the unlimited method (*UOPBE*); with multiplicity 1, by the restricted method (*ROPBE*). For multiplicity 1, an unlimited method of calculation was also used, in combination with the option GUESS = Mix; in this case, the results obtained were always similar to the results obtained using the restricted method.

RESULTS AND DISCUSSION

According to the data of our quantum-chemical calculation in the aforementioned DFT method version, the complexes of all the ions of the M(II) 4*d* elements named above with 2,7-dithio-3,6-diazaoctadiene-3,5-dithioamide-1.8 of type **I** as well as of type **II** are in principle capable of independent existence. The molecular structures of these metal macrocyclic compounds are presented in figures 2 and 3, the key parameters of these structures (bond lengths and bond angles) are given in Tables SM1-SM2 (see *Supplemental Materials*). Total energies of complexes under study are presented in the Table 1. The Mo(II), Tc(II), Ru(II), Rh(II), and Pd(II) complexes of type **I** are more stable, in terms of energy, than the complexes of type **II**, whereas for complexes of Ag(II) and Cd(II), the inverse relationship is operative. Even more interesting is that when moving from Mo(II) to Ru(II), the values of [*E*(**II**)–*E*(**I**)] increase, and when moving from Ru(II) to Pd(II), on the contrary, they decrease while remaining positive; upon transition from Pd(II) to Ag(II) and further to Cd(II) [*E*(**II**)–*E*(**I**)] not only changes in sign, but also increases sharply in absolute value (Table 1). The relative energies of the ground and excited states with different spin multiplicities (*MS*) of complexes **I** and **II** for different M(II) in the gas phase are presented in Table 2.

Table 1. Total energies (taking into account the zero-point energy) of complexes *E*(**I**) and *E*(**II**) for various M(II) in the gas phase.

M(II)	*E*(I)	*E*(II)
Mo(II)	-6021.249119	-6021.237988
	[0.0]	**[29.2]**
Tc(II)	-6250.771513	-6250.760050
	[0.0]	**[30.1]**
Ru(II)	-6487.654750	-6487.635976
	[0.0]	**[49.3]**
Rh(II)	-6732.074667	-6732.063863
	[0.0]	**[28.4]**
Pd(II)	-6984.231040	-6984.229051
	[0.0]	**[5.2]**
Ag(II)	-7243.989341	-7244.012438
	[60.6]	**[0.0]**
Cd(II)	-7511.621916	-7511.647408
	[66.9]	**[0.0]**

Values without parentheses are total energies in Hartree units, in square brackets, relative energies in kJ mol^{-1} (the total energy of the complex with the lowest value of *E* is taken as 0.0 in all cases).

Table 2. Relative energies of the ground and excited states with different M_S of complexes **I** and **II** with various M(II) in the gas phase in kJ/mol

M(II)	I	II
Mo(II)	M_S = 1 (-) *	M_S = 1 (48.7)
	M_S = 3 (0.0)	M_S = 3 (0.0)
	M_S = 5 (42.9)	M_S = 5 (29.0)
	M_S = 7 (161.6)	M_S = 7 (137.4)
Tc(II)	M_S = 2 (13.3)	M_S = 2 (35.2)
	M_S = 4 (0.0)	M_S = 4 (0.0)
	M_S = 6 (40.8)	M_S = 6 (7.6)
Ru(II)	M_S = 1 (10.8)	M_S = 1 (0.0)
	M_S = 3 (0.0)	M_S = 3 (9.0)
	M_S = 5 (11.9)	M_S = 5 (120.2)
Rh(II)	M_S = 2 (16.4)	M_S = 2 (13.1)
	M_S = 4 (0.0)	M_S = 4 (0.0)
	M_S = 6 (153.8)	M_S = 6 (102.0)
Pd(II)	M_S = 1 (3.1)	M_S = 1 (3.9)
	M_S = 3 (0.0)	M_S = 3 (0.0)
Ag(II)	M_S = 2 (0.0)	M_S = 2 (0.0)
	M_S = 4 (177.6)	M_S = 4 (100.2)
	M_S = 6 (302.1)	M_S = 6 (215.0)
Cd(II)	M_S = 1 (4.2)	M_S = 1 (39.5)
	M_S = 3 (0.0)	M_S = 3 (0.0)

The total energy of the complex with spin multiplicity corresponding to the minimum energy is taken as 0.0 in all cases.

As can be seen from it, for the complexes of almost all the M(II) ions considered by us, the M_S values of the ground states of complexes **I** and **II** turn out to be the same; for example, the ground state of the both Rh(II) complexes is the spin quartet, so that they turn out to be high-spin

complexes; the Pd(II) and Cd(II) complexes with the ground triplet state should also be classified as such complexes. The Ag(II) complexes, in full accordance with theoretical expectations, have a spin doublet as the ground state. For the Mo(II) and Tc(II) complexes, these are the spin triplet and spin quartet, respectively, and both occupy an intermediate position between the high-spin and low-spin complexes for the electronic configurations $4d^4$ and $4d^5$, respectively. The exceptions against this background are Ru(II) complexes,

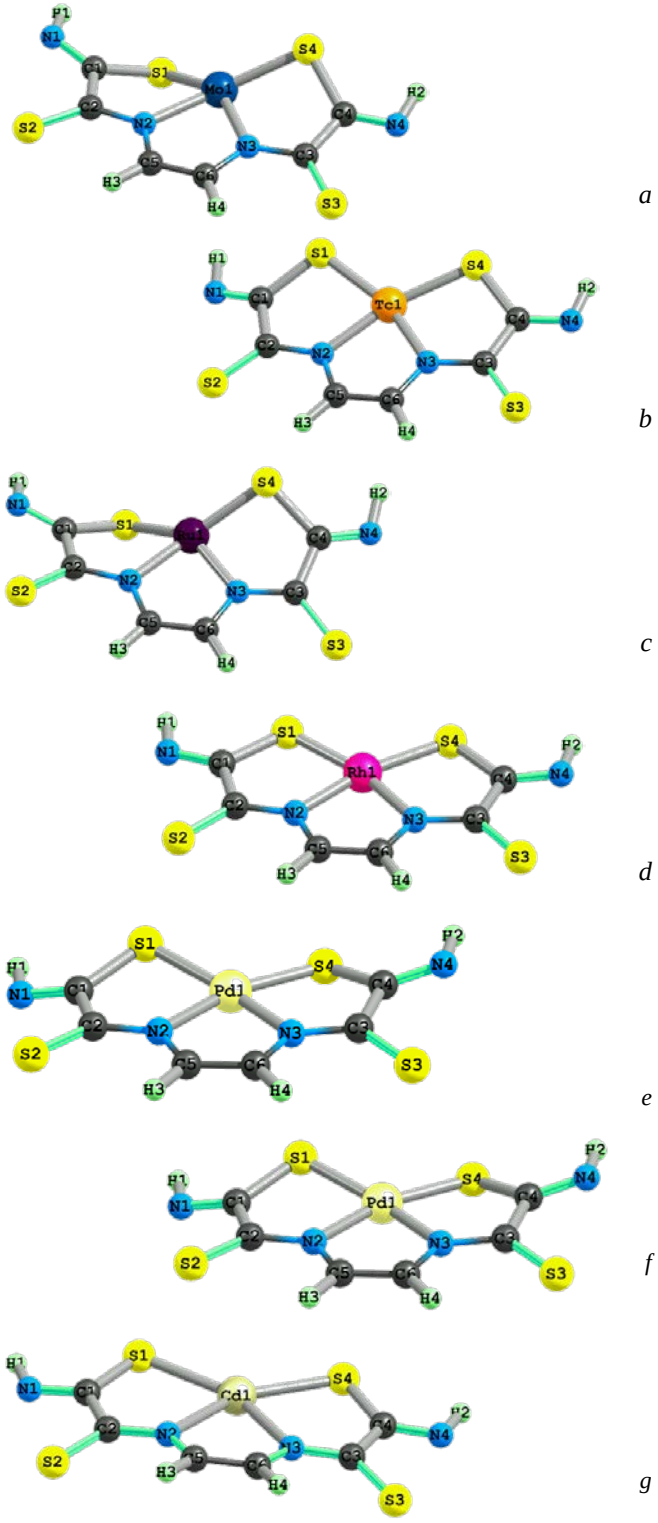


Figure 2. Molecular structures of M(II) metal chelates with (NSSN) ligand coordination: *a* – Mo(II), *b* – Tc(II), *c* – Ru(II), *d* – Rh(II), *e* – Pd(II), *f* – Ag(II), *g* – Cd(II).

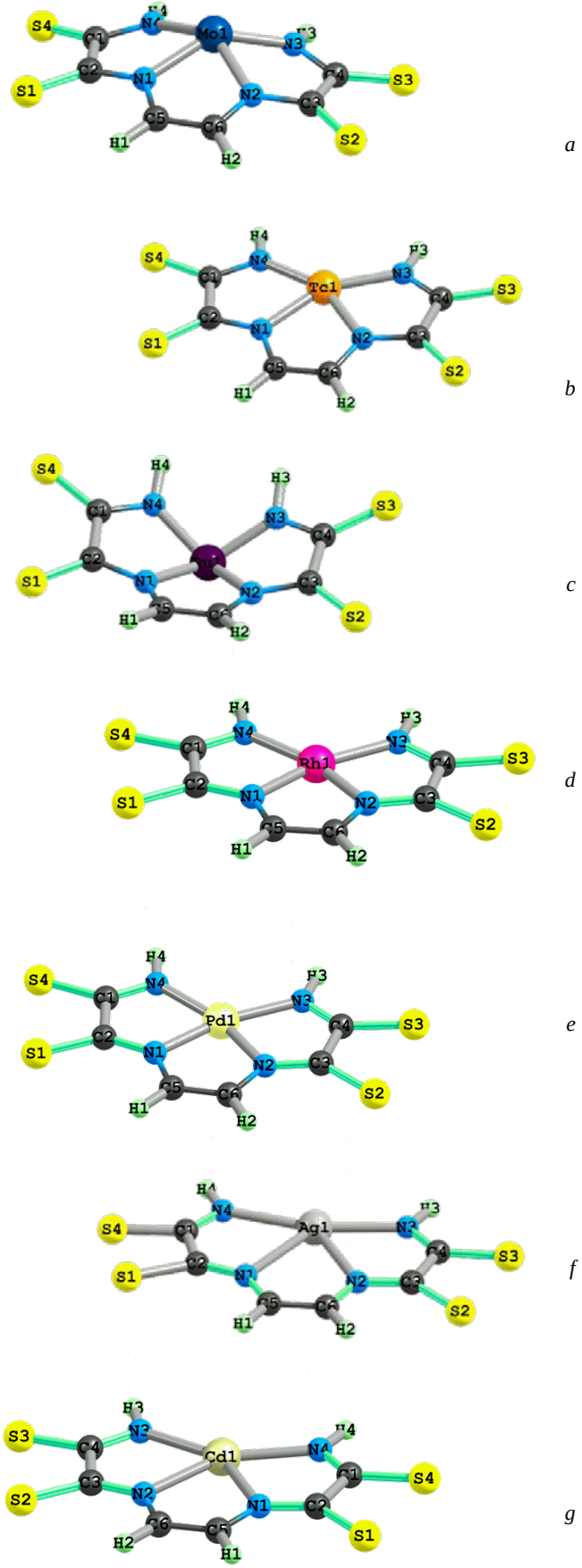


Figure 3. Molecular structures of M(II) metal chelates with (NNNN) ligand coordination: *a* – Mo(II), *b* – Tc(II), *c* – Ru(II), *d* – Rh(II), *e* – Pd(II), *f* – Ag(II), *g* – Cd(II).

for which, in the case of complex **I**, the ground state is a spin triplet, for complex **II**, a spin singlet, so that complex **II** of this M(II) is sole low-spin complex among the coordination compounds considered by us. In connection with the foregoing, it is worth noting the curious circumstance that the cadmium(II) complex of type **II** (which, as can be seen from the data in Table 1, is significantly more stable than complex **I** isomeric to it) has a triple ground state contrary to expectations for electronic configuration $4d^{10}$ singlet state. However, our conclusions about the multiplicity of the ground state of the complexes we are considering, on the one hand, relate to the gas phase, and on the other hand, the energy difference between the triplet and singlet states in the complexes Tc(II), Ru(II), Rh(II) and especially Pd(II) is very small, and if so, it is possible that when these complexes transition to the solid phase, the states with lower values of M_S will become the main ones. Moreover, manifestations of the spin-crossover phenomenon (spin isomerism) can also be expected here.

Also, it seems interesting to look at the molecular structure of the ligand that is a part of each of the complexes under examination, namely 2,7-dithio-3,6-diazaoctadiene-3,5-dithioamide-1,8 (Figure 4).

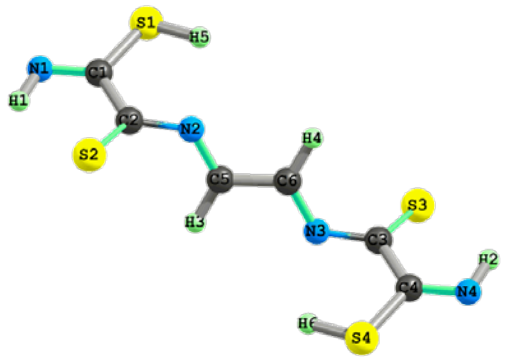


Figure 4. Molecular structures of 2,7-dithio-3,6-diazaoctadiene-3,5-dithioamide-1,8.

According to our calculation, the molecule of this ligand is very long (the distance between the most distant atoms, namely between N1 and N4, is 1042.3 pm) and at the same time is narrow (the distance between the atoms most distant from each other, namely between S1 and S2, between S3 and S4 is 437.7 pm). In contrast to the complexes formed by this ligand, it has a center of symmetry, which is located in the center of the line (C5C6) bond. It is noteworthy that the six atoms of this molecule, namely nitrogen N2, N3, carbon C5, C6, and hydrogen H3, H4 are in the one plane (!) because the dihedral angles (N2C5C6H4), (N2H4N3H3), (N2C5C6N3) and (H3C5C6H4) are equal to 0.0° or 180.0°, and the sum of the internal angles in the quadrangles (N2C6N3C5), (N2H4N3H3), (C5H4C6H3), (N2C5C6H4), (H3C5C6N3) is either 360.0° or practically does not differ from the indicated value.

It should be noted in this connection that the donor nitrogen atoms N2 and N3 are in the *trans*-position with respect to the (C5C6) bond line. That is why, for the formation of the chelate node MN_2S_2, the grouping of the atoms [H4C6N3C3(S3)C4(N4H2)S4H6] should unfold relative to the (C5C6) bond line at angle 180.0°, which is connected with certain (and considerable) energy costs. To form the chelate node MN_4, in addition to this, the [S2C2C1(N1H1)S1H5] and [S3C3C4(N4H2)S4H6] groupings of atoms must be turned relative to the (C1C2) and (C3C4) bond lines, respectively, to the same angles 180.0°, that requires large additional energy costs. In this connection, it becomes clear that it is preferable for the ligand to form complexes with the chelate node MN_2S_2, but not with the chelate node MN_4. On the other hand, Mo(II), Tc(II), Ru(II), Rh(II), and Pd(II) ions contain the corresponding chemical elements at lower oxidation states than traditional for these elements, and belong to the category of sufficiently "soft" Pearson acids. For them, more typical is coordination to atoms with low electronegativity (in our case, to sulfur atoms). In Ag(II), silver has the same degree of oxidation II, but it is anomalously high for a given element, so this ion belongs to the category of rather "hard" Pearson acids. Therefore, coordination to atoms with high electronegativity (in our case, to nitrogen atoms) should be more probable for this M(II). As for Cd(II), it actually belongs to the category of "intermediate strength" acids and for it one can expect both (NSSN)- and (NNNN)-coordination of the ligand under consideration. Thus, the data on the coordination of the 4*d*-element M(II) ions, obtained as a result of the quantum-chemical calculation, acquire a completely reasonable explanation.

CONCLUSION

As can be seen from the foregoing, for the ions of 4*d* elements under consideration, namely, Mo(II), Tc(II), Ru(II), Rh(II), Pd(II), Ag(II), and Cd(II), at complexing with 2,7-dithio-3,6-diazaoctadiene-3,5-dithioamide-1,8, formation of chelate node MN_2S_2 with coordination through two S atoms and two N atoms to the corresponding M(II), is more typical than formation of chelate node MN_4 with coordination through four N atoms. It is quite understandable, since these ions, according to Pearson's classification,[22] belong to the category of very “soft” acids and, therefore, coordination with donor atoms with relatively low electronegativity (in our case, S atoms), rather than atoms with high electronegativity (in our case, N atoms). Wherein, that is noteworthy, the difference in the total energies of structures with (NSSN) and (NNNN) coordination of the ligand to M(II) in the series Mo(II) – Cd(II) monotonically increases with the transition from Mo(II) to Ru(II) and decreases monotonically upon transition from Ru(II) to Pd(II), and in the case of Ag(II) and Cd(II), structures with a chelating site MN_4 are lower in total energy.

That is also a quite expected result due to the fact that, for Ag(II) and Cd(II), unlike the other five complexing agents M(II) considered here, coordination through donor nitrogen atoms is more characteristic in the complexes formed by them than through sulfur atoms. A significant contribution to the choice between (NSSN) and (NNNN) coordination, undoubtedly, gives the specific structure of the tetradentate chelate ligand itself (Figure 4). Nonetheless, these complexes are characterized by planar or close to it coordination of the donor centers of 2,7-dithio-3,6-diazaoctadiene-3,5-dithioamide-1.8 to M(II); in this case, the Rh(II), Ag(II), and Cd(II) complexes are almost flat, while the others exhibit to one degree or another a noticeable deviation from coplanarity, and this deviation is most pronounced in the Ru(II) complex.

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pH EFFECT ON STRUCTURAL, MORPHOLOGICAL AND OPTICAL PROPERTIES OF ZnO THIN FILMS PRODUCED BY CHEMICAL BATH DEPOSITION METHOD

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Keywords: Chemical bath deposition, ZnO, thin films, pH effect.

Zinc oxide (ZnO) thin films are widely used in the production of high value-added technological products such as photovoltic cells, sensors, flexible and wearable electronic materials, as they are abundant in nature, easy to process, low cost and can be produced with different methods. The Chemical Bath Deposition method is preferred in the production of metal oxide thin films by changing the parameters such as pH, temperature and concentration by immersing the various substrates into the prepared solution without the need for a vacuum environment. In this study, ZnO thin films were grown on glass substrates by chemical bath deposition method. The effects of pH on the structural, morphological and optical properties of the obtained films were investigated using X-ray diffraction (XRD) method, Field Emission Scanning Electron Microscopy (FESEM) and UV-Vis Spectrophotometry respectively. It was observed that the optimum film formation took place in the Z3 series at pH 10.

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INTRODUCTION

With the development of increasing technology and application techniques, thin films can be deposited on different morphologicals by using many metal oxides such as cadmium oxide,[1] copper oxide,[2] zinc oxide,[3] magnesium oxide,[4] titanium dioxide,[5,6] and vanadium oxide.[7] Metal oxide thin films can be obtained as a result of the combination of many techniques such as sol-gel spin coating,[8] pulse laser deposition,[9,10] chemical bath deposition (CBD),[11,12] and chemical spray pyrolysis.[13] Due to their electrical conductivity,[14] optical transmittance[15,16] and special band gaps, metal oxide thin films can be produced by using different techniques according to their usage areas and desired features. [17] ZnO thin films do not contain toxic chemicals, are suitable for developing alternative structures, easy-to-find and low cost. It is used as a value-added product in many different areas up to water treatment.[18-24] Metal oxide thin film deposition by chemical bath deposition method is more preferred than other techniques due to its advantages such as low cost, simple application[25] and easy change of parameters as temperature[26] and pH.[27] The system does not require quick and additional annealing. In this study, ZnO thin films were produced by preparing bath solutions at different pH values with the CBD method, and the effects of the solution pH value on the structural, morphological and optical properties of thin films were investigated.

EXPERIMENTAL

CBD method is the method of obtaining a film on suitable substrate at suitable temperature by using the chemicals prepared with an aqueous solution with suitable stoichiometry. In this method, the substrate is immersed in the prepared chemical bath and there is no need for vacuum environment to produce the film and the pH of the solution plays an important role and the pH and temperature of the solution must be kept the same during film formation. In order to produce ZnO films by CBD method, a 0.25 M zinc nitrate hexahydrate $Zn(NO_3)_2.6H_2O$ (Sigma Aldrich) solution was prepared. Then 28 % aqueous ammonia (NH_4OH) (Merck) was added to the solution to adjust the pH of the solution. To examine the effect of pH value on thin films, 4 different pH values were chosen and solutions were prepared. The naming of the selected pH values and series are given in Table 1.

Table 1. Series naming by pH values.

pH	Series Name
9	Z1
9.5	Z2
10	Z3
10.5	Z4

After the solutions were prepared, the pre-cleaned glass substrate was immersed in the bath and the solution was started to be heated while mixing the solution with the help of a heated and temperature controlled magnetic mixer. The immersed films were kept in the bath for 30 min at 85 °C bath temperature. The coated films were removed from the bath. The removed films were washed with distilled water and dried outdoors. The X-ray diffraction (XRD) method was used for the structural characterization of the films obtained. PANALYTICAL Empyrean X-Ray Diffraction (XRD) device was used to examine the structural properties of the films obtained. 45 kV voltage and 40 mA current are applied as operating conditions of the device. The scanning speed was selected at 2 degrees / minute, the wavelength of 1,5406 Å was used with CuK_α beam and samples were examined at $30^o \leq 2\theta \leq 60^o$ limit values. Morphological properties were investigated using Field Emission Scanning Electron Microscopy (FESEM) and optical properties using UV-Vis Spectrophotometry.

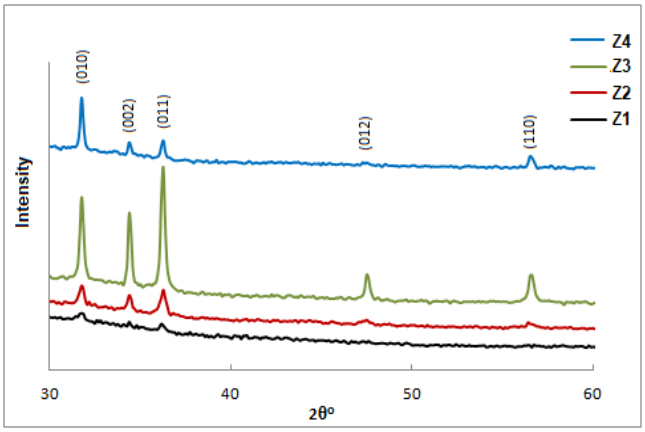

Figure 1. XRD spectra of ZnO thin films.

RESULTS AND DISCUSSION

As seen in Figure 1, all series are polycrystalline and show peaks of hexagonal ZnO structure. Peak intensities of films prepared as pH 10 in Z3 series are higher than peak intensities of other series. In the Z1 series, the crystallinity of the films prepared at pH 9 is quite low. As can be seen from the spectrum, the peaks of the (010), (002) and (011) planes belonging to the hexagonal ZnO structure started to appear in the Z1 series with very low intensities. In the Z2 series, when the pH value was brought to 9.5, the intensities of the peaks of the same planes also increased. In addition, the peaks of the (012) and (110) planes of the hexagonal ZnO structure were observed at low intensities. In the Z3 series, all of the (010), (002), (011), (012) and (110) peaks of the hexagonal ZnO structure were formed violently and sharply in the films prepared at pH 10.

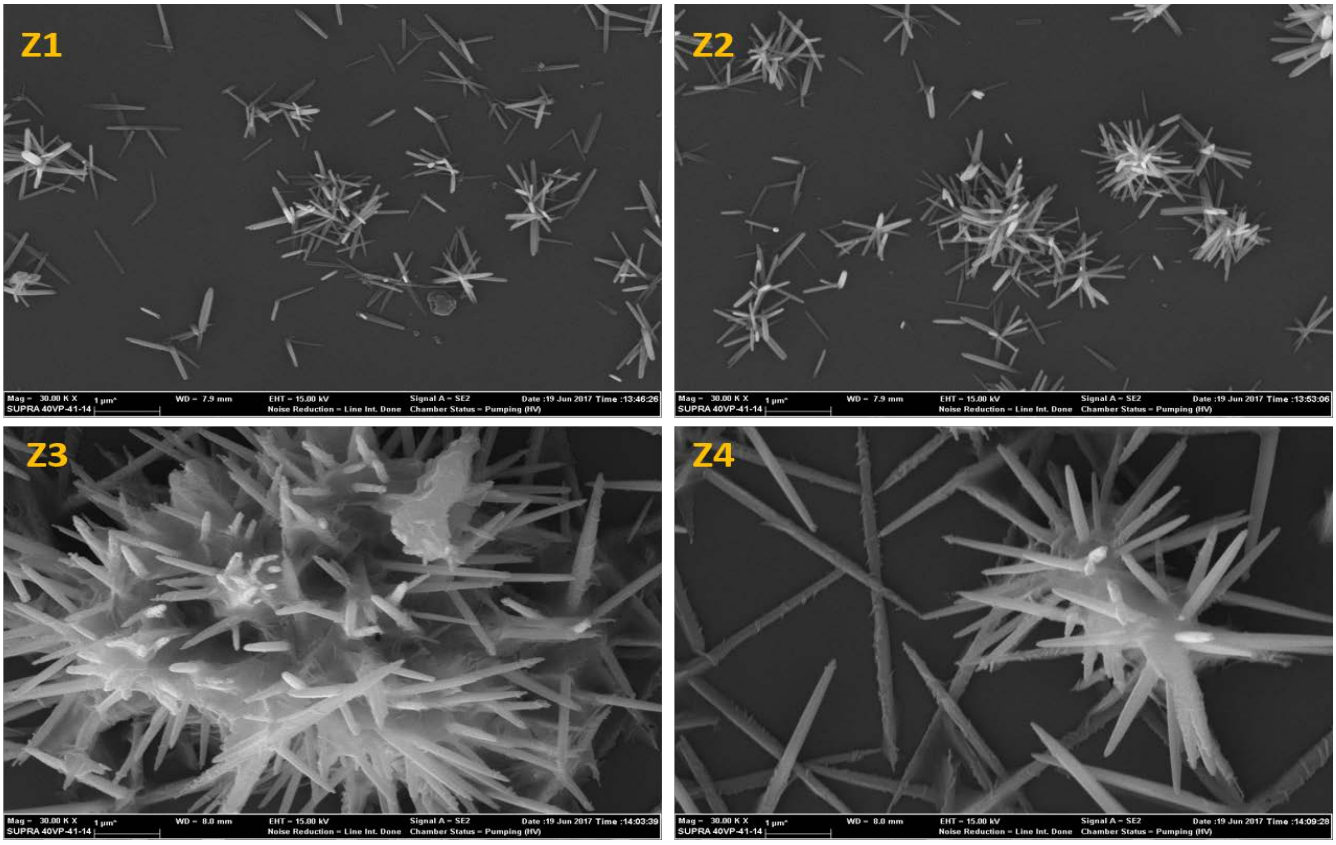

Figure 2. FESEM images of ZnO thin films.

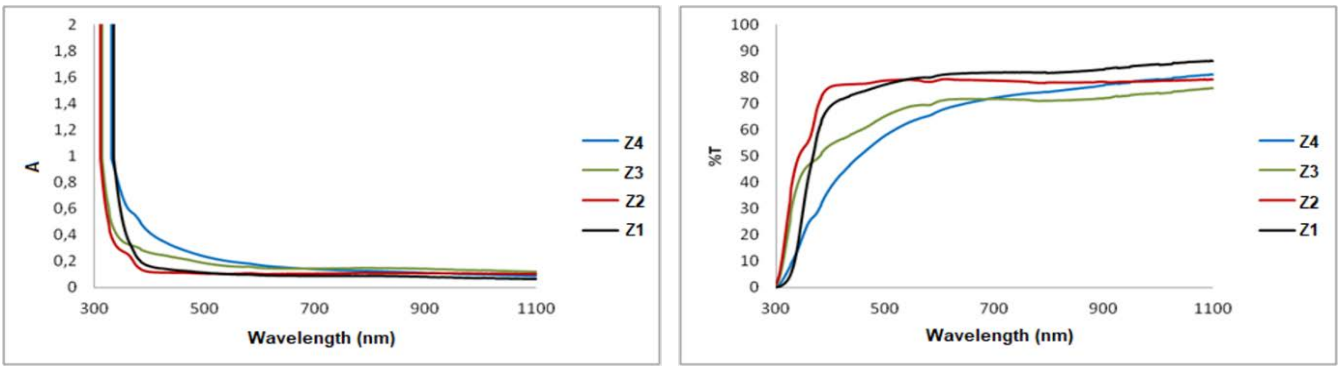

Figure 3. Absorbance and optical transmittance spectra of ZnO thin films.

As can be seen from the spectrum, the Z3 series is the series with the most severe peaks. Z3 series has preferential orientation in the direction of (011) peak formed at $2\theta \approx 36.24^{o}$. In the Z4 series, when the pH value was brought to 10.5, a reduction of the intensity of the peaks of the hexagonal ZnO structure was observed.

In Table 2, the full width half maximum (FWHM) and average grain size (D) values of thin films are given. With the information obtained from XRD spectra; The wavelength of the x-ray used is λ, the diffraction angle is θ and the half peak width in radians is β, and the average grain sizes of the films are calculated using the Scherrer formula.[28]

$$D = 0.9\lambda/\beta\cos\theta \quad (1)$$

In the Z3 series, it is seen that the grain size value is greater than 53 nm. Crystallization improves as grain sizes increase. In addition, as the full width half maximum (FWHM) decreases, crystallization improves. Considering all these data, it is understood that the best crystallization is seen in the films of Z3 series.

Table 2. Grain size values of thin films.

Serial name	FWHM	*D*, nm
Z1	0,3133	25
Z2	0,2199	39
Z3	0,1789	53
Z4	0,1966	44

ZEISS Supra 40VP Field Emission Scanning Electron Microscope (FESEM) was used to examine the morphological properties of ZnO thin films produced at different pH values. While examining the morphological properties of the device, the secondary electron (SE) detector was used and images at 30 kx magnification were obtained.

When the FESEM images given in Figure 2 are examined, it is seen that the films consist of continuous and independent nano sticks. It is also seen that these nano sticks combine to form a flower-like structure. Average grain size values calculated from FESEM images are in the range of 40-50 nm. In the Z1 and Z2 series, it is shown in the FESEM image that there are voids on the morphological and the structure is not completely formed. This data confirms the XRD results.

UV-Vis Spectroscopy measurements were taken in the range of 300-1100 nm in PERKIN ELMER LAMBDA 25 to examine the optical properties of the films obtained.

In Figure 3, absorption spectra and optical transmittance spectra of ZnO thin films at room temperature are given comparatively. The band gap values of the thin film was calculated by using Tauc method.[29] The band gap value calculated for each series is given in Table 3.

Table 3. Band gap values of ZnO thin films.

Series name	Bandgap values, eV
Z1	3.21
Z2	3.26
Z3	3.35
Z4	3.27

The band gap values of ZnO thin films are reported in the literature as about 3.3 eV.[30-32] When Table 3 is examined, the series closest to this value is the Z3 series. In addition, as seen in Figure 3, with the increase in pH value, a decrease in optical transmittance spectra is observed in the visible region (400 - 700 nm).

CONCLUSION

In this study, ZnO thin films were produced on glass substrates by CBD method. Solutions were prepared by selecting 4 different pH values between pH 9.5-10.5 values, series were named and the effect of pH on thin films was examined. When the structural properties of the films obtained were examined by the X-ray diffraction (XRD) method, it was observed that the 4 different series contain peaks of the polycrystalline structure and hexagonal ZnO structure, and the peak intensities of the films prepared in the Z3 series as pH 10 are higher than the peak intensities of the other series. When the full width half maximum (FWHM) and average grain size (D) values were calculated, it was observed that the grain size value in the Z3 series was higher than the others with 53 nm and crystallization improved as the grain sizes increased. Therefore, it was understood that the best crystallization was seen in the films of Z3 series. When the morphological properties of ZnO thin films produced at different pH values were examined by Field Emission Scanning Electron Microscope (FESEM), it was observed that they consist of independent nano sticks, combine to form a flower-like structure, and average grain size values are in the range of 40-50 nm. When the optical properties of the films were examined by UV-Vis Spectroscopy measurements. The band gap values of the Z3 series of thin films was calculated as 3.35 eV with the Tauc method. It is observed that optimum film formation occurs in the Z3 series at pH 10, where crystallization is the best compared to other series.

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THE PECULIARITIES OF THE 4-CARBOXYPHENYLGLYOXAL AND *N*-ALKOXY-*N'*-ARYLUREAS INTERACTION

Vasiliy G. Shtamburg,[a]* Victor V. Shtamburg,[a] Andrey A. Anishchenko[b] and Alexander V. Mazepa[c]

Keywords: *N*-alkoxy-*N'*-arylureas, *N*-alkoxy-*N'*-alkylureas, arylglyoxals; synthesis; 3-alkoxy-1-aryl-5-(4-carboxyphenyl)-4,5-dihydroxyimidazolidin-2-ones; 5-(4-carboxyphenyl)-4,5-dihydroxy-1-methyl-3-propyloxyimidazolidin-2-one; 3-alkoxy-4,5-dihydroxy-5-(4-nitrophenyl)-1-phenylimidazolidin-2-ones.

It was found that 3-alkoxy-4,5-dihydroxyimidazolidin-2-ones are the only products of interaction of *N*-alkoxyureas with arylglyoxals which have strong electronegative substituent in the forth position of the aryl moiety. The possibility of obtaining such products as 3-alkoxy-1-aryl-5-(4-carboxyphenyl)-4,5-dihydroxyimidazolidin-2-ones, 3-alkoxy-1-alkyl-5-(4-carboxyphenyl)-4,5-dihydroxyimidazolidin-2-ones and 3-alkoxy-1-phenyl-4,5-dihydroxy-5-(4-nitrophenyl)-imidazolidin-2-ones has been verified in the experimental way. In most the cases 3-alkoxy-4,5-dihydroxyimidazolidin-2-ones were produced as a mixture of diastereomers.

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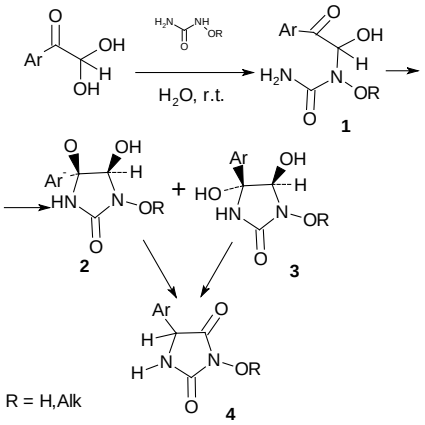
INTRODUCTION

As it was shown in our previous publications[1-6] the arylglyoxals' interaction with *N*-hydroxyurea and *N*-alkoxyureas is a very promising way to get valuable pharmaceutical materials. Three types of products can be produced by this reaction. As we have shown some of the products transform into others.

The following products can be obtained from this reaction: substituted ureas **1**, diastereomers of 3,4,5-trihydroxy-5-arylimidazolidin-2-ones, 3-alkoxy-4,5-dihydroxy-5-arylimidazolidin-2-ones **2** and **3** respectively, or 3-hydroxy- or 3-alkoxyhydantoins **4**.



Scheme 1. The products of interaction of arylglyoxals with *N*-hydroxyurea or *N*-alkoxyureas.

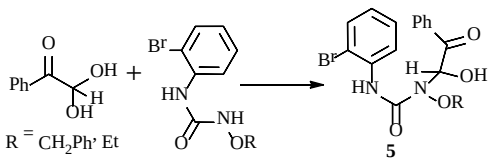
The mechanism of this interaction could not be completely established because of lack of experimental evidence. In any case the formation pattern of each product type is valuable. It is important to know this pattern not only in order to determine the reaction mechanism, but also to get further perspective synthones and materials in pharmacy, organic synthesis and bioorganic chemistry.

The relevance of the products which can be obtained by the interaction of arylglyoxals with *N*-hydroxyurea or *N*-alkoxyureas is significant because of the importance of imidazolidin-2-ones and imidazolidin-2,4-diones among pharmaceutical materials.[7-10] Arylglyoxals are widely used in synthesis of these biologically active nitrogen-containing heterocycles.[11]

Despite the differences between the products of the arylglyoxals interaction with *N*-hydroxyurea or *N*-alkoxyureas we have observed several patterns in their formation. In fact, the type of the product strongly depends on the glyoxal reagent. However, when we use arylglyoxals with electron-donating groups in aryl moiety, the substituted ureas **1** might be not the only products of this reaction.[1] As usual the first type products, substituted ureas **1,** forms imidazolidin-2-ones **2** and **3**, which further turns into hydantoins **4**. Nevertheless, it is possible to obtain only the substituted ureas **5** in this interaction.[2,6] For this result the strong intramolecular effects should take place in the compounds **5** (Scheme 2).

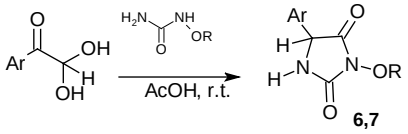
The mixture of the second type products, 4,5-dihydroxyimidazolidin-2-ones **2** and **3**, and the third type of products, hydantoins **4**, are obtained in all the other cases. This fact serves as clear evidence that the cyclization of substituted ureas into 5-arylimidazolidin-2-ones is an easy process. This process could be retarded by intramolecular effect or steric factor.[1,2,4-6]

Very often the second type products, 4,5-dihydroxyimidazolidin-2-ones **2** and **3**, turn into third type products, hydantoins **4,**[1,6] but not always.



Scheme 2. Formation of the substituted ureas as the only product in the interaction of arylglyoxals with *N*-alkoxyureas.

For now the most convenient method of getting only the third type product is using acetic acid as a solvent for the reaction of arylglyoxals with *N*-hydroxyurea or *N*-alkoxyureas.[3] The products are only 3-hydroxyhydantoines **6** or 3-alkoxyhydantoines **7** respectively (Scheme 3).

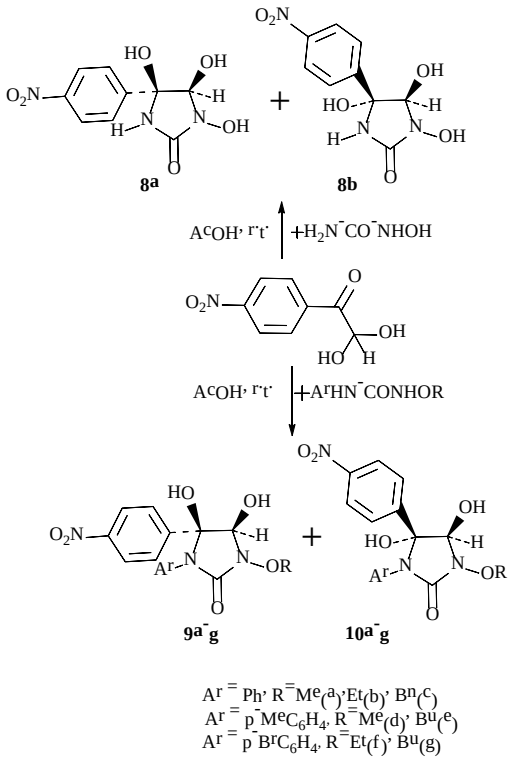


Ar = p-XC_6H_4, X = H (a), F(b), Cl(c), Br(d)

R=H(**6**), Me, Et, Bu(**7**)

Scheme 3. The products of interaction of arylglyoxals with *N*-hydroxyurea or *N*-alkoxyureas in acetic acid.

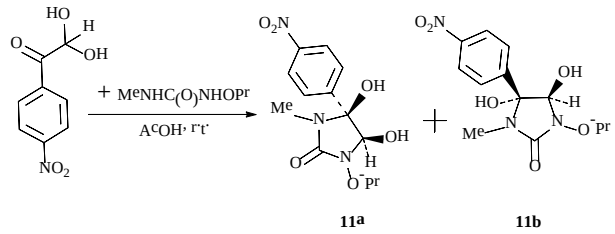
Only the second type products were formed in the reactions of 4-nitrophenylglyoxal with *N*-hydroxyurea[4] or *N*-alkoxy-*N*-arylureas.[5] In fact 4-nitrophenylglyoxal reacts with *N*-hydroxyurea producing only the mixture of 5-aryl-3,4,5-trihydroxyimidazolidin-2-ones **8a** and **8b** in molar ratio approximately 3:1[4] (Scheme 4).



Scheme 4. The products of 4-nitrophenylgyoxal interaction with *N*-hydroxyurea[4] and *N*-alkoxy-*N'*-arylureas.[5]

Also, 4-nitrophenylglyoxal reacts with *N*-alkoxy-*N'*-arylureas in acetic acid at room temperature mainly producing 3-alkoxy-1-aryl-4*S*,5*S*-dihydroxy-5-(4-nitrophenyl)imidazolidin-2-ones **9a-g**[5] (Scheme 4). These compounds have 4-hydroxyl and 5-hydroxyl groups in the *cis*-conformation to each other.

It was shown that the reaction of 4-nitrophenylglyoxal with *N*-*n*-propyloxy-*N'*-methylurea in acetic acid leads mainly to the formation of 3-*n*-propyloxy-1-methyl-4*S*,5*S*-dihydroxy-5-(4-nitrophenyl)imidazolidin-2-one **11a** (**11a**:**11b**=99:1)[5] (Scheme 5).



Scheme 5. The products of 4-nitrophenylgyoxal interaction with *N*-*n*-propyloxy-*N'*-methylurea[5].

The diastereomers of 5-aryl-4,5-dihydroxyimidazolidin-2-one **8a**,**9a**,**11a** with *cis* orientation of 4-HO- and 5-HO-groups to each other prevailed over the *trans* isomers for all the experiences.

To sum up all the information about arylglyoxals interaction with *N*-hydroxyurea derivatives we should note that the experimental investigation of the second type product formation overall pattern needed to be continued. For this reason we have chosen to explore the reaction of 4-carboxyphenylglyoxal with different *N*-alkoxy-*N'*-arylureas in acetic acid medium and for at least one case to change this alkoxyurea's reagent to the one of the *N*-alkoxy-*N'*-alkylureas.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian VXP-300 spectrometer (300 MHz) and VARIAN VNMRS 400 spectrometer (400 MHz). ^{13}C NMR spectra were recorded on a Varian VXP-300 spectrometer (75 MHz). The solvents DMSO-d_6 and $CDCl_3$ were used. ^{1}H NMR chemical shifts relative to the residual solvent protons as an internal standard [$(CD_3)_2SO$: 2.500 ppm, $CDCl_3$: 7.260 ppm] were reported. Solvent carbon atoms served as an internal standard for ^{13}C NMR spectra [$(CD_3)_2SO$: 39.52 ppm]. Mass spectra were recorded on a VG 70-70EQ mass spectrometer in fast atom bombardment mode (FAB). The solvents were purified and dried according to the standard procedures.

4-Nitrophenylglyoxal hydrate was obtained according to the standard procedure[4] by oxidation of 4-nitroacetophenone with H_2SeO_3 in boiling acetic acid for 2h, then removing AcOH under vacuum and crystallization of the residue from boiling water, as yellow powder, m.p. 87–89 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.66 (1H, t, *J* = 6.8, C<u>H</u>(OH)$_2$), 7.03 (2H, d, *J* = 6.8, CH(O<u>H</u>)$_2$), 8.29 (2H, d, *J* = 9.2, H Ar), 8.34 (2H, d, *J* = 9.2, H Ar).

4-Carboxyphenylglyoxal hydrate was obtained according to the similar standard procedure[4] by oxidation 4-acetylbenzoic acid oxidation by H_2SeO_3 in boiling acetic acid for 3h, then removing AcOH under vacuum and crystallization of the residue from boiling water, as an unstable pink powder. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.672 (1H, s, CH), 6.885 (2H, br. s, OH), 8.051 (2H, d, ^3J = 8.0 Hz, Ar), 8.161 (2H, d, ^3J = 8.0 Hz, Ar), 13.321 (1H, br. s, COOH).

_N-n_-Butyloxy-_N'_-phenylurea

A solution of phenylisocyanate (1.240g, 10.413 mmol) in benzene (5 mL) was added to a solution of *n*-butyloxyamine (0.975 g, 10.933 mmol) in benzene (8 mL), the reaction mixture was kept at 60 ºC for 30 min, then the solvent was evaporated under vacuum (20 mmHg) and hexane (8 mL) was added. After keeping at -5ºC for 20 h the obtained precipitate was filtered off, washed by cold (-5ºC) hexane, dried under vacuum (5 mmHg), giving 1.843 g (85 %) of *N-n*-butyloxy-*N'*-phenylurea, colorless crystals, m.p. 77–79 ºC. ^{1}HNMR (300 MHz, DMSO-d_6): δ = 0.900 (3H, t, ^3J = 7.5 Hz, NO(CH$_2$)$_3$Me), 1.356 (2H, sex, ^3J = 7.5 Hz, NOCH$_2$CH$_2$CH$_2$Me), 1.608 (2H, quint, ^3J = 7.2 Hz, NOCH$_2$CH$_2$CH$_2$Me), 3.765 (2H, t, ^3J = 7.2 Hz, NOCH$_2$), 6.983 (1H, t, ^3J = 7.8 Hz, C(4)H Ph), 7.257 (2H, t, ^3J = 7.8 Hz, C(3)H, C(5)H Ph), 7.551 (2H, t, ^3J = 7.8 Hz, C(2)H, C(6)H Ph), 8.665 (1H, s, NH), 9.431 (1H, s, NHO). MS (FAB) m/z 209 [M+H]$^+$ (100). Calc. for $C_{11}H_{16}N_2O_2$: C 63.44, H 7.74, N 13.45. Found: C 63.31, H 7.56, N 13.15.

3-_n_-Butyloxy-4,5-dihydroxy-5-(4-carboxyphenyl)-1-phenylimidazolidin-2-one (12)

4-Carboxyphenylglyoxal hydrate (71.2 mg, 0.3634 mmol) was added to the solution of *N-n*-butyloxy-*N'*-phenylurea (75.9 mg, 0.364 mmol) in acetic acid (5 mL), the reaction mixture was stirred for 29 h at 22 °C, then the negligible precipitate was filtered off, the filtrate was evaporated under vacuum (4 mmHg) at 20 °C, the residue was washed by water and dried under vacuum (4 mmHg), giving 134 mg (91 %) of monohydrate of 3-*n*-butyloxy-4,5-dihydroxy-5-(4-carboxyphenyl)-1-phenylimidazolidin-2-one **12**, colorless crystals, m.p. 108–111 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.899 (3H, t, ^3J = 7.2 Hz, NO(CH$_2$)$_3$Me), 1.399 (2H, sex, ^3J = 7.2 Hz, NOCH$_2$CH$_2$CH$_2$Me), 1.611 (2H, quint, ^3J = 7.2 Hz, NOCH$_2$CH$_2$CH$_2$Me), 3.999 (2H, t, ^3J = 6.0 Hz, NOCH$_2$), 4.856 (1H, d, ^3J = 6.3 Гц, CHOH), 6.987–7.082 (3H, m, OH, CHOH и C(4)H Ph), 7.188 (2H, t, ^3J = 7.5 Hz, C(3)H, C(5)H Ph), 7.385 (2H, d, ^3J = 7.5 Hz, C(2)H, C(6)H Ph), 7.586 (2H, d, ^3J = 8.4 Hz, C(2)H, C(6)H C$_6$H$_4$), 7.855 (2H, d, ^3J = 8.4 Hz, C(3)H, C(5)H C$_6$H$_4$), 12.977 (1H, s, COOH). ^{1}H NMR (300 MHz, CD$_3$CN): δ = 0.938 (3H, t, ^3J = 7.35 Hz, NO(CH$_2$)$_3$Me), 1.440 (2H, sex, ^3J = 7.35 Hz, NOCH$_2$CH$_2$CH$_2$Me), 1.663 (2H, quint, ^3J = 7.1 Hz, NOCH$_2$CH$_2$CH$_2$Me), 4.031 (2H, t, ^3J = 6.1 Hz, NOCH$_2$), 4.975 (1H, s, CHOH), 7.095 (1H, t, ^3J = 7.5 Hz, C(4)H Ph), 7.214 (2H, t, ^3J = 7.5 Hz, C(3)H, C(5)H Ph), 7.387 (2H, d, ^3J = 7.5 Hz, C(2)H, C(6)H Ph), 7.619 (2H, d, ^3J = 8.4 Hz, C(2)H, C(6)H C$_6$H$_4$), 7.914 (2H, d, ^3J = 8.4 Hz, C(3)H, C(5)H C$_6$H$_4$). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 13.87 (Me), 18.66 (CH$_2$), 30.14 (CH$_2$), 75.67 (NOCH$_2$), 87.35 (CHOH), 88.12 (COH), 124.71, 125.19, 127.01, 128.26, 129.29, 130.53, 136.29 (C Ar), 144.83 [C(1) PhN], 157.05 [NC(=O)N], 166.99 (COOH). MS (FAB) m/z 387 [M+H]$^+$ (22), 369 [M+H–H$_2$O]$^+$ (9), 250 (26), 209 (100), 149 (49). Anal. Calc. for $C_{20}H_{22}N_2O_6$.H$_2$O, %: C 59.40, H 5.98, N 6.93. Found, %: C 59.07, H 6.13, N 6.85.

4,5-Dihydoxy-5-(4-carboxyphenyl)-3-methoxy-1-(4-methylphenyl)imidazolidin-2-one (13)

4-Carboxyphenylglyoxal hydrate (97.9 mg, 0.499 mmol) was added to the solution of *N*-methoxy-*N'*-4-methylphenylurea[5] (89.9 mg, 0.499 mmol) in acetic acid (8 mL), the reaction mixture was stirred for 38 h at 20 °C, then the negligible precipitate was filtered off and the filtrate was evaporated under vacuum (2 mmHg) at 20 °C, yielding 175 mg (93 %) the mixture of the diastereoisomers **13a** and **13b** in molar ratio 91:9 (^{1}HNMR spectrum). This mixture was extracted by water (4 mL) at 4°C for 23 h, the obtained precipitate was filtered off and dried under vacuum giving 118 mg (63 %) of monohydrate of 4,5-dihydroxy-5-(4-carboxyphenyl)-3-methoxy-1-(4-methylphenyl)imidazolidin-2-one **13a**, white solid, mp. 81–83 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.164 (3H, s, Me), 3.817 (3H, s, NOMe), 4.891 (1H, d, ^3J = 5.4 Hz, CHOH), 6.991 (2H, d, ^3J = 8.7 Hz, C(3)H, C(5)H C$_6$H$_4$Me), 7.017–7.076 (2H, m, CHOH and OH), 7.241 (2H, d, ^3J = 8.7 Hz, C(2)H, C(6)H C$_6$H$_4$Me), 7.577 (2H, d, ^3J = 8.1 Hz, C(2)H, C(6)H C$_6$H$_4$COOH), 7.842 (2H, d, ^3J = 8.1 Hz, C(3)H, C(5)H C$_6$H$_4$COOH), 12.952 (1H, br. s, COOH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.40 (Me), 63.95 (NOMe), 87.23 (CHOH), 87.90 (COH), 125.13, 127.00, 128.70, 129.08, 130.45, 133.41, 134.63 (C Ar), 144.67 [C(1) C$_6$H$_4$Me, C–N], 156.92 (NC(=O)N), 166.90 (COOH). MS (FAB) m/z 359 [M+H]$^+$ (41), 341 [M+H–H$_2$O]$^+$ (10), 256 (7), 238 (9), 208 (100), 181 (37), 149 (76), 133 (28), 121 (8), 106 (19). Calc. for $C_{18}H_{18}N_2O_6$.H$_2$O, %: C 57.44, H 5.35, N 7.44. Found, %: 55.78, H 5.54, N 7.42.

5-(4-Carboxyphenyl)-4,5-dihydroxy-1-methyl-3-propyloxy-imidazolidin-2-one (14)

4-Carboxyphenylglyoxal hydrate (74.6 mg, 0.380 mmol) was added to a solution of *N*-propyloxy-*N'*-methylurea[5] (55.7 mg, 0.421 mmol) in acetic acid (5 mL). The reaction mixture was stirred for 26 h at 22 °C, then the negligible precipitate was filtered off and the filtrate was evaporated under vacuum (2 mmHg) at 20 °C. The residue was dissolved in water (5 mL), the aqueous solution was filtered and evaporated under vacuum (2 mmHg) at 20 °C. The obtained residue was washed by Et$_2$O (2 mL) and dried under vacuum (2 mmHg), yielding 104 mg (84 %) of monohydrate of 5-(4-carboxyphenyl)-4,5-dihydroxy-1-methyl-3-propyloxyimidazolidin-2-one **14**, colorless crystals, m.p. 124–127 °C (with decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.898 (3H, t, ^3J = 7.2 Hz, NO(CH$_2$)$_2$Me), 1.597 (2H, sex, ^3J = 6.9 Hz, NOCH$_2$CH$_2$Me), 2.465 (3H, s, NMe), 3.831–3.910 (2H, m, NOCH$_2$), 4.645 (1H, d, ^3J = 7.8 Hz, CHOH), 6.569 (1H, s, OH), 6.609 (1H, d, ^3J = 7.8 Hz, CHOH), 7.529 (2H, d, ^3J = 8.7 Hz, C(2)H, C(6)H C$_6$H$_4$COOH), 7.970 (2H, d, ^3J = 8.7 Hz, C(3)H, C(5)H C$_6$H$_4$COOH), 12.997 (1H, br. s, COOH). ^{13}C NMR (75 MHz, DMSO-d_6): δ =10.35 (Me), 21.39 (CH$_2$), 25.17 (NMe), 77.44 (NOCH$_2$), 85.97 (CHOH), 88.63 (COH), 126.76, 129.50 [C(H) C$_6$H$_4$], 130.75 [C(4) C$_6$H$_4$], 144.62 [C(1) C$_6$H$_4$, C–N], 158.94 [NC(=O)N], 167.08 (COOH). MS (FAB) m/z

311 $[M+H]^+$ (77), 293 $[M+H-H_2O]^+$ (36), 235 (83), 209 (59), 149 (100). Anal. Calc. for $C_{14}H_{18}N_2O_6.H_2O$ %: C 51.22, H 6.14, N 8.53. Found, %: 50.98, H 6.35, N 8.26.

N-*n*-Octyloxy-*N*'-phenylurea

A solution of phenylisocyanate (0.714 g, 5.994 mmol) in benzene (5 mL) was added to a solution of *n*-octyloxyamine (0.959 g, 6.600 mmol) in benzene (5 mL). The reaction solution was maintained at 20 °C for 72 h, then benzene was evaporated under vacuum (20 mmHg), hexane (11 mL) was added to the residue and the obtained mixture was kept at -5°C for 20 h. The formed precipitate was filtered off, washed by hexane (6 mL) and dried under vacuum (2 mmHg), giving 1.335 (84 %) of *N*-*n*-octyloxy-*N*'-phenylurea, colorless crystals, m.p. 73–75 °C. ^{1}H NMR (300 MHz, DMSO-d_6): 0.854 (3H, t, ^3J = 6.9 Hz, $NO(CH_2)_7\underline{Me}$), 1.217–1.378 (10H, m, $NOCH_2CH_2(\underline{CH_2})_5Me$), 1.614 (2H, quint, ^3J = 6.9 Hz, $NOCH_2\underline{CH_2}(CH_2)_5Me$), 3.751 (2H, t, ^3J = 6.9 Hz, $NOCH_2$), 6.982 (1H, t, ^3J = 8.1 Hz, C(4)H Ph), 7.253 (2H, t, ^3J = 8.1 Hz, C(3)H,C(5)H Ph), 7.546 (2H, d, ^3J = 8.1 Hz, C(2)H,C(6)H Ph), 8.660 (1H, s, NH), 9.421 (1H, s, NHO). MS (FAB) m/z 265 $[M+H]^+$ (100). Anal. Calc. for $C_{15}H_{24}N_2O_2$ %: C 68.15, H 9.15, N 10.60. Found, %: C 67.98, H 9.27, N 10.32.

N-*n*-Dodecyloxy-*N*'-phenylurea

A solution of phenylisocyanate (0.596 g, 5.003 mmol) in benzene (2 mL) was added to a solution of *n*-dodecyloxyamine (1.007 g, 5.001 mmol) in benzene (8 mL). The reaction solution was maintained at 20 °C for 95 h, after that it was boiled 0.5 h, then the benzene evaporated under vacuum (20 mmHg), hexane (8 mL) was added to the residue and the obtained mixture was maintained at -5°C for 20 h. The formed precipitate was filtered off, washed by hexane (6 mL) and dried under vacuum (2 mmHg) giving 1.345 (83.9 %) of *N*-*n*-dodecyloxy-*N*'-phenylurea, colorless crystals, m.p. 50–51°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.880 (3H, t, ^3J = 6.8 Hz, $NO(CH_2)_{11}\underline{Me}$), 1.221–1.449 (18H, m, $NOCH_2CH_2(\underline{CH_2})_9Me$), 1.706 (2H, quint, ^3J = 6.8 Hz, $NOCH_2\underline{CH_2}(CH_2)_9Me$), 3.915 (2H, t, ^3J = 6.8 Hz, $NOCH_2$), 7.100 (1H, t, ^3J = 8.0 Hz, C(4)H Ph), 7.329 (2H, t, ^3J = 8.0 Hz, C(3)H,C(5)H Ph), 7.470 (2H, dd, ^3J = 8.0 Hz, J = 0.8 Hz, C(2)H,C(6)H Ph), 7.566 (1H, s, NH). MS (FAB) m/z 321 $[M+H]^+$ (100). Anal. Calc. for $C_{19}H_{32}N_2O_2$, %: C 88.06, H 10.06, N 8.74. Found, %: C 87.95, H 10.11, N 8.65.

4,5-Dihydroxy-5-(4-nitrophenyl)-3-*n*-octyloxy-1-phenylimidazolidin-2-one (15)

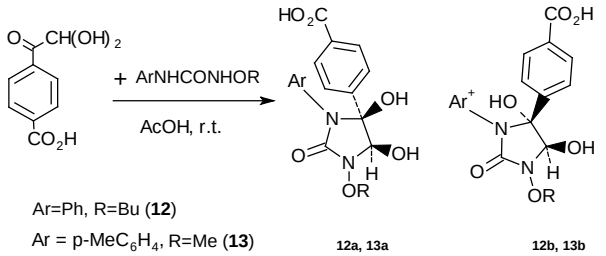
4-Nitrophenylglyoxal hydrate (87 mg, 0.441 mmol) was added to a solution of *N*-*n*-octyloxy-*N*'-phenylurea (116.6 mg, 0.441 mmol) in acetic acid (5 mL) with stirring. The reaction solution was maintained at 10 °C for 22 h, then acetic acid was evaporated under vacuum (2 mmHg) at 25 °C. Water (3 mL) was then added to the obtained residue, this mixture was maintained at 10°C for 20 h and then water was evaporated under vacuum (2 mmHg) at 25 °C yielding 196 mg (97 %) the mixture of *cis*-4,5-dihydroxydiastereomer **15a** and *trans*-4,5-dihydroxy-diastereomer **15b** (in the ratio 97:3) of 4,5-dihydroxy-5-(4-nitrophenyl)-3-*n*-octyloxy-1-phenylimidazo-lidin-2-one **15**. The pure 4*S*,5*S*-dihydroxy-5-(4-nitrophenyl)-3-*n*-octyloxy-1-phenylimidazolidin-2-one **15a** was obtained by crystallization (benzene-hexane), colorless crystals, m.p. 53–54 °C (PhH–C_6H_{14}). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.851 (3H, t, ^3J = 6.3 Hz, $NO(CH_2)_7\underline{Me}$), 1.178–1.329 (10H, m, $NOCH_2CH_2(\underline{CH_2})_5Me$), 1.563–1.680 (2H, m, $NOCH_2\underline{CH_2}(CH_2)_5Me$), 3.944–4.021 (2H, m, $NOCH_2$), 4.887 (1H, d, ^3J = 5.4 Hz, $\underline{CH}OH$), 7.048 (1H, d, ^3J = 5.4 Hz, $CHO\underline{H}$), 7.083 (1H, t, ^3J = 8.0 Hz, C(4)H Ph), 7.203 (2H, t, ^3J = 8.0 Hz, C(3)H,C(5)H Ph), 7.275 (1H, s, OH), 7.390 (2H, d, ^3J = 7.8 Hz, C(2)H,C(6)H Ph), 7.762 (2H, d, ^3J = 8.4 Hz, C(2)H,C(6)H $C_6H_4NO_2$), 8.151 (2H, d, ^3J = 8.4 Hz, C(3)H,C(5)H $C_6H_4NO_2$). ^{13}CNMR (75 MHz, DMSO-d_6): δ =13.93 (Me), 22.12, 25.38, 28.03, 28.68, 28.87, 31.26 (CH_2), 75.98 ($NOCH_2$), 87.14 (CH–OH), 87.81 (C–OH), 119.48, 123.25, 124.65, 125.26, 128.26, 128.27, 136.05 (C Ar), 147.29 [C(4) $C_6H_4NO_2$], 156.86 (C=O). MS (FAB) m/z 444 $[M+H]^+$ (11), 307(18), 265(87), 195(37), 150(61), 120(43), 76(48), 70(40), 55(100).

3-*n*-Dodecyloxy-4,5-dihydroxy-5-(4-nitrophenyl)-1-phenylimidazolidin-2-one (16)

4-Nitrophenylglyoxal hydrate (105 mg, 0.533 mmol) was added to a solution of *N*-*n*-dodecyloxy-*N*'-phenylurea (171 mg, 0.533 mmol) in acetic acid (4 mL) with stirring. The reaction mixture was stirred at 16 °C for 1 h, maintained at 16°C for 23 h, then acetic acid was evaporated under vacuum (2 mmHg) at 16°C. The obtained residue was washed by water (10 mL) at 6°C for 18 h, the formed precipitate was filtered off, washed by water (10 mL) and dried under vacuum (2 mmHg) to give 263 mg (95 %) mixture of *cis*-4,5-dihydroxydiastereomer **16a** and *trans*-4,5-dihydroxydiastereomer **16b** in the ratio 89:11 (^{1}H NMR). Crystallization of this mixture from CH_2Cl_2–hexane yields 3-*n*-dodecyloxy-4*S*,5*S*-dihydroxy-5-(4-nitrophenyl)-1-phenylimidazolidin-2-one **16a**, colorless crystals, m.p. 98-100 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.844 (3H, t, ^3J = 6.2 Hz, $NO(CH_2)_{11}\underline{Me}$), 1.174–1.426 (18H, m, $NOCH_2CH_2(\underline{CH_2})_9Me$), 1.564–1.685 (2H, m, $NOCH_2\underline{CH_2}(CH_2)_9Me$), 3.929–4.033 (2H, m, $NOCH_2$), 4.888 (1H, s, $\underline{CH}OH$), 7.041 (1H, s, $CHO\underline{H}$), 7.079 (1H, t, ^3J = 7.5 Hz, C(4)H Ph), 7.201 (2H, t, ^3J = 7.5 Hz, C(3)H,C(5)H Ph), 7.265 (1H, s, OH), 7.395 (2H, d, ^3J = 7.5 Hz, C(2)H,C(6)H Ph), 7.762 (2H, d, ^3J = 8.7 Hz, C(2)H,C(6)H $C_6H_4NO_2$), 8.151 (2H, d, ^3J = 8.7 Hz, C(3)H,C(5)H $C_6H_4NO_2$). ^{13}C NMR (75 MHz, DMSO-d_6): δ =13.99 (Me), 22.14, 25.38, 28.04, 28.76, 28.92, 28.93, 29.05, 29.07, 29.11, 31.34 (CH_2), 75.97 ($NOCH_2$), 87.15 (CH–OH), 87.80 (C–OH), 123.30, 124.16, 124.70, 125.32, 128.29, 128.32, 136.0 (C Ar), 147.28 [C(4) $C_6H_4NO_2$], 156.87 (C=O). MS (FAB) m/z 500 $[M+H]^+$ (13), 482 $[M+H-H_2O]^+$ (6), 363 (22), 321 (100), 243 (15), 194 (54), 150 (44), 120 (67).

RESULTS AND DISCUSSION

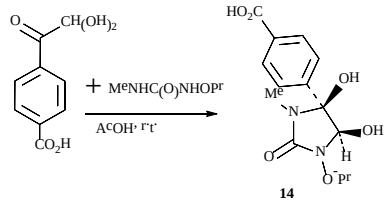
We found that *N*-alkoxy-*N*'-arylureas react with 4-carboxyphenylglyoxal in acetic acid medium at room temperature yielding the mixtures of diastereomers of 3-alkoxy-1-aryl-5-(4-carboxyphenyl)-4,5-dihydroxyimidazo-lidin-2-ones **12**,**13** (Scheme 6).



Scheme 6. The products of interaction of 4-carboxyphenylglyoxal with *N*-alkoxy-*N'*-arylureas.

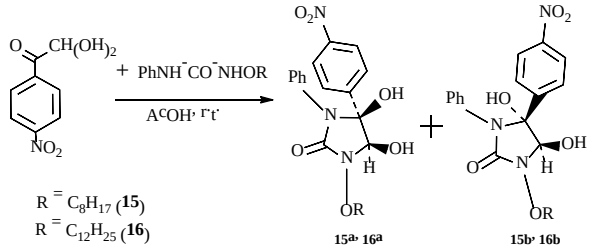
We assume, in the interaction of 4-nitrophenylgyoxals with *N*-alkoxy-*N'*-arylureas,[5] that the main product in both cases is similar. In the last case it is the diastereomer **12a** or **13a** with 4-hydroxyl- and 5-hydroxyl groups in the *cis*-conformation to each other. Their percentage in the products' mixtures is approximately 91-98 %.

In a similar way the *N*-propyloxy-*N'*-methylurea's interaction with 4-carboxyphenylglyoxal produces only 5-(4-carboxyphenyl)-4,5-dihydroxy-1-methyl-3-propyloxy-imidazolidin-2-one **14** (Scheme 7). In this interaction the only one diastereomer **14** is formed. It became clear that it has *cis* orientation of 4-HO- and 5-HO-groups in the *cis*-conformation to each other. So, the result is similar to the 4-nitrophenylgyoxal's interaction with *N*-propyloxy-*N'*-methylurea[5].



Scheme 7. Interaction of 4-carboxyphenylglyoxal with *N*-propyloxy-*N'*-methylurea.

Thus, the formation pattern of the second type products, 3-alkoxy-4,5-dihydroxyimidazolidin-2-ones, in the arylglyoxals reaction with *N*-alkoxyureas has been clarified. It is necessary to use arylglyoxals with a strong electron-withdrawing substituent in 4-position of the aryl moiety to obtain these products. Additionally we have studied the interaction of 4-nitrophenylglyoxal with *N*-*n*-alkoxy-*N'*-phenylureas which have a long carbon chain in order to obtain 3-alkoxy-4,5-dihydroxy-5-(aryl)-1-phenylimida-zolidin-2-ones with lipophilic *N*-alkoxy moiety. The main reason for this was to find out whether the alkoxyl substituent in urea reagent influences the reaction or not.

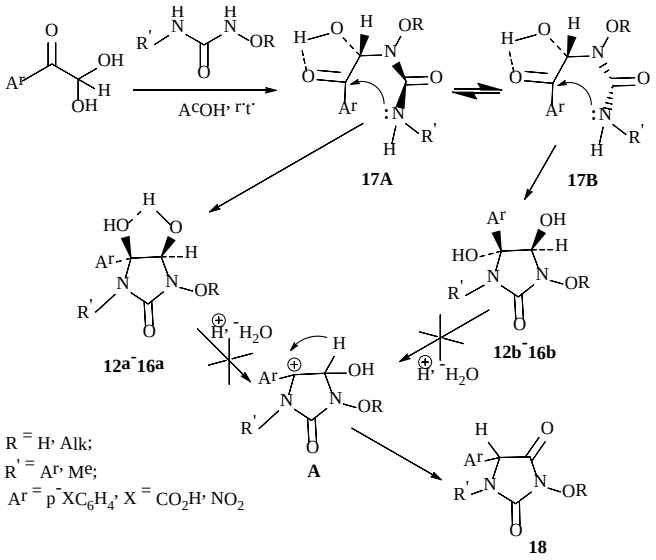


Scheme 8. The interaction of 4-nitrophenylglyoxal with *N*-alkoxy-*N'*-arylureas.

As the experimental results have shown, *N*-*n*-octyloxy-*N'*-phenylurea and *N*-*n*-dodecyloxy-*N'*-phenylurea interact with 4-nitrophenylglyoxal forming only a mixture of diastereomers of hydrophobic 3-alkoxy-4,5-dihydroxy-5-(4-nitrophenyl)-1-phenylimidazolidin-2-ones **15,16** (Scheme 8).

The mixture of these diastereomers contains more than 90 % of *cis*-4,5-dihydroxy diastereomers **15a**,**16a**. The trace amounts of *trans*-4,5-dihydroxy diastereomers **15b**,**16b** can be easily removed by crystallization. The products of the 4-nitrophenylglyoxal interaction's with *N*-*n*-octyloxy-*N'*-phenylurea and *N*-*n*-dodecyloxy-*N'*-phenylurea demonstrate, that the nature of the *N*-alkoxy substituent in urea does not influence the reaction.

We propose the next scheme of the arylglyoxals interaction with *N*-hydroxyurea or *N*-alkoxyureas (Scheme 9) to explain the fact that diastereomers with *cis* orientation of 4-HO- and 5-HO-groups dominate over the *trans* 4,5-dihydroxy diastereomers in all the reactions which are reported in this study.



Scheme 9. The proposed mechanism of the interaction of *N*-alkoxy-*N'*-arylureas and *N*-alkoxy-*N'*-alkylureas with 4-carboxyphenylglyoxal and 4-nitrophenylglyoxal.

According to this scheme in the beginning of the interaction the open-chain *N*-substituted urea **17** is formed. Compounds **17** may be stabilized by the intramolecular hydrogen bond. The acyclic urea **17** form further the compounds **12**–**16**. Thus, the diastereomers **12a**-**16a** with 4-HO- and 5-HO-groups in the *cis*-conformation to each other have been produced. It is probable that the diastereomers **12a**-**16a** are also stabilized by the intramolecular hydrogen bond. *N*-Alkoxyurea **17A** slowly transforms into a conformation **17B** by the rotation of carbamoyl moiety around N–C bond or the *N*-alkoxy nitrogen inversion. The conformation **17B** eventually forms *trans*-4,5-dihydroxy diastereomers **12b**-**16b**.

Probably the low process temperature (approximately 20°C) preserves the further isomerization of the formed *cis*-4,5-dihydroxy diastereomers **12a**-**16a** into *trans*-4,5-dihydroxy diastereomers **12b**-**16b**.

It is evident that the presence of a strong electronegative substituent in the forth position of 5-aryl moiety, such as carboxyl group or nitro group, destabilizes "benzylic" cation **A** and makes the further transformation of the compounds **12-16** into hydantoins **18** impossible.

CONCLUSIONS

We have shown that reaction of 4-carboxyphenylglyoxal with *N*-alkoxy-*N*'-arylureas in acetic acid at room temperature produces only 3-alkoxy-1-aryl-5-(4-carboxyphenyl)-4,5-dihydroxyimidazolidin-2-ones. It is the new practical evidence of the possibility of obtaining only the second type products, 3-alkoxy-4,5-dihydroxyimidazolidin-2-ones, from the interaction of arylglyoxals with *N*-hydroxyurea derivatives. Using *N*-propyloxy-*N*'-methylurea as a reagent in this reaction leads to the similar product – 5-(4-carboxyphenyl)-4,5-dihydroxy-1-methyl-3-propyloxyimidazolidin-2-one. Obtaining 3-alkoxy-4,5-dihydroxy-5-arylimidazolidin-2-ones with lipophilicity fragment is also possible in this reaction. Thus, a new practical application of the interaction between arylglyoxals and *N*-alkoxyureas has been found.

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[BMIM]BF_4: AN EFFICIENT IONIC LIQUID MEDIUM FOR ONE-POT OF 1*H*-IMIDAZOLE-5(4*H*)-ONE DERIVATIVES

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Keywords: [BMIM]BF_4, Schiff base, One-pot reaction; 1H-imidazole-5(4H)-ones

The environment-friendly one-pot condensation reaction of (*Z*)-4-benzylidene-2-methyloxazol-5(4*H*)-one with phenylhydrazine and (phenyliminomethyl)benzene in the presence of [BMIM]BF_4 as medium at 80-85 ºC for 1-1.5 h to form 4-(benzylidene/substituted benzylidene)-N-aryl amino-2-(styryl/substituted styryl)-1*H*-imidazole-5(4*H*)-one compounds with good yields. The main advantages of this method are short reaction time, easy workup and good yields.

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INTRODUCTION

Multi component and eco-friendly reactions are major techniques for the efficient and rapid synthesis of a wide variety of heterocyclic molecules. These reactions are investigated widely in heterocycles synthesis, initially due to their ability to produce complex heterocyclic compounds with functionality groups form simple starting materials via multi component one-pot reactions.[1]

In the past few decades, the preparation of new heterocyclic molecules has been the focal point of drug discovery research.[2] Among a wide variety of heterocyclic compounds, imidazole scaffold has its significance due to its promising pharmacological and biological activities.

In recent, among the other ionic liquids 1-butyl-3-methyl imidazolium salts have attracted considerable attention as an environmentally sustainable and efficient media and immense uses in various heterocyclic transformations that include hydrogenations,[3] Heck reactions,[4] Friedel-craft reactions,[5] Bishler-Napieral reactions.[6] Among these, in the last decade many applications of the ionic liquid 1-butyl-3-methyl imidazolium tetrafluoroborate ([BMIM]BF_4) in various organic conversions have been reported.[7] The weak electrostatic interactions of tetrafluoroborate with the imidazolium cation display good thermal and electrochemical stability of [BMIM]BF_4. The other favorable physical and chemical properties like lack of inflammability, neutral nature, commercial availability, low volatility, environmentally sustainable and admirable solubility with many organic products make this ionic liquid of greater use than others.[8]

Imidazolinone ring system is of biological and chemical interest since long. The imidazolinone units are found in many biologically active compounds. The imidazolone compounds having diverse bioactivities including anticancer,[9] anti-HIV agents,[10] anticonvulsant,[11] monoaminooxidase (MAO) inhibitory,[12] antiparkinsonian,[13] CNS depressant, antimicrobial, anthelmintics etc.[14]

Bearing the above results in mind, here we now wish to report synthesis of a series of 4-(benzylidene/substituted benzylidene)-N-aryl amino-2-(styryl/substituted styryl)-1*H*-imidazole-5(4*H*)-one derivatives by a one-pot three component process in [BMIM]BF_4 as medium at 80-85 ºC for 60-90 min with good yields.

EXPERIMENTAL

IR spectra were recorded with help of KBr pellets and Perkin-Elmer 1000 instrument.

^{1}H and ^{13}C NMR were recorded in DMSO-d_6 solvent in a Bruker 400 MHz spectrometer. Chemical shifts are expressed in δ ppm units using TMS as internal standard. Mass spectra were recorded on Agilent-LCMS instrument under CI conditions and given by Q+1 value only.

Melting points are uncorrected and taken in open capillary tubes in sulphuric acid bath.

General procedure of synthesis

A mixture of (*Z*)-4-benzylidene-2-methyloxazol-5(4*H*)-one (**1**) (10 mmol) and phenylhydrazine (**2**) (10 mmol) in [BMIM]BF_4 (4 eq.) was to heated at 80-85 ºC for 10 min. Then to this reaction mass, added (phenylimino-methyl)benzene (**3**) (10 mmol) and maintained at 50-80 min at 80-85 ºC. After completion of the reaction, as monitored by TLC, the reaction mass was cooled to 30-35 ºC, water (50 ml) was added and stirred for 15-20 min at the same temperature. A colourless solid separated out from the reaction mixture which was collected by filtration. The isolated solid was washed with water (50 ml) and dried at 50-55 ºC for 10 h. The crude product was recrystallized from ethanol to get **4**.

RESULTS AND DISCUSSION

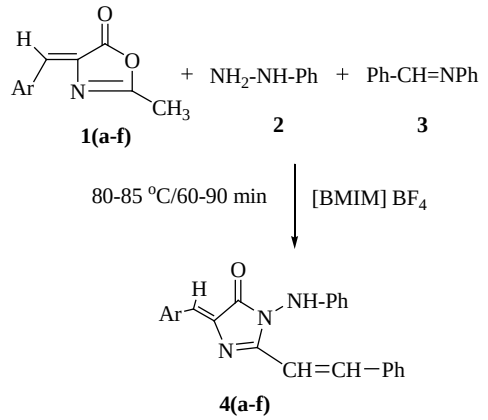
Initially, the one-pot three component reaction was initiated with (*Z*)-4-benzylidene-2-methyloxazol-5(4*H*)-one (**1a**), **2** and **3** to form 4-(benzylidene)-N-aryl amino-2-(styryl)-1*H*-imidazole-5(4*H*)-one (**4a**) in the presence of [BMIM] BF_4 as medium at 80-85 ^oC for 60 min with 80 % yield. The structure of the compound **4a** has been characterized and confirmed by ^{1}H-NMR, IR and mass spectroscopy. This model reaction was performed in different ionic liquids ([DBUH][OAc], [bmim][OH] and [bmim][Br]) at different temperatures. The results are summarized in Table 1. The best results are produced in the presence of [BMIM] BF_4 (4 eq.) as ionic liquid at 80-85 ^oC for 60 min to form title compound with 80 % yield by using **1** (1 eq.), **2** (1 eq.) and **3a** (1 eq.).

Encouraged by above results, the model reaction was examined in the presence of different amount of ionic liquid [BMIM] BF_4 (2 eq., 4 eq. and 5 eq.) with respect to **1**. However, it was found that the one-pot reaction of **1** (1 eq.), **2** (1 eq.), and **3a** (1 eq.), in the presence of [BMIM]BF_4 as a medium (4 eq.) for 60 min at 80-85 ^oC gave the highest yield (80 %) (Table 1, entry 6).

Table 1. Effect of Ionic liquid (4 eq), temperature and on the yield of **4a.**

Entry	Medium, 4 eq.	Temp., °C	Time, min	4a, %
1	[BMIM] BF_4	80-85	60	80
2	[bmim][Br]	80-85	120	63
3	[DBUH][OAc]	80-85	90	61
4	[bmim][OH]	80-85	90	64
5	[BMIM] BF_4	90-95	50	75
6	[bmim][Br]	90-95	90	54
7	[DBUH][OAc]	90-95	80	50
8	[bmim][OH]	90-95	85	52

Based on optimisation condition, the scope of the one-pot three component reaction process was explored, using the best optimized conditions by changing the **1a-1f** (Table 3). The results are displayed in **Table 2.** The structures of the products were assigned on the basis of their spectral properties -IR, NMR & Mass spectra (for details, please see the supplementary material).



4(a-f)

Ar = **1a**, p-MePh; **1b**, p-MeOPh; **1c**, p-FPh
1d, p-NO_2Ph; **1e**, o-ClPh; **1d**, p-clPh

Scheme 1. Synthesis of 4-(benzylidene/substituted benzylidene)-N-aryl amino-2-(styryl/substituted styryl)-1*H*-imidazole-5(4*H*)-one derivatives.

Mechanism

Initially, nucleophilic addition of phenylhydrazine to 4-benzylidene-2-methyl oxazolin-5-one (**1**) results in the formation of (*Z*)-2-acetamido-N-phenyl-3-(phenyl/substituted phenyl)prop-2-enamides (**X**). The mechanism can be explained as Michael type addition of the active methyl group of **1** across the carbon-nitrogen double bond of the shiff bases leading to the generation of styryl group by the loss of aniline. The resulting unstable intermediates readily undergo cyclocondensation to form stable imidazolin-5-one derivatives **4**.

Table 2. Effect of quantity of ionic liquid and time on the yield of **4a.**

Entry	Quantity, eq.	Time, min	4a, %
1	3 eq.	80	80
2	4 eq.	60	80
3	5 eq.	50	78

Table 3. Synthesis of **4a-4f** from **1a-1f** with **2** and **3** in [BMIM] BF_4 at 80-85 ^oC.

Starting material	Product	Time, min	Yield %	M.P., ^{0}C
1a	**4a**	60	80	164-166
1b	**4b**	70	80	165-167
1c	**4c**	65	78	160-163
1d	**4d**	80	80	169-173
1e	**4e**	70	75	155-157
1f	**4f**	60	80	180-185

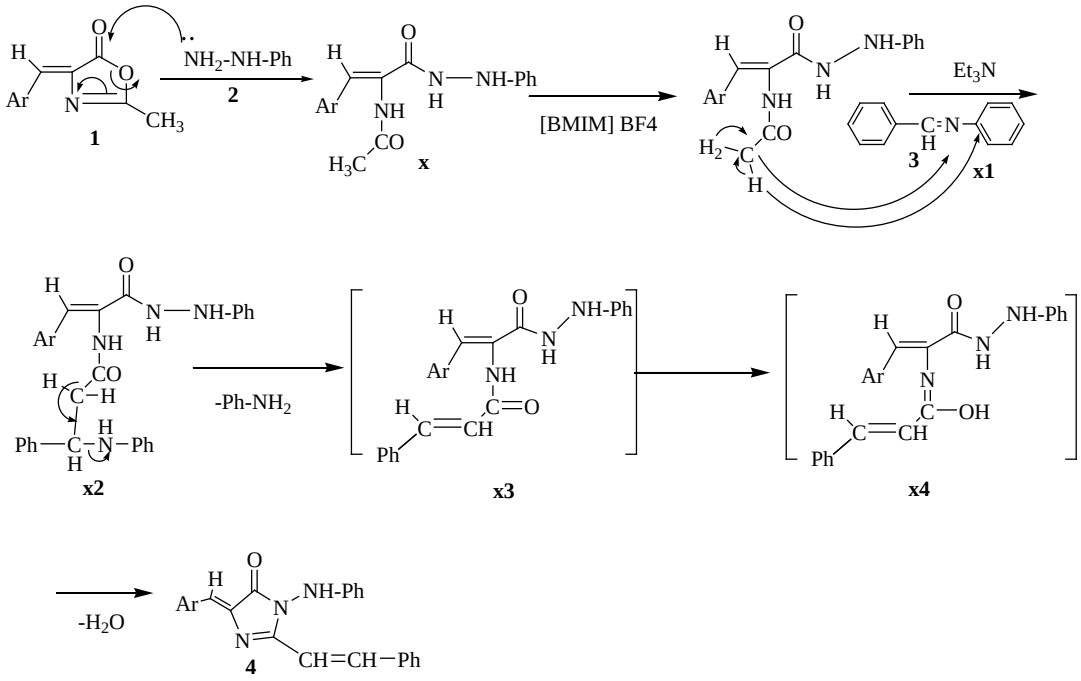
Spectral analysis of 4a-4f

4a: IR (KBr): 3444 (-NH), 1668 (-C=O), 3252(Ar), 1595(C=C),1256(C-N) cm^{-1}. ^{1}H NMR δ= 6.8 (d, 2H, HC=CH), 7.4-8.0(m,15H, Ar-H), 8.0-8.2 (s, 1H(-NH), 8.4 (s, 1H, NH).δ 8.4 (s, 1H, NH). ^{13}C NMR (100MHz) δ = 116(-C=C), 119 (-C=C), 123(-C=C)Ar, 137(C-N), 141(-C=N), 167 (C=O). Mass (*m/z*) = 366 (M+1) (100 %).

4b: IR (KBr): 3436 (-NH), 1674 (-C=O), 3250(Ar), 1590(C=C),1254(C-N) cm^{-1}. ^{1}H NMR δ = 4.2 (s,3H,-OCH_3), 6.7 (d, 2H, HC=CH), 7.4-8.0 (m, 14H, Ar-H), 8.0-8.2(s, 1H(-NH), 8.4 (s, 1H, NH). ^{13}C NMR δ = 116 (-C=C), 118 (-C=C), 122 (-C=C)Ar, 138(C-N), 143 (-C=N), δ 166 (C=O). Mass (*m/z*): 396 (M+1) (100 %).

4c: IR (KBr): 3423 (-NH), 1661(-C=O) 3166 (Ar), 1555 (C=C), 1262 (C-N) cm^{-1}. ^{1}H NMR δ= 6.9 (d, 2H, HC=CH), 7.4-8.0 (m,14H, Ar-H), 8.0-8.2 (s, 1H(-NH), 8.4 (s, 1H, NH). ^{13}C NMR δ= 117 (-C=C), 118 (-C=C), 121 (-C=C)Ar, 137 (C-N), 144 (-C=N), 166 (C=O). Mass (*m/z*): 385 (M+1) (100 %).

4d: IR (KBr): 3455 (-NH), 1662 (-C=O) 3064(Ar), 1598(C=C), 1272(C-N) cm^{-1}. ^{1}H NMR δ 6.8 (d, 2H, HC=CH), 7.5-8.0(m, 14H, Ar-H), 8.0-8.2(s, 1H(-NH), δ 8.4 (s, 1H, NH). ^{13}C NMR δ 116 (-C=C), 118 (-C=C), 123 (-C=C) Ar, 138 (C-N), 145 (-C=N), 167 (C=O). Mass (*m/z*): 411 (M+1) (100 %).



Scheme 2. Mechanism of the formation **4**.

4e: IR (KBr): 3434 (-NH), 1693 (-C=O) 3146(Ar),1570(C=C),1265(C-N) cm^{-1}. ^1H NMR δ = 6.9 (d, 2H, HC=CH), 7.5-8.0 (m,14H, Ar-H), 8.0-8.2 (s,1H(-NH), 8.4 (s, 1H, NH). ^{13}C NMR δ = 117 (-C=C), (-C=C), 124 (-C=C) Ar, 137 (C-N), 144 (-C=N), 168 (C=O). Mass (*m/z*): 400 (M+1) (100 %).

4f: IR (KBr): 3434 (-NH), 1653 (-C=O) 3250(Ar), 1593(C=C), 1254(C-N) cm^{-1}. ^1H NMR δ= 6.8 (d, 2H, HC=CH), 7.4-7.9 (m,14H, Ar-H), 8.0-8.2(s, 1H(-NH), δ 8.4 (s, 1H, NH). ^{13}C NMR δ= 116 (-C=C), 118 (-C=C), 123 (-C=C)Ar, 138 (C-N), 145 (-C=N), 167 (C=O). Mass (*m/z*): 400 (M+1) (100 %).

CONCLUSION

In conclusion we have developed an efficient and environmental benign protocol for the synthesis of title compounds using ionic liquid and green principles. This one-pot three component reaction proceeded in short time with high yields, straightforward work-up procedure and no need to use column purifications.

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ELECTROCHEMICAL STUDIES ON THE CORROSION RESISTANCE OF 18 K GOLD IN ARTIFICIAL SALIVA, IN THE ABSENCE AND PRESENCE OF GEMER-2 TABLET (ORALLY TAKEN BY TYPE 2 DIABETES)

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Keywords: biomaterial; artificial saliva; corrosion resistance; Gold, Gemer-2 tablet; electrochemical studies.

The corrosion resistance of 18 K gold in artificial saliva, in the absence and presence of Gemer-2 Tablet (orally taken by type 2 Diabetes) has been evaluated by polarization study and AC impedance spectra. Polarisation study reveals that in the presence of Gemer-2, *LPR* value increases and corrosion current decreases. That is in presence of Gemer-2, the corrosion resistance of 18K Gold in artificial saliva increases. AC impedance study reveals that in the presence of Gemer-2, R_t value increases and C_{dl} decreases. That is in the presence of Gemer-2 the corrosion resistance of 18 K Gold in AS increases. It is concluded that people clipped with orthodontic wire made of 18K Gold need not hesitate to take Gemer-2 orally.

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INTRODUCTION

Symmetrical and regularly arranged objects are beautiful. Especially regularly arranged teeth are attractive and leads to beautiful smiles. In some people the teeth are not regularly arranged by birth. To regularise the growth of teeth people, consult the dentists. They recommend the use of orthodontic wires made of various alloys such as SS316L, SS18/8, 22K gold etc. After the clipping of these orthodontic wires, people orally take many of items, tablets and juices. Hence the orthodontic wires may undergo corrosion. Many research activities have been undertaken in this regard.

The corrosion resistance of AISI 316L stainless steel orthodontic archwire in many fruit juices has been carried out by electrochemical studies. The surface morphology of protective film has been analysed by Scanning Electron Microscopy and Atomic force microscopy.[1]

Sharma et al. have used electrochemical studies such as polarization study and AC impedance spectra to investigate the corrosion behaviour of orthodontic archwire made of AISI 316L stainless steel in presence of chloride ions and many fruit juices. The protective film has been analysed by Scanning electron microscopy.[2]

Kamiński et al,. have used electrochemical studies to study the corrosion behaviour orthodontic arch-wires made of AISI304 steel in simulated saliva.

After conventional glow-discharge nitriding, they have observed an increase in corrosion resistance of AISI304 steel.[3]

The corrosion resistance of titanium alloys in synthetic saliva has been studied by Affi et al.[4] The experiments have been carried out at various temperatures. Interesting observations were made. It has been observed that under these conditions the hardness of the material decreased and the corrosion rate of orthodontic wires increased.[4]

The influence of snakefruit extract in controlling the inhibitive release of chromium and nickel ion from stainless steel orthodontic wire in saliva has been studied by Erwansyah and Susilowati.[5]

The influence of oral antiseptics on the corrosion of nickel–titanium (NiTi) alloys with various coating has been investigated by Rincic-Mlinaric et al. It is observed that in most cases changes of mechanical characteristics induced by antiseptics are small and would not have a clinically significant impact.[6]

The influence of simulated erosive conditions on the frictional behavior of diverse orthodontic bracket-wire combinations have been studied by Stefański et al.[7] It has been noted that erosive conditions do not change the frictional behavior of SS, Ni-Ti and TMA orthodontic archwires at a clinically significant level.

Simionescu et al. have investigated corrosion resistance of 316L stainless steel for orthodontic applications in artificial saliva. They have employed electrochemical studies for this purpose. It is concluded that the corrosion resistance is high when pH is low (acidic condition) and chloride ion concentration is less.[8] It has been concluded that snakefruit

seeds extract controlled the release of chromium and nickel ion from stainless steel orthodontic wire in saliva.

Employing electrochemical studies, Nahusona and Koriston have studied the corrosion behaviour of stainless-steel orthodontic wire in saliva in presence of watermelon rind extract. It is observed that the corrosion resistance of stainless steel orthodontic wire in saliva in presence of watermelon rind extract increases.[9] Hence it implies that people clipped with orthodontic wire made of stainless steel need not hesitate to take watermelon rind extract orally.

Musa Trolic et al. have investigated the corrosion resistance of three types of NiTi orthodontic wires and stainless steel in simulated saliva. Influence of *Lactobacillus reuteri* has also been studied. It was observed that the added substances from probiotic supplement are responsible for the localized corrosion of the studied wires.[10]

Present work is undertaken to investigate the corrosion resistance of 18 K Gold in artificial saliva in the absence and presence of Gemer-2 Tablet, orally intaken by type 2 Diabetes, by electrochemical studies such as polarisation study and AC impedance spectra.

EXPERIMENTAL

Gemer-2 tablet

Gemer-2 is a drug that treats patients suffering from type 2 diabetes. It is also used in combination with other antidiabetic medicines. This drug is a type of sulfonylurea antidiabetic medicine that helps the pancreas in releasing insulin. This tablet reduces the blood sugar level. It belongs to a class of drugs known as sulfonylureas.[11]

Preparation of artificial saliva

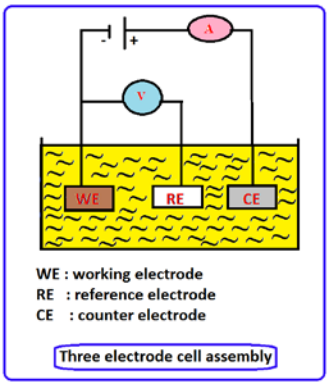
The preparation of artificial saliva was done using the composition of Fusayama-Meyer artificial saliva (AS). Artificial saliva was prepared in laboratory and the composition of artificial saliva was as follows: KCl-0.4 g L^{-1}, NaCl-0.4 g L^{-1}, $CaCl_2.2H_2O$ - 0.906 g L^{-1}, $NaH_2PO_4.2H_2O$ - 0.690 g L^{-1}, $Na_2S.9H_2O$ - 0.005 g L^{-1}, urea – 1 g L^{-1}.

Electrochemical studies

Electrochemical studies are used to measure the corrosion resistance of metals and alloys in various media.[12-27] The corrosion resistance of 18K gold in aritificial saliva, in the absenc and presence of Gemer-2 has been evaluated by electrochemical studies such as polarization study and AC impedance spectra.

Potentiodynamic polarization study

A CHI 660 A workstation model was used in the electrochemical studies. Polarization study was carried out using a three electrodes cell assembly (Scheme A). 18K Gold was used as working electrode, platinum as counter electrode and saturated calomel electrode (SCE) as reference electrode. After having done iR compensation, polarization study was carried out, at a sweep rate of 0.01 V s^{-1}.



Scheme A. Three electrode cell assembly

The corrosion parameters such as linear polarization resistance (*LPR*), corrosion potential E_{corr}, corrosion current I_{corr} and Tafel slopes [b_a (anodic Tafel slope) and b_c (cathodic Tafel slope)] were measured.

AC impedance spectra

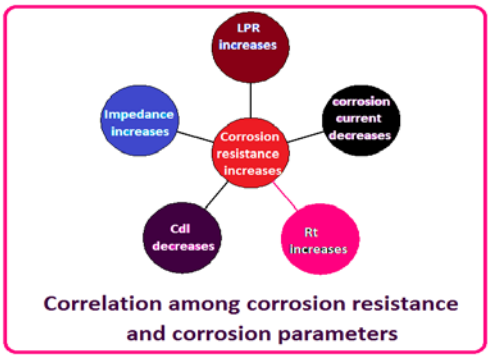
In the present investigation the same instrumental set-up used for polarization study was used to record AC impedance spectra also. A time interval of 5 to 10 min was given for the system to attain a steady state open circuit potential. The real part (Z') and imaginary part (Z'') of the cell impedance were measured in ohms at various frequencies. AC impedance spectra were recorded with initial E(V) = 0, high frequency (1×10^5 Hz), low frequency (1 Hz), amplitude (V) = 0.005 and quiet time (s) = 2. From Nyquist plot the values of charge transfer resistance (R_t) and the double layer capacitance (C_{dl}) were calculated. From Bode plot impedance values were derived,

RESULTS AND DISCUSSION

Influence of Gemer-2 on corrosion resistance of 18K gold in artificial saliva

Corrosion resistance of orthodontic wire made of 18 K Gold in presence of Gemer-2 Tablet has been investigated by electrochemical studies, namely, polarisation study and AC impedance spectra. Interesting results have been obtained. They are presented and discussed in this section.

It is a fact that when corrosion resistance of a metal or alloy increases, the linear polarization resistance (*LPR*) value increases and corrosion current (I_{corr}) value decreases. Similarly, when corrosion resistance value increases. Charge transfer resistance value increases, impedance value increases and double layer capacitance value decreases (Scheme B). This is due to the fact that when a protective film is formed on the metal surface the flow of corrosive ions on to the metal surface is prevented. Further the loss of electron from the metal surface is also prevented.[12-27]



Scheme B. Correlation among corrosion resistance and corrosion parameters

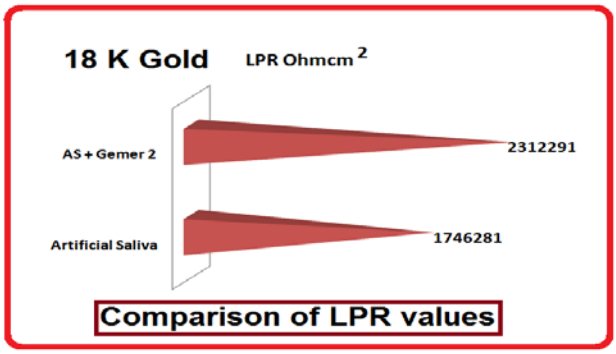


Figure 3. Column chart of linear polarization resistance value of 18 K Gold in the absence and presence of Gemer-2

Analysis of polarization study

The polarization curves of 18K gold immersed in various test solutions are shown in Figures 1 and 2. Corrosion resistance of 18K gold in artificial saliva in presence of Gemer-2 is given in the Table 1. The linear polarization resistance values of 18K gold artificial saliva in the absence and presence of Gemer-2 tablet are compared graphically in Figure 3.

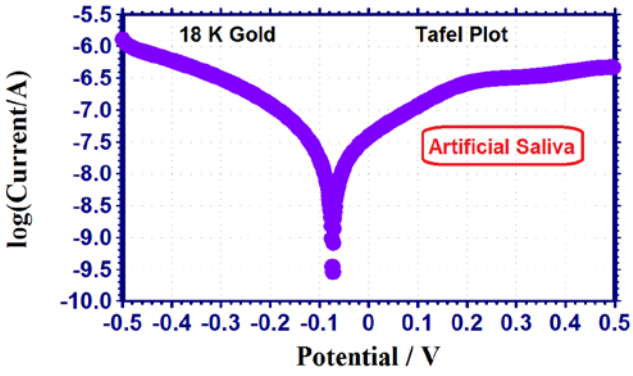


Figure 1. Polarization curve of 18K gold immersed in artificial saliva

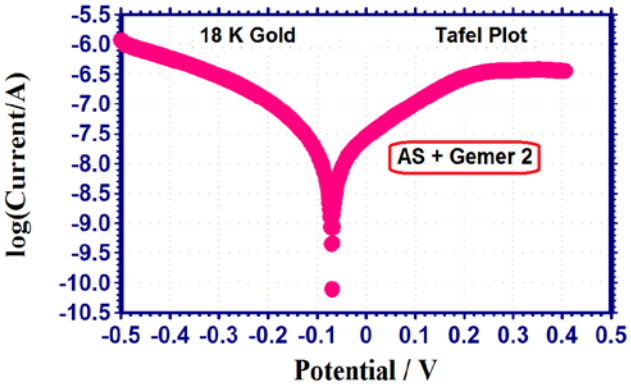


Figure 2. Polarization curve of 18K gold immersed in artificial saliva in the presence of Gemer-2

When 18K gold is immersed in artificial saliva, E_{corr} (corrosion potential) is -0.072 V *vs* SCE. The corrosion current (I_{corr}) is 2.166 × 10^{-8} A cm^{-2}. Cathodic Tafel slope (b_c) is 6.735 V $decade^{-1}$. The anodic Tafel slope (b_a) is 4.758 V $decade^{-1}$. The linear polarization resistance (*LPR*) is 1746281 Ohm cm^2.

Influence of Gemer-2

When Gemer-2 (500 ppm) is added to artificial saliva, the corrosion potential (E_{corr}) is -0.069 V vs SCE. The corrosion current (I_{corr}) is 1.500 × 10^{-8} A cm^{-2}. Cathodic Tafel slope (b_c) is 7.327 V $decade^{-1}$. The anodic Tafel slope (b_a) is 5.211 V $decade^{-1}$. The linear polarization resistance (*LPR*) is 2312291 Ohm cm^2. It is observed from the Table 1 that when Gemer-2 is added to AS, the *LPR* value increases from 1746281 Ohm cm^2 to 2312291 Ohm cm^2. The corrosion current decreases from 2.166 x 10^{-8} to 1.500 x 10^{-8} A cm^{-2}.

This indicates that in presence of Gemer-2, the corrosion resistance of 18K gold in artificial saliva increases (Scheme B). Hence people clipped with orthodontic wire made of 18K gold need not hesitate to take Gemer-2 orally.

Implication

Hence people clipped with orthodontic wire made of 18 K Gold need not hesitate to take Gemer-2 Tablet orally.

Analysis of AC impedance spectra

The AC impedance parameters such as charge transfer resistance (R_t), double layer capacitance (C_{dl}) and impedance values of 18K gold immersed in AS in the absence and presence of Gemer-2 are given in Table 2. The Nyquist plots are shown in Figures 4 and 5.

The Bode plots are shown in Figures 6 and 7. The charge transfer resistance and double layer capacitance values are derived from Nyquist plot. The impedance values are derived from Bode plot.

Table1. Corrosion parameters of 18 K Gold immersed in artificial saliva (AS) in the absence and presence of Gemer-2 (500 ppm) obtained by polarization study

System	E_{corr}, V (SCE)	b_c, V decade^{-1}	b_a, V decade^{-1}	*LPR*, Ω cm^2	I_{corr}, A cm^2
Artificial saliva(AS)	-0.072	6.735	4.758	1746281	2.166 x 10^{-8}
AS + Gemer-2	-0.069	7.327	5.211	2312291	1.500 x 10^{-8}

Table 2. Corrosion parameters of SS 18/8 immersed in Artificial Saliva (AS) in the absence and presence of Gemer-2 (500 ppm) obtained by AC impedance spectra

System	R_t, ohm cm^2	C_{dl}, F cm^{-2}	Impedance, log(Z ohm^{-1})
Artificial saliva	113500	4.493 x10^{-11}	5.368
AS + Gemer-2	217900	2.341 x10^{-11}	5.613

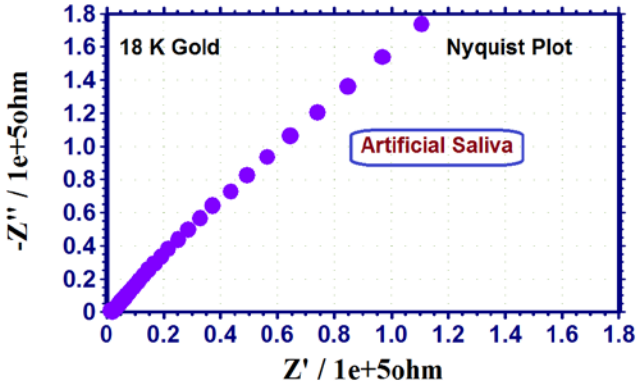


Figure 4. AC impedance spectrum of 18K gold immersed in artificial saliva (Nyquist Plot)

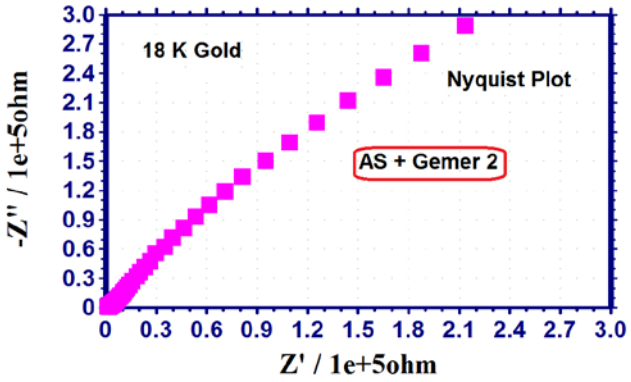


Figure 5. AC impedance spectrum of 18K gold immersed in artificial saliva in the presence of Gemer-2 (Nyquist Plot)

The charge transfer values of SS18/8 in artificial saliva in the absence and presence of Gemer-2 tablet are compared graphically in Figure 8.

When 18K gold is immersed in artificial saliva, R_t (charge transfer resistance) is 113500 Ohm cm^2. C_{dl} (double layer capacitance) is 4.493 × 10^{-11} F cm^{-2}. Impedance is 5.368 log *Z* ohm^{-1}.

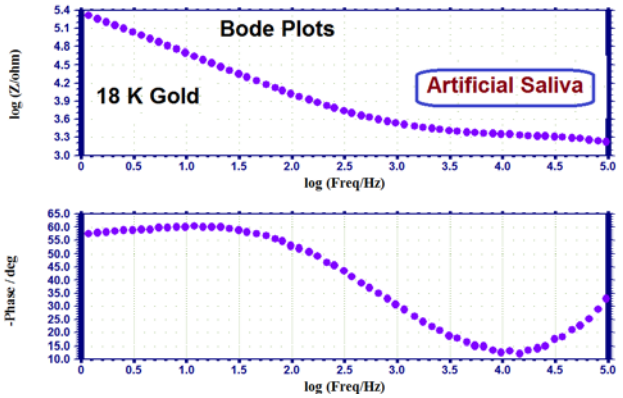


Figure 6. AC impedance spectrum of 18K gold immersed in artificial saliva (Bode plot)

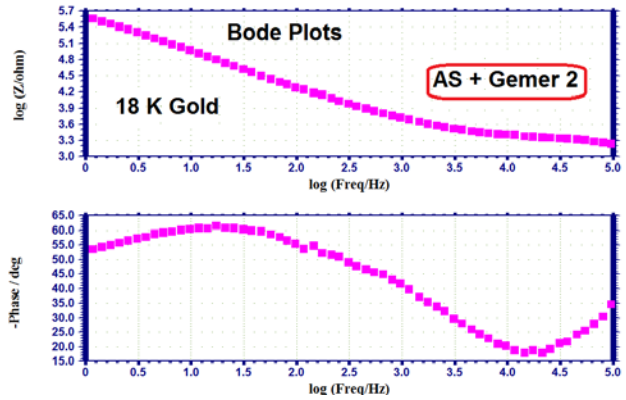


Figure 7. AC impedance spectrum of 18K gold immersed in artificial saliva in the presence of Gemer-2(Bode plot)

Influence of Gemer-2

When Gemer-2 is added to artificial saliva, the R_t (charge transfer resistance) is 217900 Ohm cm^2. C_{dl} (double layer capacitance) is 2.341 × 10^{-11} F/ cm^2. Impedance is 5.613 log (Z ohm^{-1}). It is observed from the Table 3 that when Gemer-2 is added to AS, the R_t value increases from 113500 to 217900 Ohm cm^2. Double layer capacitance decreases from 4.493 × 10^{-11} to 2.341 × 10^{-11} F cm^{-2}. This indicates that in presence of Gemer-2, the corrosion resistance of 18K gold in artificial saliva increases. Hence people clipped with orthodontic wire made of 18K gold need not hesitate to take Gemer-2 orally.

Implication

Hence people clipped with orthodontic wire made of 18K gold need not hesitate to take Gemer-2 orally.

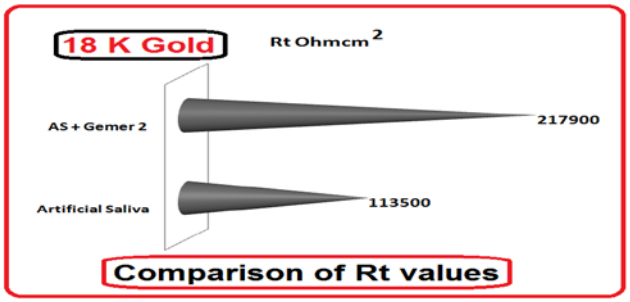


Figure 8. Comparison of charge transfer resistance (R_t) values of 18K gold in the absence and presence of Gemer-2

CONCLUSIONS

- The corrosion resistance of 18K gold in artificial saliva, in the absence and presence of Gemer-2 has been evaluated by polarization study and AC impedance spectra.
- Polarisation study reveals that in the presence of Gemer-2, *LPR* value increases and corrosion current decreases.
- That is in presence of Gemer-2, the corrosion resistance of 18K gold in artificial saliva increases.
- AC impedance study reveals that in the presence of Gemer-2, R_t value increases and C_{dl} decreases.
- That is in the presence of Gemer-2 the corrosion resistance of 18K gold in AS increases.
- It is concluded that people clipped with orthodontic wire made of 18K gold need not hesitate to take Gemer-2 orally

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DEGRADATION KINETICS OF CARBOFURAN INSECTICIDE IN TOMATO FRUITS

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Keywords: Carbofuran, kinetic parameters, degradation rate, tomato.

The degradation rate and kinetic parameters of carbofuran insecticide in tomato fruits were calculated. The degradation of carbofuran was found to follow first-order reaction kinetics. The rate constants for carbofuran were 0.082 day^{-1} and 0.073 day^{-1} for the recommended application rate (10 kg $feddan^{-1}$) and for the application rate used by farmers (13.5 kg $feddan^{-1}$) respectively. The half-life time ($t_{1/2}$) values for the recommended application rate and for the application rate used by farmers were 8.45 days and 9.50 days, respectively. The safe application time of carbofuran insecticide for the recommended application rate and for the application rate used by farmers were after 28 days and after 35 days , respectively. Spectrophotometry was employed to determine the carbofuran residues in tomato fruits, with a limit of detection (LOD) of 0.039 ppm and percent recovery in the range from 92.87 to 95.54%

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INTRODUCTION

Carbofuran belongs to the carbamate class of pesticides, which is often applied directly to the soil. Kinetic parameters as well as the degradation of carbofuran are widely affected by different factors, such as temperature, soil type, soil and water pH, microorganisms present in the environment and matrix under study. Hence, it is appropriate to investigate these parameters under specific environmental conditions. Moreover, these parameters reflect the degradation behaviour of carbofuran in a specific environment. Several studies have reported the degradation of carbofuran in different matrices and environments.

3-Ketocarbofuran is the major metabolite of carbofuran in soil, while the higher conversion rate occurs in the muck soil.[1] Yang et al. have employed response surface methodology to investigate the photodegradation kinetics of carbofuran in TiO_2 and determined nine degradation intermediates.[2] Rouchaud et al. have reported that carbofuran is converted to 3-ketocarbofuran, carbofuran phenol, and 3-ketocarbofuran phenol.[3] Gong et al. have investigated the use of chlorpyrifos and carbofuran, which are applied together to control pests, and reported that a higher degradation rate is observed in non-inoculated soils.[4] Wang et al. have measured the degradation rates of carbofuran by employing the embedding-adsorption method and reported that the use of immobilized fungal laccase can attain an 86 % degradation rate for carbofuran in soil.[5] Gong et al. have utilized the engineered biosafe strain *Pseudomonas putida* KT2440 and reported the degradation of carbofuran within 30 h; moreover, the complete removal of carbofuran is observed within 15 days.[6] Kaur and Balomajumder have investigated the degradation of carbamate mixtures using *Ascochyta* sp. CBS 237.37 and reported a rate constant of 0.03412 day^{-1} and a $t_{1/2}$ of 26 days.[7] Bachman and Patterson have investigated the photodecomposition of carbofuran in different samples of dissolved organic matter and reported that degradation follows the first-order reaction kinetics.[8] Ying-Chih et al. have employed the ultrasound/Fenton process to examine the effects of H_2O_2 and Fe^{2+} on the degradation of carbofuran and reported a >99 % degradation rate of carbofuran.[9] Tomasevic et al. have performed a comparative examination of pure carbofuran and Furadan 35-ST (commercial product) to assess the effects of inert ingredients present in Furadan 35-ST. They reported that the degradation rate of pure carbofuran is greater than that of Furadan 35-ST.[10]

Different analytical techniques have been employed to determine carbofuran residues and carbofuran degradation processes.[11-16] Zhnag et al. have employed time-resolved fluorescent immunochromatographic method for the detection of carbofuran residues in agricultural products and reported a limit of detection (LOD) in the range of 0.04–0.76 μg cm^{-1}.[17] Ogawa et al. have developed a solid phase extraction technique with LC analysis using a UV detector for the determination of carbofuran and 3-hydroxycarbofuran in coconut water and reported an LOD in the range of 0.008 to 0.01 ppm (μg g^{-1}).[18] Appaiah et al. have developed a spectrophotometric method to determine carbofuran residues in rice, wheat, jowar, and pigeon pea and reported the maximum absorbance at 475 nm.[19] Yong-jia et al. have employed a fluorospectrophotometric technique to determine carbofuran residues in vegetables and reported a detection limit of 0.025 mg kg^{-1} and linear dynamics in the range of 0.09–1.2 mg L^{-1}.[20]

In this study, the degradation rate of carbofuran in tomato under environmental conditions was investigated. Kinetic parameters such as the degradation rate, order of the reaction, percentage degradation (%), half-lifetime ($t_{1/2}$), and rate constant were determined.

Experimental

Chemicals and Reagents

All analytical-grade chemicals and reagents were used. Carbofuran (99.0 % purity) was obtained from Riedel-de-Haen Company. The standard solution was prepared by

dissolving carbofuran in methanol. The granular form of Furadan 10, containing 10 % of carbofuran, was produced by FMC corporation agricultural production group.

Field experiment and sample collection

The study was conducted in Khartoum North, near the Nile River, with clay soil; its cultivation area was 18 Sarabs (ridge) with a length of 15 m and a width of 1m, and its total area was 270 m^2. Every Sarab contained 30 plants of tomato. 90 m^2 of this area was treated with Furadan 10 at a rate of 10 kg $feddan^{-1}$ (10 kg 4200 m^{-2}), which was sown beside the roots of the plants. Another area of 90 m^2 was treated with Furadan 10 approximately at a rate of 13.5 kg $feddan^{-1}$ (as farmers used to sow Furadan 10).The remaining 90 m^2 was kept for control samples and recovery tests. Each area of 90 m^2 was divided into four plots, and eight fruits were randomly picked from each plot. Collection and transportation were conducted to avoid analyte loss and sample contamination. The fruits were chopped into small homogenous pieces with a stainless-steel knife.

Extraction of carbofuran

100 g of an immature tomato or 200 g of a mature tomato was taken and homogenized using a mechanical shaker for 30 min in 150 mL dichloromethane. Next, the liquid was decanted, and the cake was filtered, followed by the addition of 100 g of anhydrous sodium sulphate powder and subsequent filtration. The extract volume was evaporated to ~4 mL.

Sample clean-up

Sample clean-up was performed using the method reported by Leppert et al. with some modifications,[21] and further purification was performed using a coagulation solution, containing 0.5 g of ammonium chloride in 400 mL double-distilled water and 1mL of 85 % phosphoric acid.

Qualitative analysis

The extracts were subjected to thin layer chromatography (TLC) to confirm the presence of carbofuran according to the method reported by Mondoza and shield, Bevalkar et al.[22-23]

Quantification and kinetic analysis

Sample extracts were spectrophotometrically analyzed according to the procedure reported by Appaih et al.[19] The standard calibration curve, LOD, and percent recovery were determined. The environmental conditions were measured and recorded (soil pH, water pH, and pH of tomato fruits, temperature, and rainfall).

The kinetic parameters for carbofuran degradation, such as degradation rate, percentage (%) degradation, rate constant, order of the reaction, and $t_{1/2}$, were calculated by the following equations.

$$ln(a - x) = -k \times t + \ln a \quad (1)$$

$$ln(\text{residue ppm}) = -k \times t + \ln a \quad (2)$$

$$k = -\text{slope} \quad (3)$$

$$t_{1/2} = ln\, 2/k \quad (4)$$

RESULTS AND DISCUSSION

All concentrations obtained here were expressed as $x \pm s$, (x and s represent the mean values and standard deviation, respectively). Microsoft Excel was used for statistical analysis. LOD and percentage (%) recovery of spiked carbofuran were 0.039 ppm and 92.87 % to 95.54 %, respectively (Table 1). Correlation coefficient (R^2) for the standard calibration curve was 0.999, indicative of a good linear relationship (Table 2 and Figure 1). To confirm the presence of carbofuran residues in tomato samples, TLC was employed, and the retention factor (R_f) of carbofuran was 0.38. The pH values of soil and water samples are 7.3 and 7.4, respectively, while the pH of tomato fruits ranges between 4.5 and 4.9. During this study, the temperature in the winter season in Sudan was recorded for 45 days, with an average maximum temperature of 32 °C and an average minimum temperature of 21 °C.

Table 1. Recovery(%) of carbofuran in tomato.

Carbofuran spiked, µg	Absorbance	Carbofuran detected, µg	Recovery, %
15	0.051	13.93	92.87
100	0.346	95.54	95.54
250	0.868	237.16	94.86

Table 2. Standard calibration curve of carbofuran.

Concentartion, ppm	Absorbance	SD of 6 blank readings
0.6	0.05	
1	0.091	
2	0.183	
4	0.366	0.001169
8	0.744	
12	1.095	
16	1.46	
20	1.82	

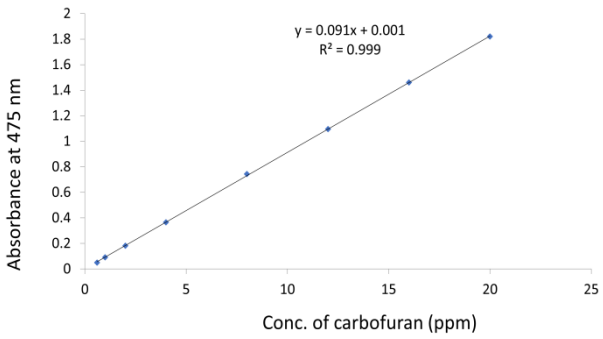

Figure 1. Standard calibration curve of carbofuran.

Table 3. Carbofuran residues in tomato (application rate 10 kg fedd^{-1}).

Day after application	Carbofuran residues, ppm	ln[Residue ppm]	Degradation %
5	0.31	-	-
8	0.42	-0.8675	0
14	0.22	-1.5141	47.62
21	0.13	-2.0202	69.05
28	0.079	-2.5383	81.19
35	0.048	-3.0366	88.57
45	0	-	100

Table 4. Carbofuran residues in tomato (application rate 10.3 kg fedd^{-1}).

Day after application	Carbofuran residues, ppm	ln[Residue ppm]	Degradation %
5	0.36	-	-
8	0.49	-0.7133	0
14	0.31	-1.1712	36.7
21	0.19	-1.6607	61.22
28	0.12	-2.1203	75.51
35	0.065	-2.7334	86.73
45	0	-	100

Each value is a mean of three replications after recovery correction.

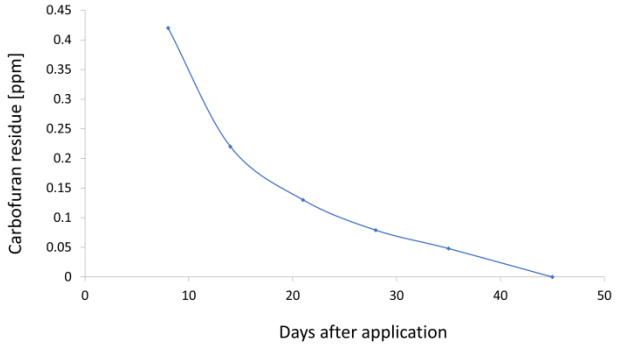

Figure 2. Degradation rate of carbofuran in tomato (application rate 10 kg feddan^{-1}).

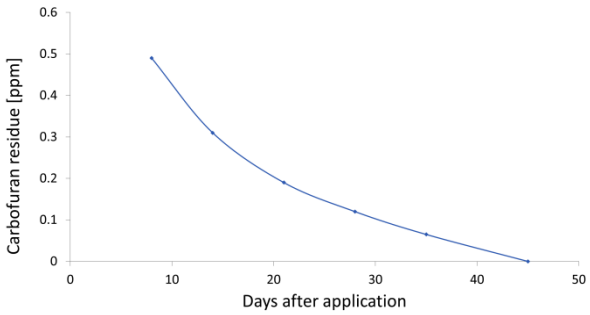

Figure 3. Degradation rate of carbofuran in tomato (application rate 13.0 kg feddan^{-1}).

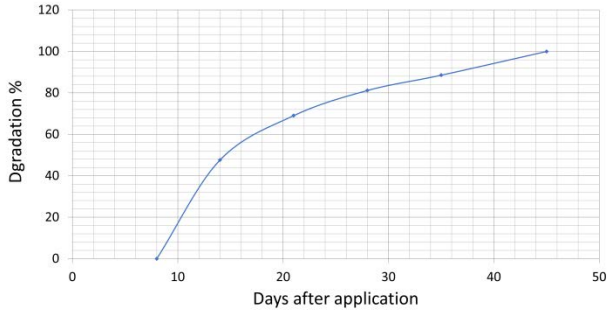

Figure 4. Degradation % of carbofuran in tomato (application rate 10 kg feddan^{-1}).

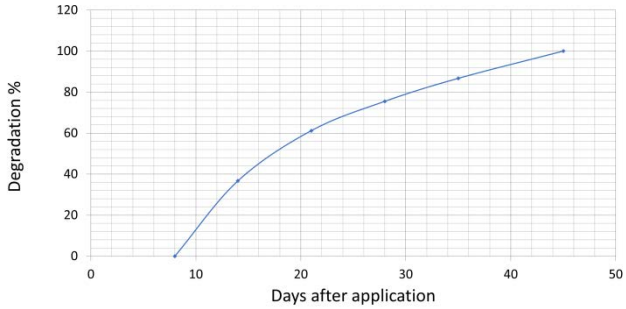

Figure 5. Degradation % of carbofuran in tomato (application rate 13.0 kg feddan^{-1}).

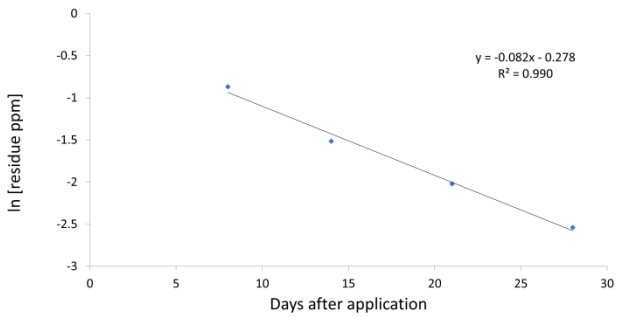

Figure 6. First order plot of residual carbofuran in tomato (application rate 10 kg feddan^{-1})

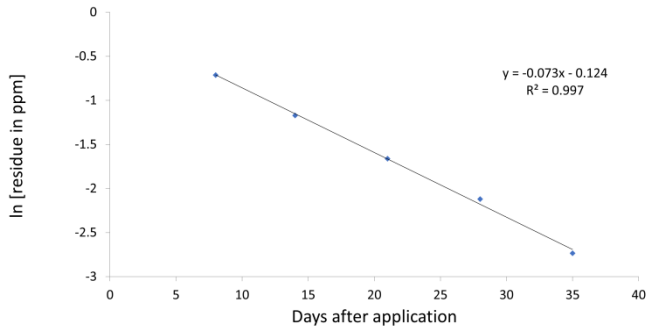

Figure.7. First order plot of residual carbofuran in tomato (application rate 13.0 kg feddan^{-1}).

Residues of carbofuran in tomato at an application rate of 10 kg feddan^{-1} (recommended rate) after 5, 8, 14, and 21 days were greater than the maximum residue limit (0.1 ppm) (Table 3), but after 28 days, the residue was less than 0.1 ppm, and the residue was not detected after 45 days, hence it is safe after 28 days.[24,25] Moreover, residues of carbofuran in tomato at an application rate of 13.5 kg feddan^{-1} after 5, 8, 14, 21, and 28days (Table 4) were greater than 0.1 ppm, and after 35 days, the residue was less than 0.1 ppm. The results indicate that it is safe after 35 days of application. Moreover, a higher application rate led to the increase in not only the residue concentration but also the degradation time. As Furadan 10 was sown in the soil beside the plant roots, carbofuran probably penetrated via the roots and stem until

it reached the fruits of the tomato plant; hence, this need a time before the beginning of the degradation of carbofuran in tomato fruits. As a result, residues detected in tomato fruits after 5 days are excluded from the first-order plot, degradation rate plot, and percentage (%) degradation plot (Figures 2–7). The degradation of carbofuran was more rapid in alkaline media than in acidic media (Table 5),[1] hence, owing to the acidic media in the matrix under study (pH 4.5–4.9 of tomato fruits), degradation took a long time. Figures 2 and 3 show the degradation rate, and Figures 4 and 5 show the percentage (%) degradation. In the first 7 days, rapid degradation was observed, and complete degradation was observed after 45 days after the application of Furadan 10 (Figures 2–4), according to the LOD of the method (0.039 ppm).

Table 5. Half-lives of carbofuran insecticide in water.

Water type	Temp., ^{0}C	pH	$t_{1/2}$, h
paddy	27±2	7.0	240
paddy	27±2	8.7	13.9
paddy	27±2	10.0	1.3
deionized	27±2	7.0	864
deionized	27±2	8.7	19.4
deionized	27±2	10.0	1.2

Table 6. Rate constant of carbofuran degradation of tomato from the curves of figures 6 and 7.

Rate of application	Slope from the curve	Rate constant, day^{-1}	R^2
10 kg fedd^{-1}	-0.082	0.082	0.990
13.0 kg fedd^{-1}	-0.073	0.073	0.997

The first-order reaction obeys Eqn. (1). By applying this equation and equation 2 and by plotting ln (a–x) against t, Figures 6 and 7 are obtained. The curves are straight lines with R^2 values of 0.99 and 0.997 for the recommended rate (10 kg feddan^{-1}) and for the application rate used by farmers (13.5 kg feddan^{-1}), respectively. The results indicate that the degradation of carbofuran follows the first-order reaction kinetics, and this result is in agreement with that reported by Ying-Shih et al.[9] In addition, similar rate constants were obtained (using eqn. 3) for both application rates (Table 6). Half-life time ($t_{1/2}$) was calculated for the recommended application rate and the application rate used by farmers by using eqn. (4), which were 8.45 day^{-1} and 9.50 day^{-1}, respectively. The obtained results were in slight agreement with those obtained at pH 7 in paddy water, but were different from other results in the same study (Table 5).

CONCLUSION

Degradation of carbofuran followed first-order reaction kinetics. Similar rate constants were calculated for the recommended application rate (10 kg feddan^{-1}) and the application rate used by farmers (13.5 kg feddan^{-1}). The corresponding half-life ($t_{1/2}$) values were 8.45 and 9.50 days. The safety time of carbofuran insecticide for the recommended rate (10 kg feddan^{-1}) and for the application rate used by farmers (13.5 kg feddan^{-1}were after 28 days and after 35 days, respectively. Farmers should be advised to apply the recommended application rate of Furadan 10.

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HAZARDOUS ELEMENTS IN AQUEOUS LEACHATES OF COAL FLY ASH AROUND THERMAL POWER PLANTS DISPOSAL AREA

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Keywords: Thermal power plant; leachate; fly ash; pollution; human health

The fossils fuels are main resources of energy worldwide. Huge production of coal fly ash creates water and air pollution. Coal fly ash generally contains trace toxic metals like Ni, Hg, As, Cr, Cd, Ba, Mn, and Pb etc., so coal fly ash is considered as an environmental hazard worldwide. These toxic elements leached from coal fly ash into soil and water which contaminate soil, ground water and other water sources. In present paper is the study of water samples collected from different locations near fly ash disposal area. We found that the water samples contain hazardous trace metals in concentration higher than the permissible limits of drinking water standard. Coal fly ash and other constituents which are generated from coal can create harmful effect on environment, society, health and life. A better method is required to disposal of coal fly ash generated from thermal power plant in India to stop contamination of environment as it is a matter of great concern to human health.

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INTRODUCTION

The human life depends a lot on energy and its resources. The fossils fuels are the main resources to generate energy world-wide apart from nuclear and other renewable energy resources. Coal and oil are two fossils fuels are present world-wide and coal is used extensively to generate energy worldwide.[1]

Mainly coal-based thermal power plants meet energy requirements of developing countries and play major role to meet global energy demand. Its low cost and easy availability made it the fuel that launched industrial revolution in world. The geological resources of coal reserve of India have so far been estimated at about 326.05 billion tonnes in 2018. Total annual production reached from 675.40 million tons (Mt) in 2017-18 to 730.35 Mt in India during 2018-19. The import of coal reached up to about 235.24 Mt in 2018-19 and it was 166.86 Mt in 2013-14.[2] Coal contributed about 60 % (194,402.88 MW) of total installed capacity (329,204.53 MW) power generation in India as on 30 April 2017. Total 624.88 million tons coal was consumed by 167 coal-based power plants in 2017-18. Coal-based power generation produces massive amounts of fly ash worldwide. About 196.44 Mt coal fly ash generated in 2017-18 as the coal comprises of 31.44 % of fly ash and 67.13 % of utilization. Management of fly ash in coal based thermal power stations in country is a challenging task in view of large quantity of fly ash generated and target of achieving 100% utilization.[3,4]

India together China and US accounted for more than two thirds of global increase in energy demand. India imports fossil fuels equivalent to 373.3 Mt oil equivalent (Mtoe) which is equal to 46.13 % of total primary energy consumption in 2018. It is anticipated that amount of coal consumed, in India, per year will be increase from 3840 Mtoe in 2015 to 4032 Mtoe in 2035.[5] India is largely dependent on fossil fuel imports to meet its energy demands by 2030, India's dependence on energy imports is expected to exceed 53 % of the country's total energy consumption.[6]

Carbon, sulphur, oxygen, hydrogen and nitrogen are the main components of coal. In addition, coal has some traces of heavy metals. Coal fly ash is one of the major concerns for the scientific community due its huge amount of production worldwide and its toxicity.[7] With increasing poisoning incidents related with hazardous trace elements in recent years, the adverse effects of these elements on human health and eco-environment have been highlighted.[8] The U. S. Clean Air Act Amendments,[9] European Union and the Canadian Environmental Protection Agency[10] have listed some hazardous trace elements such as Hg, As, Pb, etc., as the main environmental concerns. Coal combustion for power generation is considered as one of the major emission sources of hazardous trace elements.[11] The phase transformations that mineral matter in coal undergoes during high temperature combustion may render the toxic trace elements in the original coal matrix susceptible to leaching, likely to be release into environment after encountering water on application/storage/disposal in landfills or lagoon.[12] However, the borderless nature of the environment could result in the transfer of pollutants into groundwater and river systems, either in dissolved or particulate form. This may pose serious threats for aquatic organisms, while metal inputs in groundwater resources may entail a significant health hazard. The worldwide standard leaching tests can be found in various studies.[13-15].The hazardous trace elements can be leached out from the fly ash and may contaminate soil, groundwater, and surface water.[16,17]

The leached concentrations of elements expressed in terms of absolute value may certainly differ, but the leaching behavior appears relatively common patterns. It can cause water and soil pollution, disrupt ecological cycles and pose environmental hazards.[17] Coal fly ash has many heavy metals including As, Cu, Ni, Zn, Pb, Cd, Cr, Hg, that are usually implicated in causing adverse effect on living systems. The effects have been attributed to various oxidative stress reactions.[18,19]

The coal fly ash contains Si, Al, and Fe as major elements. Ca in coal fly ash is found as the dominant cation followed by Mg, Na, and K.[20] It also has great adverse effects on environment as it releases substantial amounts of trace metals like Mo, Mn, Zn and Cu along with significant amount of other toxic elements (i.e. As, Cr, Co, Pb, Ni, Se) which are major source of soil and water pollution.[21,22] Arsenic contamination has turned into a major global concern with constantly growing pollution of soil, water, and crops. The fuel gas cools down after combustion and volatile elements such as As, B, Hg, Cl, Cr, Se and most prominently S, condense on the surface of the fly ash particles, forming compounds with a high leachability. Furthermore, coal fly ash contains a high amount of soluble salts which support contaminants to move from soils into groundwater through leaching and results in water pollution.[20] Thus, disposal of huge amount of coal fly ash leads to the release of toxic elements which in turn contaminate soil and groundwater resulting in a potential environmental hazard and great effect on the environment throughout the globe. The extensive amount of coal fly ash imposes serious environmental threat[23]. The human health may be negatively influenced by leachate and its noxious compounds in the vicinity of a coal fly ash landfill site[23-25] and some studies have shown that leachate produced by landfills can be toxic to groundwater, and even to humans in the proximity to the landfill.[26] It is imperative to develop new techniques for reuse, recycling and recovery of various elements from coal fly ash.[27,28] Huge amounts of coal fly ash are produced globally but only 1/4th of the total production of coal fly ash is utilized.[29] Toxins present in coal fly ash contaminate air quality when it exposed to the environment. Oversized ash pond unable to control huge amount of ash and breach, causing numerous ecological problems and severe below the ground and above the ground distress to environment and local communities.[30]

STUDY AREA

The study area is near Sardar Gobind Ballabh Pant Sagar also known as Rihand Dam near village Pipri in Sonbhadra district of the state of Uttar Pradesh, India. Its reservoir area is located on the border of Madhya Pradesh and Uttar Pradesh sates. Rihand Dam is based on the Rihand River, a tributary of the Son River. The catchment area of this dam extends over Uttar Pradesh, Madhya Pradesh and Chhattisgarh states whereas it supplies irrigation water in Bihar state located downstream of the river. The water stored in Rihand Dam is released into River Son periodically for irrigation purpose throughout the year. The Dam lies between latitude 24^0 00′ 00″ and 24° 12′43 ″N and longitudes 82^0 38′00″ and 83^0 00′00″ N. It has power house of 300 MW (6 units of 50 MW each) installed capacity. The water collected in the Govind Ballabh Pant Sagar reservoir is diverted to the Son canal which irrigates about 2.5 lakh hectares of the agricultural land in Champaran, Darbhanga and Muzaffarpur districts of Bihar (India).

The southern region of Sonebhadra district, Eastern Uttar Pradesh is referred as Energy Capital of India because the region has large reserves of coal and numbers of power plants of UPRVUNL and NTPC are installed around the Govind Ballabh Pant Sagar. The region produces more than 10,000 MW of electricity. This area is used for coal mines, coal-fired power plants, coal fly ash and coal slurry disposal areas. Many super thermal power stations are located in the catchment area of the dam. These are Singrauli, Vindyachal, Rihand, Anpara and Sasan super thermal power stations and Renukoot thermal station. The highly contaminated water from the ash dumping area of these coal-fired power stations ultimately collects in this reservoir enhancing contamination of its water.

EXPERIMENTAL

Coal fly ash sample collection

The detail information studied three coal-fired power plants is shown in Table 1. The coal fly ash samples were collected from electrostatic precipitator (ESP) of the three power plants, transported and mixed uniformly. The fly ash was collected four times at every two hours from each unit of all power plants to get representative sample. Total 104 number of samples collected from all 26 units of different capacity of all three plants. The fly ash collected from electrostatic precipitators has temperature about 60-70 °C, fly ash was allowed to cool down at ambient temperature before mixing. All samples were mixed thoroughly to get representative sample. A composite sample has prepared by mixing the separate samples in equal proportion. About 250 g of composite sample of coal fly ash was used for elemental analysis.

Table 1. List of locations of sample collection.

Power	Location	Capacity	Total
No. 1	NTPC, Shaktinagar, U.P.	2000 MW	5x200 2x500
No. 2	NTPC, Rihandnagar,U. P.	3000 MW	6x500
No. 3	NTPC, Vindhyanagar, M. P.	4760 MW	6x210 7x500

Coal fly ash elemental analysis

Coal fly ash is hygroscopic in nature. Approximately 250 g of composite sample was put in muffle furnace (M/s Usha Instrument Pvt Ltd.) at108 ± 2 $^\circ$C for one hour to one and half hour, as per IS 1350 part 2, to dry fly ash and to determine the moisture contain on air dried basis. Sample was sent to ATMY Analytical Labs Pvt. Ltd. (NABL/ISO 17025 Accredited Laboratory), I-38, DLF Industrial Area phase-1, Faridabad (Haryana) India for fly ash elemental analysis and rest of the composite sample was stored for future elemental analysis.

Fly ash collected from ESP is solid in nature, it was required to convert in solution form to run sample in ICP-OES. The trace metal concentrations in coal fly ash sample were determined by ICP-OES after acid digestion. To digest coal fly ash, 0.10 g of coal fly ash sample was digested in microwave with aqua regia at 220 ˚C for 30 min and made up with ultrapure distilled water. Analysis of coal fly ash done by using instrument ICP-OES model Optima™ 3300 RL ICP-OES make PerkinElmer® equipped with WinLab32™ for ICP Version 4.0 software for simultaneous measurement of all wavelengths. Plasma, auxillary and Nebulizer gas flows (argon) were 16, 1 and 0.95 L min^{-1} L, respectively. RF power was 1100 W.

Standard solution prepared by Perkin Elmer and VHG NIST® traceable quality control standards for ICP-OES (N9302946, 987841-2) standard used as the stock standards for preparing different working standards. Millipore water acidified with 5 % nitric acid was used as blank. All standard was prepared in ultrapure distilled water acidified with nitric acid with a range of 0.05 ppm to 25 ppm, the standard solution was prepared from 1000 ppm stock solution.

Unburned carbon content

Unburned carbon content in coal fly ash sample was determined by weight loss as per ASTM D 7348. The sample were placed in muffle furnace make at 815 ± 10 ˚C for 1 h after being dried at 108 ± 2 ˚C.

Water sample collection from different locations near fly ash pond

Sonebhadra of Uttar Pradesh known as power capital, contributed more than 10000 MW power generation, huge coal is consumed in this area and coal fly ash is disposed in Ash ponds near Rihand dam. Huge amount of coal extracted by Northern Coal Fields Ltd in this area also contribute to water pollution. Water sample collected from different locations near fly ash pond has been shown in Table 2.

RESULTS AND DISCUSSION

Coal fly ash characterization

The concentration of elements presents in the samples collected from various locations around fly ash disposal area is shown in Table 2. The elements are present mainly in the form of oxides/silicates. The three major constituents of fly ash are silicon, aluminium and iron, which are presents in the form of their oxides. Figure 1 shows silicon is the main constituents of coal fly ash, 28.69 % silicon is present in coal fly ash, second major components of coal fly ash is aluminium which contribute 14.48 %. Various studies have been conducted to develop technologies to clean extraction of aluminium from coal fly ash which has high alumina content. High-alumina coal fly ash would be beneficial to achieve better overall coal fly ash utilization, environmental and economic benefits. Alumina extraction from sulphuric acid leachate of high-alumina coal fly ash by electrolysis is nonhazardous.[27] The elements, present in coal fly ash meet the specific requirements of ASTM C-618 class F coal fly ash (ASTM, C-618, 2015) and Indian Standard (IS:3812, 1981) to use as pozzolana in cement, cement mortar and concrete; total percentage sum of SiO_2, Al_2O_3 and Fe_2O_3 content in coal fly ash should not be more than 70 % and CaO content should be less than 10 %. Similar results have been shown in other studies.[31] The three major constituent elements make up 96.8 % of coal fly ash. Minor constituents are calcium, magnesium, phosphorous in the form of oxides, calcium oxide (CaO), magnesium oxide (MgO), phosphorous pentoxide (P_2O_5) and sulphur trioxide (SO_3) are present as oxides of silicates and aluminosilicates.[32]

Heavy trace elements

The ICP-OES elemental analysis has been shown, 13 heavy trace metals also present in composite coal fly ash sample. All thirteen toxic trace heavy metals were found in detectable concentration in coal fly ash sample. Seven hazardous trace elements have been studied in coal and corresponding fly ash from four power plants in China and it is reported the elements concentration in coal fly ash is more than that in coal. The concentration of Hg, As, Cr, Cd, Ba, Mn and Pb in the four samples of coal fly ash are in the range of 0.17–1.26, 5.15–25.74, 43.25–64.61, 0.56–0.56, 777.05–970.70, 163.83-831.47 and 28.94–119.57 mg kg^{-1}, respectively.[33]

Water sample analysis

ICP-OES study of water samples collected from various locations around coal fly ash disposal area has been shown in Table 2, all elements which are included in table are present in all samples. Elements are present in all 08 samples collected from different locations around coal fly ash disposal area has been shown in Figure 2, highest concentrations of mercury and titanium are present in No. 4 sample (Raja Paraswar Hand Pump 120 feet deep) which is approximate 500m distance from fly ash coal disposal area. Mercury concentration is much more than the permissible limit of drinking water, many studies has been shown mercury is very toxic in nature and hazardous for human. In sample No. 6 (NTPC Vidyut Vihar SBI) barium concentration is highest. Antimony concentration is highest in sample No. 8 (Rihand Dam Upstream). Many studies have shown that, near coal fly ash disposal area, leaching of heavy toxic metals is main reason for water contamination. The TCLP leaching experiments has been done from coal fly ash and coal fly ash bricks which is found leaching trend of heavy metals as Al > Fe > Mg > Zn > Cr > Cu > B > Pb > Ni > Co > As > Cd. The SPLP test also shows the trends of heavy metal leaching similar to that of TCLP.[31]

Elements in samples below permissible limit as per IS 10500:2012

Water sample analysis has been shown, calcium, magnesium and zinc concentrations are under permissible limits in all water samples collected from different locations, concentration of barium is under permissible limit except Rihand Dam water and NTPC Vidyut Vihar SBI hand pump, chromium is under permissible limit in Rihand upstream, AWRS and Raja Paraswar 50 feet deep

Table 2. Concentrations of elements in fly ash and water samples.

S.No.	Elements	(1), %	(2), ppm	(3) ppm	(4) ppm	(5) ppm	(6) ppm	(7) ppm	(8) ppm	(9) ppm	(10) ppm
1	Silicon	28.69	75.5	60.2	47.8	56.3	75.6	52.3	68.2	41.2	-
2	Aluminium	14.84	7.5	2.5	1.9	6.3	4.6	1.3	6.9	1.5	0.03/ 0.2
3	Magnesium	0.391	91	42	32	81.2	49.6	23	54	31	30/100
4	Phosphorus	0.028	0.4	0.1	0.1	0.2	0.1	0.1	0.3	0.2	-
5	Sulphur	0.053	0.6	0.1	0.1	0.7	0.4	0.2	0.4	0.1	-
6	Calcium	0.634	120.6	47.5	64	112	93	96	88.5	34.6	75/200
7	Titanium	0.802	0.8	0.1	0.06	0.9	0.2	0.2	0.2	0.1	-
8	Manganese	0.052	0.7	0.5	0.4	0.7	0.5	0.4	0.8	0.4	0.1/0.3
9	lron	4.48	16.2	17.2	11.5	16.5	18.3	13.6	17	14.1	0.3/0.3
10	Nickel	0.007	0.3	0.3	0.2	0.4	0.1	0.2	0.1	0.1	0.02/0.02
11	Copper	0.005	3.1	0.8	0.6	2.5	1.8	1.1	0.8	0.5	0.05/1.5
12	Chromium	0.007	0.2	0.07	0.05	0.2	0.09	0.08	0.04	0.03	0.05/0.05
13	Vanadium	0.032	0.6	0.1	0.1	0.6	0.3	0.1	0.1	0.1	-
14	Zinc	0.021	7.1	1.8	0.4	5.6	7.2	1.2	0.12	0.09	5/15
15	Lead	0.007	0.04	0.03	0.04	0.06	0.03	0.05	0.06	0.01	0.01/0.01
16	Mercury	0.002	0.006	0.04	0.06	1.7	0.3	0.1	0.05	0.01	0.001/0.001
17	Barium	0.001	0.2	0.8	0.4	0.1	0.1	5	0.4	0.5	0.7/0.7
18	Arsenic	0 002	1.3	0.9	1.5	1.5	0.9	1.4	1.4	1	0.01/0.05
19	Selenium	0.002	0.02	0.01	0.01	0.03	0.02	0.01	0.01	0.01	0.01/0.01
20	Cadmium	0.004	0.01	0.01	0.02	0.01	0.02	0.01	0.03	0.01	0.003/0.003
21	Antimony	0.002	0.004	0.001	0.001	0.002	0.002	0.003	0.01	0.001	-

(1) Fly Ash (2) Ash Dyke Khadia Hand Pump (within 10-meter range) (3) Rihand dam (Near Ash Pond) (4) Raja Paraswar Hand Pump 50 feet deep (within 500-meter range) (5) Raja Paraswar Hand Pump 120 feet deep (within 500-meter range) (6) Tarapur Hand Pump 120 feet deep (within 1000-meter range) (7) NTPC Vidyut Vihar SBI (within 5000-meter range) (8) AWRS Water (9) Rihand Dam Upstream (10) Acceptable/ permissible limit by IS 10500

hand pump samples, copper is under permissible limit except in Ash dyke, Raja paraswar and Tarapur hand pump sample, lead is under permissible limit only in Rihand upstream sample.

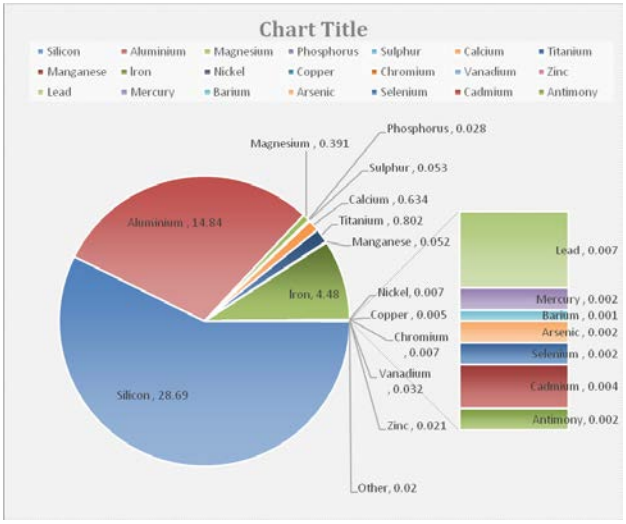

Figure 1. Concentration of elements present in coal fly ash.

Elements above permissible limit as per IS 10500:2012

The concentrations of Fe, Hg, As and Cd are above the permissible limit in all water sample. These all are toxic trace metals in nature, only Pb is under limit in upstream sample of Rihand Dam.

Physico-chemical characteristics

Indian coal has high sulphur contents, which causes acid rain after it enters in environment. Sulphur content is also high in coal fly ash, which brings the pH down as when coal fly ash is mixed with water, oxides of sulphur adsorbed on highly reactive and extremely fine ash particles produce H_2SO_3 or H_2SO_4 in solution. Acid formation results in low pH of fly ash slurry. Several factors may influence pH behaviour of leachate, as quantity of CaO and MgO increases, pH of leachate may increase with time.

CONCLUSION

The present study is an assessment of leaching from coal fly ash disposal area and its effect on nearby water sources. Leaching is likely to deteriorate soil and ground water quality in the vicinity of the thermal power plant.

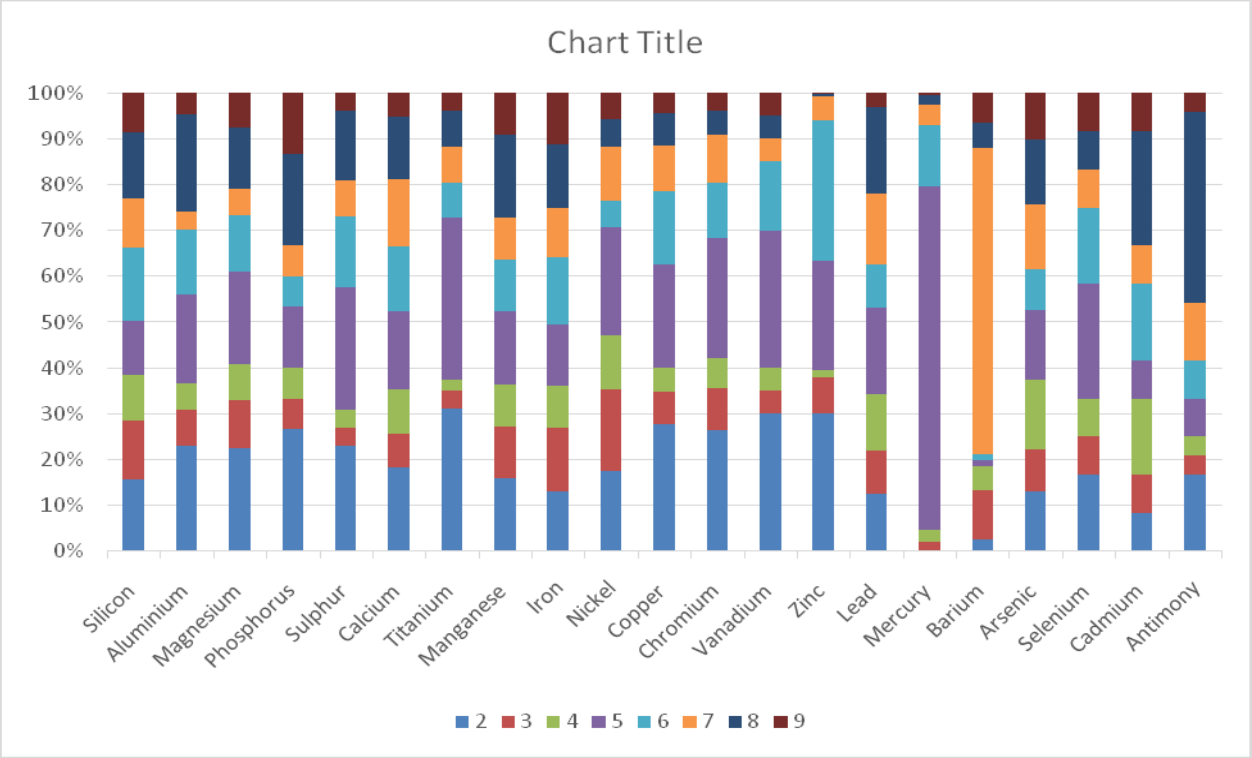

Figure 2. Concentration of toxic elements in water samples.

This research work provides significant evidence to the scientific community for taking adaptive measures to dispose of coal fly ash in better manner and application of appropriate processes for its uses or disposal to stop contamination of ground water and soil. The major conclusions are as follows:

Coal fly ash contain various heavy metal which are toxic in nature as As, Cr, Hg, Pb, Cd and Ni, etc. The most of the samples contains concentration higher than the permissible of drinking water, hazardous trace elements Ni, Pb, Hg, Cd, Mn and As are detected in samples above the prescribed limit. Heavy toxic metals leach into water from coal fly ash disposal area and contaminate ground water and soil also which is dangerous to human health. A better and full proof plan required to use and disposal of such huge amount of fly ash to stop contamination of environment. It is a matter of great concern to human health.

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AMARANTHACEAE PLANTS OF ISRAEL AND PALESTINE: MEDICINAL ACTIVITIES AND UNIQUE COMPOUNDS

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Keywords: *Amaranthaceae*, amaranthine, betanin, saponins, flavonoids, nerolidol derivatives, medicinal activities.

Amaranthaceae family is one of the largest and most diverse in the plant kingdom. While some of the plants of this family have important nutritional value, others are considered toxic and/or hazardous weeds and many efforts have been made in controlling them. But both categories were used by humans for traditional medicinal purposes, and some of them were extensively studied by modern science. In this review article, we will present some ethnomedicinal uses of the plants of this family, along with comprehensive literature survey of medicinal, biological and other activities. Information will be presented in tables for the convenience of readers, and many structures of natural products are presented. The extensive discussion section will focus mainly (but not only) on studies of active compounds production. This review article is about plants of this family in general and in particular about *Amaranthaceae* plants of our region. Conclusions and future research recommendations are also presented.

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INTRODUCTION

Amaranthaceae plant family is one of the largest in the plant kingdom. This family is botanically considered part of the *Amaranthaceae-Chenopodiaceae* alliance, where the *Amaranthaceae* family includes ca. 69 genera and 1,000 species and the *Chenopodiaceae* includes ca. 100 genera 1,400 species.[1]

Archeological studies carried out in different locations suggest that *Amaranthaceae* plants were used by humans for various purposes. Las Canopas inhabitants used what the report authors refer to as *Amaranth* grains as food.[2] Despite the fact that specific species is not indicated, it is reported that these plants were domesticated and cultivated by these humans. They conclude that the plant species might be *Amaranthus hypochondriacus* or *A. cruentus*, with higher possibility of the second species. Rastogi and Shukla indicate in their comprehensive review article about human use of Amaranth plants that early archeological evidence shows that plants of this family were domesticated for nutritional uses, as early as 8000 years ago by Mayan civilizations.[3] Pre-Hispanic (1000-1550 AD) of Northwest Argentina, domesticated *Amaranthus caudatus* for food.[4] This conclusion was made based on isotopic (carbon and nitrogen) analysis of human remains found in that area. *Amaranthus retroflexus* grains were used as food, by humans who lived on the Eastern shores of the Mediterranean, in late Bronze age, 1550-1180 BC.[5]Another early evidence of consumption of Amaranth by humans was found in archeological studies in Mexico, where these plants were eaten around 4000 BC.[6]

Some of the domesticated plants of the *Amaranthaceae* family were modified and selected mutations proved to be very successful and widely cultivated by humans. For example, Quinoa (*Chenopodium quinoa*) is one of the healthiest grains, and its nutritional and economical importance is rising rapidly.[7] Spinach (*Spinacia oleraccea*) has been extensively studied, and its very high health benefits are well known.[8] Another domesticated species of this family, which was thoroughly studies, and has very high nutritional value, is Beet (*Beta vulgaris*).[9] Finally, some species on *Amaranthus* were domesticated for gardening and beauty purposes. A good example of these species is *Amaranthus tricolor*. Both domesticated and wild varieties of this species, are very beautiful and has notable medicinal and other biological activities.[10,11] But this review article, will focus only on wild species of the *Amaranthaceae* family that grow in Israel and Palestine. These are *Achyranthes aspera*, *Aerva javanica*, *Alternanthera pungens*, *Alternanthera sessilis*, *Amaranthus albus*, *A. blitoides*, *A. blitum*, *A. cruentus*, *A. graecizans*, *A. muricatus*, *A. palmeri*, *A. retroflexus*, *A. rudis*, *A. spinosus* and *A. viridis*.

Figure 1. *Amaranthus retroflexus*

Table 1. Ethnomedicinal and ethnobotanical uses of *Amaranthaceae* plants.

Species, region	Region, uses, methods and references
Achyranthes aspera	India. Detailed review article about the many ethnomedicinal uses of this plant, with methods and plant parts. The publication presents some modern research findings.[12] This publication is titled "research article" despite being a typical review article. Less detailed than ref. 12, but it provides detailed presentation of folk medicine uses of the plant, according to rural areas people.[13] Zambia. To treat HIV, cancer, pneumonia, cough, diarrhea, fungal infections of the skin and genital warts. Root infusion or whole plant decoction is administered orally, paste of the plant is applied to skin.[14] Pakistan. Whole plant decoction, extract or powder are used to treat kidney stone, pneumonia, chest pain, puncture wounds, ulcer, dysmenorrhea, aerodontalgia and asthma.[27]
Aerva javanica	Skin diseases, headaches, wounds, injuries, snake bite, insect stings, malaria, kidney stones and bone fractures. Leaf paste is applied on the skin, or infusions are taken orally.[15] Egypt. Roots and leaves are used to treat acne-like diseases and against "evil eye".[16]
Alternanthera pungens	Ghana. Leaves are ground and used for treatment of constipation and headaches.[17]
Alternanthera sessilis	Pakistan. Leaves juice or whole plant decoction, or cooked, are used for eye pain, galactagogue, leucorrhea, snake bite, diarrhea.[27]
Amaranthus cruentus	Pakistan. Eating cooked leaves has laxative effect.[18]
Amaranthus graecizans	Egypt. Leaves are used against constipation.[16]
Amaranthus retroflexus	Turkey. Leaves infusion is used for obtaining sterility.[21] Leaves are used as food.[22,23]
Amaranthus spinosus	Ghana. Whole plant is supplied as a decoction for treating malaria and fever. If crushed and used as a bath, it is used for baby refreshing.[17] Pakistan. Dried seeds powder is taken orally with water to treat eye vision weakness.[19] Aerial parts extract to treat diarrhea, antidote, fever.[25] Whole plant decoction is used to treat gynecological disorders.[26] Iran. This publication indicates the use of this plant in folk medicine but does not outline this use. It briefly presents some modern research results.[20] Leaves are cooked, squeezed for juice, extracted or prepared as decoction, to use for vermifuge, dyspepsia, diuretic, odontalgia, cataract, constipation.[27] Tanzania. Leaves are cooked with milk for ulcer treatment.[24]
Amaranthus viridis	Pakistan. Dried seeds powder is taken orally with water to treateye vision weakness.[19] Leaves Extract, decoction, paste, are used to treat constipation, skin tonic, antidote, diuretic, cooking.[25] Whole plant decoction is used to treat gynecological disorders.[26] Leaves are extracted, powdered or prepared as a decoction, to treat painful urination, eye pain, constipation, piles, snakebite, cough andasthma.[27] Leaves or roots juice or decoctions are used to treat inflammations.[28] Leaves are crushed with sugar, mixed with tea to treat constipation. Extract is mixed with mustard oil to treat skin infections.[29] Iran. This publication indicates the use of this plant in folk medicine but does not outline this use. It briefly presents some modern research results.[20] Italy. Young leaves are used for pies.[30]

Ethnobotanical uses of *Amaranthaceae* family

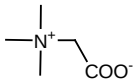
Many human societies have discovered the nutritional and medicinal potential of these plants since many millennia. But compared with other plant families, the published articles about the ethnomedicinal and ethnobotanical uses of *Amaranthaceae*, are few. Moreover, some species were not mentioned at all (6 *Amaranthus* species). In Table 1, these published reports are summarized.

While studying the published review articles about the plants of *Amaranthaceae* plants, we noticed that unlike most other plant families that were reviewed, in the case of this family, there are more review articles about single species, than about the entire family. This is one of the main reasons to write the present review article.

In addition to several review articles about ethnobotany and ethnomedicine of these plants (see previous section), a large number of articles have been published, presenting various properties, especially medicinal activities and chemical composition. The most important among them have been selected and their summaries are presented here.

Achyranthes aspera

This is the most studied and most reviewed of all plants of this family. One of the earliest review articles about this plant, is by Goyal and her colleagues.[31] It presents the known medicinal activities of the plant in folk medicine as well as modern research. It provides general chemical composition, and it its main importance is a table that presents the activities of different parts of the plant, their medicinal activities and active components (no structures), if known. Unlike that, the mini review article of Varuna *et al*., introduces a very limited scope of the medicinal activities of this plant.[32] It also provides very limited chemical composition, with one structure of Betaine (see Figure 2), with a minor error. There are several photos of the plant, but some of them are of very low quality.



Betain
(Ref. 32)

Figure 2 Structure of Betaine, isolated from *Achyranthes aspera*.

Dey in his review article summarized enormous amount of scientific research and reports.[33] The article cites 265 publications, and it provides detailed chemical composition (no structures), and detailed presentations of botanical properties, traditional uses and reported medicinal activities of the plant. Compared with that, the review article of Shukla *et al* is highly valuable.[34] It contains detailed chemical composition, with structures of some important natural products, folk medicine uses and modern research reports, including highlighted antivenom activity. Among these natural products, there are few long chain alcohols (see Chemical Composition section). Tables are provided in the last pages of the article. There is one point that needs additional attention. Practically, there is no difference between sections 3 and 4. Both discuss chemical composition, despite having two different titles.

An excellent review article about *A. aspera* was published in 2011 by Srivastav and his colleagues.[35] It is comprehensive and presents all important aspects of this plant research, especially detailed chemical composition, with structures. The only weakness of this article is the detailed presentation of natural products names that occupied large space in the article, and were provided, anyhow, in the original research articles. On the contrary, the minireview of Hasan is very brief, does not present chemical composition and even the presentation of medicinal activities is very limited.[36] Photos of the plant are of low quality. In the review article of Srivastava, photos have high quality, chemical composition is extensively presented, medicinal activities are introduced, and traditional uses are mentioned.[37] There are two weakness points of this good review. First, many of the presented natural products have been isolated from other plants long time before detecting them in *A. aspera*, thus there was no need to show their structures. Secondly there is a mistake in the structure of Betaine, which is presented as an aldehyde, but it is an amino acid (see Figure 2).

In 2015, many review articles about this plant were published. Sharma and Chaudhary[38] presented the three major aspects of this plant (chemical composition, but no structures provided, ethnobotanical uses and modern research findings. They also presented a good comparison between traditional medicine and recent scientific medicinal activities. The minireview of Sureshkumar has the same structure.[39] The short minireview of Parmar and D. Sharma lacks ethnobotanical uses.[40] Ghimire and her colleagues published a large, good review article, in terms of chemical composition (some structures are presented) and modern research results of pharmacological activities.[41] It does not indicate ethnomedicinal uses.The review of Sanjay is disappointing. It looks like a copy of ref. 36 with exactly the same low quality photos.[42]

The review article of Vijayaraj and Vidhya, lists most of the active chemical components of the plant, presents many medicinal activities, but does not refer to folk medicine.[43] Anyhow, in our humble opinion, this article is of poor quality. It has two major weaknesses. First, the photos, which evidently were copied from other documents, have very low quality, including those that present chemical structures.

Second, the journal classifies the article as “review”, and the title of the publication is “Biological Activity of *Achyranthes Aspera* Linn. - A Review”, but in the introduction, there is a section titled “Collection and Authentication of Plant”, and a procedure for that is described. It is not clear why authors collected samples of the plant for writing review article. In the same year Saini published a very small review article about *A. aspera* that lists most of the active natural products, some of the published medicinal research articles, but did not relate to traditional medicine.[44]

Later in 2016, Verma published her review article.[45] This is a very short publication, that if informational part is extracted, it will not be more that two pages. But as far as we understand the term “review article”, even though its size is very small, this publication should not be named this way. It lists very partial chemical composition, does not mention traditional uses, cites only two publications (treatment of blindness and anticancer activity), and concludes that *Achyranthes aspera* L. (Latjeera) is a very important medicinal herb.

The size of the review article of Lakshmi and his colleagues is the same as ref. 45, three pages, but its quality is much higher.[46] After a short introduction, high quality photo, there is a brief presentation of major medicinal activity. Chemical compositions as well as traditional uses are indicated in brief. Another excellent review article was published in the same year by Rehman and her colleagues.[47] It presents all major aspects of interest about this plant. The two notes that should be given here are, first, there are many unnecessary common names, and, despite presenting detailed chemical composition, no structures were provided. Finally, the publication of Singh *et al*. is comprehensive and detailed for all aspects, but it lacks structures of important natural products that this plant contains.[48]

Aerva javanica

As far as our literature scan could reach, we found only two relevant review articles about this plant. First, the article of Vinit and Zaveri.[49] It focuses more on botanical studies, and lacks structures of important natural products, but the overall value of this article is high.But the review article of Payal and colleagues is low in quality.[50]

First, it is a 4 pages minireview titled “A Review on Phytochemistry and Biological Activities of *Aerva*”, but most of the article presents photos and botany of the plant. Second, the presented structure on Narcissin includes R group, without explaining what R stands for (L-rhamnosyl-β(1-6)-D-glucosyl-β-1- group). Third, the presented structures are of natural products contained in many other plants, while one of these natural products that were mentioned in the article, and contained only in the genus of *Aerva*, aervitin, was not presented (see Figure 3). Fourth, the presented structure of feruloyltyramine is wrong (see Figure 3).

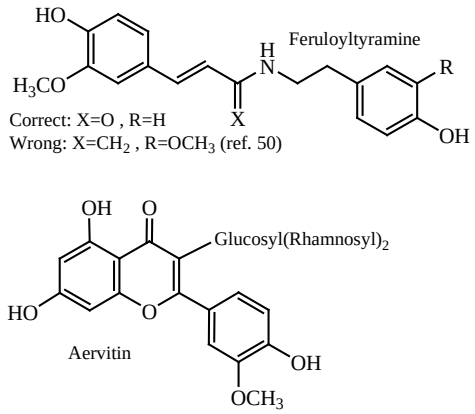


Figure 3. Structures of aervitin and feruloyltyramine

Alternanthera sessilis

Except for deserts and other arid landscapes, this plant is relatively widespread in the reviewed region, Israel and Palestine, but it is a typical fresh water-neighboring plant. The review article of Walter and his colleagues provides a limited view of this plant.[51] It presents botanical introduction, traditional uses, with a notable table that lists all Indian traditional medications (Siddha) that contain this plant or parts of it. But the presentation of modern research results is very partial. And the major weakness of this article is the presentation of the phytochemistry. The natural products that are introduced (β-Carotene and three natural phytosterols) are present in other plants in much higher concentrations and are not typical of this plant.

The review article of Laxmi *et al*., is misleading, the least to say but itcan be classified as scientific fraud.[52] It provides short botanical introduction, mentions chemical composition and some traditional uses, including for nutritional purposes. In this introduction, it cites 11 articles, including ref. 51 here. This is followed by the main part of that article, titled "activities reported of *Alternanthera sessilis*". Here the reporting is exactly as in research articles, including very detailed experimental procedures, and even plant collection and identification. No references cited in this section, and readers could be misled to think that this is an original article. The presentation of each activity includes all research steps, discussion and conclusions. It is not easy to believe that all these investigations were done in a single work. But the detection of misleading is quite easy: there are many mistakes of copying and pasting from original articles. For example, on page 3 of the article, page 2847 of the journal issue, there is a table titled "table 2". But the table was copied as an image from the original article of Kumar and Sanjib.[53] There, it appears as "table 1" (page 4), and Laxmi *et al*. did not pay attention to that numbering. Ref. 52 includes many other faults.

Rao focused in his review article on the botanical and ethnobotanical aspects of this plant.[54] The article mentions very briefly partial chemical composition (no structures) and few pharmacological activities. Contrary to that, the review article of Shehzad and his colleagues is of a high quality, comprehensiveness and photos.[55] Its only weakness is that it does not present unique natural products of this plant, and it does not present any chemical structures. The minireview of Chandrashekhar is satisfactory for this size article, but it lacks chemical structures of important active natural products.[56]

Amaranthus cruentus

This impressive plant annual, 70 cm high on an average, is very widespread in reviewed region (see Figure 1) and yet only one review article was found about it. The article of Wolosik and Markowska is of very high quality, despite having two weaknesses.[57] Its major strength is its comprehensiveness in terms of presenting the topics mentioned in the title. Its first weakness is that it focuses on big and macromolecules (fats, saccharides, amino acids and peptides), but almost ignores small molecules that are contained in the seeds and have notable medicinal activities. Secondly, the structures and the activities of the mentioned small molecules are not presented.

Amaranthus palmeri

Except for very dry areas, this plant is very widespread all over the reviewed region. It is immensely consumed by all plant eating animals. But despite that, only one review article was published about it by Ward and her colleagues.[58] This article focuses on the biological and agricultural aspects of this plant, and does not present traditional uses, medicinal activities or chemical composition. The only relation that it has to this section, is its high resistance to synthetic herbicides, such as the compounds shown in figure 4.

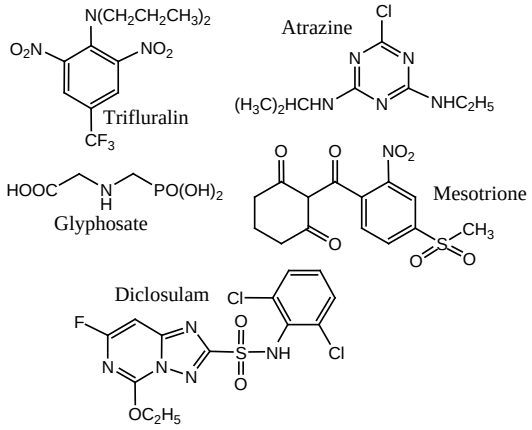


Figure 4. Herbicides that *Amaranthus palmeri* showed resistance to (ref. 58).

Amaranthus spinosus

It is considered invasive species in the reviewed region,[59] like all plants of *Amaranthus* genus, but *A. spinosus* is one of the most recent invaders, unlike some others (*A. rudis*), that invaded this region many centuries ago. It can be easily distinguished from other *Amaranthus* species, that all thrive in cultivated areas, since *A. spinosus* is spiny and painful if mistakenly touched.

The first review article that we present here about this plant, was published by Jhade and his colleagues.[60] It is comprehensive with wide medicinal activities presentation

but limited in review of traditional uses and chemical composition. The review by Kawade and his colleagues, that was published 4 years later, has basically the same structure and size.[61] The traditional uses presentation is even smaller than in ref. 60, and the phytochemical section is slightly larger, but despite mentioning unique natural products to this plant (spinoside), no structures are presented. A very good review was published by Kumar and his colleagues.[62] It includes all expected and needed informational parts, with high quality photos and structure of unique natural products to this plant (Betanin and Amaranthine, Figure 5). It lacks a discussion section. And in the same year, Tanmoy and her colleagues published their review article.[63] It is comprehensive with structures of many natural products, but the images are vague and unclear. In addition, the traditional uses section is very small, but all other parts are satisfactory.

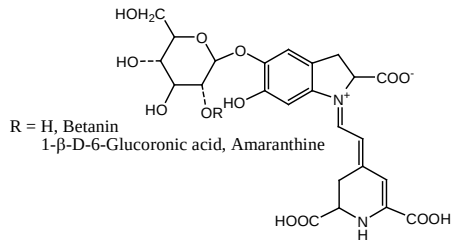


Figure 5. Betanin and Amaranthine isolated from *A. spinosus* (ref. 62).

Despite being properly written and arranged, we found the review article of K. Chandrashekhar, having low usefulness for readers that do not know Hindi.[64] The article have the requisite components needed for such a review, but tables 1 and 2 are meaningless for English readers. Since the journal is titled "International Journal of Ayurvedic Medicine", and since the article is in English, translation of words from Hindi is totally inadequate. We are fully aware that such international articles can include some local common names, but not whole tables, which are supposed to be important parts of the text. Finally, the review article of Raut is superb. It is comprehensive, includes all needed components, well arranged, very useful tables and high-quality photos.[65]

Amaranthus viridis

This plant is unmistakable, it grows around and in human habitats, flowering almost all year except for few cold weeks in the winter, has serrated dark green leaves with white coloring that has the leaf shape.

The minireview of Sowjanya and her colleagues about this plant is informational, satisfactorily written, but has three weaknesses.[66] First, the traditional uses part is very partial. Second, even though, the article is supposed to present "phytochemical and pharmacological potential" of this plant, the phytochemistry section is notably limited (one paragraph) and does not present structures of natural products. Third, the citation of literature is not appropriate. For example, in the paragraph of phytochemistry, the components of methanolic extract of leavesare presented and an article is cited. Directly after that, in the same paragraph, there is a brief description of the content of the roots of the plant and no reference is cited.

A year later, Ferdous and his colleagues published another minireview (that they titled as "comprehensive review") about this plant.[67] It includes useful botanical information, relatively enough information about medicinal activities, high-quality photos, but lacks the parts of traditional uses and phytochemistry. Finally, the minireview of Singh and her colleagues provides very limited information about this plant, probably due to its small size (3 pages), and literature citation is poor, especially in the traditional uses part.[68]

***Amaranthaceae* Family**

M. Graca Miguel published an outstanding review about the family of natural compounds, Betalains, in the *Amaranthaceae* plant family.[69] But since this family includes many genera that some of them are not represented in the reviewed area, some vauable information presented in this superb review, is not relevant to our review. Anyhow, it presents this natural products family from different and comprehensive points of view. From this information, we present here the classification of Betalains, which is shown in Figure 6. So, Betanin and Amaranthine shown in Figure 5, are part of the Betalains subfamily of Betacyanins.

There are no published review articles for *Alternanthera pungens*, *Amaranthus albus*, *Amaranthus blitoides*, *Amaranthus blitum*, *Amaranthus graecizans*, *Amaranthus muricatus*, *Amaranthus retroflexus* and *Amaranthus rudis.*

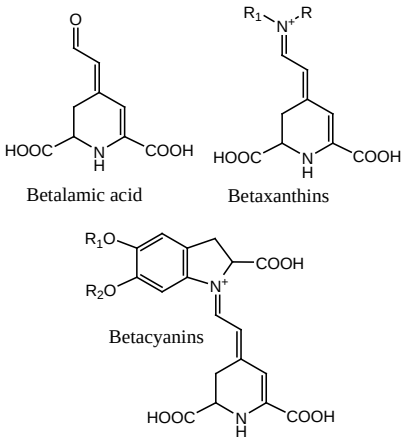


Figure 6. General structures of Betalains (ref. 69).

Amaranthus genus

The review article of Alegbejo is informative regarding the species that the author chose to review.[70] But it is also confusing. In the abstract she states that "Amaranth consists of 60-70 species, 40 of which are considered native to the Americas". Practically, this information is inaccurate: there are about 60 species native to America".[71] Using any count, the author did not review most of these species. In addition, the author is from Nigeria, and she relate to traditional Nigerian medicinal uses of *Amaranthus*, that are not known to the traditional medicine of American peoples. The article lacks presentation of active ingredients and the traditional medicine part is very limited. Comparing with that, the review article of K. Peter & P. Gandhi is an excellent one.[72] It is very clear, highly informative with excellent figures. The only weakness of it is that traditional medicine and phytochemistry sections are very limited.

Biological, chemical and other properties of *Amaranthaceae* plants

When studying the published research literature about the plants of *Amaranthaceae* family that grow wild in the reviewed region, the result is quite interesting and not easy to understand. While some of these plants were extensively studies for almost every possible property, some others are completely missing in this type of scientific literature. These "missing" species are not particularly rare or highly toxic. We will refer to this fact in the discussion section.

So, to make it easier for scholars and interested readers, we summarized the published properties of each species in a separate table.

The data related to *Achyranthes aspera*, *Aerva javanica*, *Alternanthera pungens*, *Alternanthera sessilis*, *Amaranthus cruentus*, *Amaranthus graecizans*, *Amaranthus retroflexus*, *Amaranthus spinosus* and *Amaranthus viridis* are given in tables 2-10, respectively.

Amaranthus blitoides, in this interesting report, the allelopathic effect of this plant on common bean (*Phaseolus vulgaris*) was studied by three methods. First, the two plants were grown together. Second, shoots aqueous extract of *A. blitoides* was supplied to common bean seedlings, in greenhouse conditions. Third, active allelochemicals were extracted with ethanol from the aqueous extract, and they were administered to common bean seedlings. In all cases, the allelopathic effect was clearly observed.[255]

The general chemical composition of the plant with focus on antioxidants and minerals of *Amaranthus blitum* has been reported. Antioxidant capacity of ethanolic leaves extract was determined (DPPH) and its high value confirmed the high values of the antioxidant compounds concentrations.[256]

Amaranthus muricatus

This plant was very scarcely studied. Nutrients and antinutrients were determined in aerial parts before flowering.[280] General chemical composition was studied twice by the same research group.[281,282]

Amaranthus palmeri

This species was also very limitedly investigated. Water soluble organic compounds were isolated by solid-phase separation techniques, and they had slow, but clear allelopathic effect on onions and carrots.[283]A follow up study showed that volatiles (detailed GC analysis) that were released from aerial parts, had allelopathic effect on onion.[284]Since this plant has allergic effect on humans, a study revealed that the allergen in the pollen is profilin (14 kDa protein).[285] Finally, to the best of our knowledge, there are no publications that present novel natural products that were isolated from this plant, though the general chemical composition has been published.[286]

No research articles relevant to this review have been published regarding *Amaranthus albus* and *Amaranthus rudis*.

DISCUSSION

After scanning the published literature about the *Amaranthaceae* plants of Israel and Palestine, the general but the very clear fact that arises is that some of these plants were extensively studied, while others were completely "ignored". We have indicated this explicitly in the previous and main section of this review article.

The plant species of the family that was and still being most investigated is undeniably *Achyranthes aspera*. Evidently, the major mass of research and publication about this plant originate from India. Among the numerous medicinal properties of this plant, using its products as snakebite treatment is very notable. This use, as we have indicated earlier, is known in traditional Indian medicine and in modern research in this country. Based on the shocking, annual number of snakebite cases in this country, and even the more astonishing annual number of fatalities, 58000 in average,[401] it is very understandable why the use of this plant to treat snakebites is very common in India.

A. aspera is mentioned quite frequently in ethnomedicine literature of snakebite treatment,[402] along with modern research. But based on the availability of this plant (very widespread) and the number of deaths, this treatment needs very extensive research in order to make more effective.

The chemical composition of this plant was extensively studied, and in addition to know natural products, some very interesting compounds were isolated and characterized from its different parts (see Figure 7). But some of the reports about this chemical composition are misleading.

Generally, for the identification of a known compound in plant extract or essential oil, HPLC device and standards preparations are all what is needed. It is almost obvious that when detailed spectroscopic characterization is reported, they refer to a novel compound, which is not the case in some reports.[403]

In the previous section we have cited some reports of general chemical composition, and many more were published but we chose not to cite them. Here is another one.[404]

The *Achyranthes* genus is represented by a single species (among 16 in the world), *A. aspera*, and it is the same for the genus of *Aerva*, it is also represented by a single species (11 globally), *A. javanica*. This plant was moderately studied. But despite this, novel, interesting natural products were isolated from this plant (Figure 8). For this reason, there were many attempts to grow and cultivate it. In our region, anyhow, it's a desert and arid regions plant, so it is not widespread but it is very well adapted to this habitat.[405]

Table 2. Biological, medicinal and other properties of *Achyranthes aspera.*

Activity/Property	Major Findings/Reference
Analgesic and pain related activities	Aerial parts were extracted with methanol. The extract has analgesic activity in acetic acid-induced writhing test. [73] Leaves were extracted with 95% aqueous ethanol, and it proved antinociceptive in rat. Three pain-inducing methods were used: tail flick response, hot plate and formalin .[111] Roots were extracted with 95% aqueous methanol and extract (oral administration) was found antinociceptive in mice (acetic acid induced writhing).[112]
Antiallergy, skin protection, wound healing	Allergy was induced in mice by potassium dichromate and treated with methanolic whole plant extract. Positive results were recorded.[74] Seeds were extracted successively with petroleum ether, chloroform and methanol. Extracts found irritant to the inner surface of rabbit ear.[126] An ointment was prepared by using 5% leaves methanolic extract. This formulation was used to treat wounds (burn, wound) in healthy and diabetic (STZ-induced) mice. In both cases, the ointment showed clear wound healing activity.[128] Seeds were defatted with petroleum ether and extracted with 90% aqueous ethanol. Extract had wound healing activity (rats) in three tests: excision, incision, and burn wound.[129]
Antibacterial, antifungal, antiviral and related activities	Stem and leaves were separately extracted with chloroform, methanol, ethanol and ethyl acetate, to obtain 8 extracts. None of them had any antibacterial activity against 5 bacteria species.[78] Leaves and callus were extracted with ethanol, methanol, chloroform, benzene and petroleum ether. Contrary to the previous report, ethanol and chloroform extracts were active against all five species of tested bacteria, including *E. coli*, which ref. 78 reported no activity against it. All callus extracts except petroleum ether, were active against all bacteria species.[79] 70% Aqueous ethanol was used to extract leaves and shoots. This extract showed activity against 3 types of bacteria.[80] This interesting report, tested three variables. First, the yield of extraction of roots, stem, leaves and seeds, with hexane, ethyl acetate, methanol, ethanol and water; in three different months: January, May and September. Highest yields were in January. Second, antibacterial activity of these extracts against several bacteria species. Third, hexane stem extract was most active.[81] Trypsin inhibitor was isolated from seeds by standard protocol. It was tested and found active against 6 bacteria species and 4 fungi.[82] Stems and leaves were extracted separately with petroleum ether, chloroform, ethyl acetate, ethanol and methanol. All eight extracts were tested and found active against 3 bacteria species, except stem extracts that showed no activity against *Enterococcus faecalis*.[83] Used part of the plant was not indicated by authors, but in this important report, plant material was extracted with water, ethanol, methanol and chloroform. None of these extracts was successful antibacterial against all 6 species of multi-drug resistant clinical bacteria isolates, but none of them was completely inactive.[84] Leaves, roots, stemand flowers were extracted separately with petroleum ether, benzene, chloroform, ethyl acetate, ethanol and water. All extracts were partially active against cultured bacteria, but none was active against all species.[85] Aqueous extract of stems and roots was active against *Streptococcus mutans*.[86] Leaves were extracted with diethyl ether, ethyl acetate and acetone, separately. All extracts showed very mild activity against 2 bacteria species, but none was active against *Bacillus subtilis*.[87] Leaves and stems were extracted separately with petroleum ether, methanol, ethanol, ethyl acetate and chloroform. All extracts were active against 3 bacteria species, except stem extracts that were inactive against *E. faecalis*.[88] Methanol, chloroform and petroleum ether extracts of leaves were prepared, and tested against several species of bacteria and fungi. It is reported that (contrary to previous reports), only methanolic extract was active. In addition, extraction yields are notably low.[89] Acetone and aqueous extracts of leaves that were collected from different areas and mixed, were prepared. These extracts were active against 5 bacteria species. Extracts were analyzed for phenolic acids.[90] Seeds were extracted sequentially with chloroform, petroleum ether, acetone, methanol and water. All extracts had antibacterial activity against 8 bacteria species, except aqueous extract that had no activity against *Klebsiella pneumonia*.[91] This report is very interesting, since part of its result contradict most of previous cited reports. Leaves were extracted separately with water, ethanol and methanol and tested against 12 species of bacteria and fungi. All aqueous extracts were completely inactive, while other extracts had notable activity.[92] Whole plant methanolic extract was active against 4 fungi species.[93] Ethanolic leaves extract had notable activity against 3 fungi species.[94] 17-Pentatriacontanol (see Figure 7) was isolated from shoots, and it had activity against *Aspergillus carneus*.[95] Methanolic extract (plant part not indicated) was active against HIV viruses.[96]
Anticancer and related activities	Whole plant was extracted separately with petroleum ether, chloroform, ethanol and water. These extracts had cytotoxic activity (brine shrimp lethality), where aqueous extract was most active.[97] Roots were extracted separately with water and ethanol. Both extracts had anticancer activity against human colon cancer cells (COLO-2015). Aqueous extract had higher activity.[98]

Antidiabetic, anti-obesity and related activities	Whole plant and methanolic extract were orally administered to normal and alloxan-induced diabetic rabbits. It both methods, significant lowering of blood glucose was recorded.[99] Leaves ethanolic extract had significant effect on STZ-induced diabetes in rats.[100] Plant commercial extract (part/s not indicated) had advanced inhibition of formation of glycation end products.[101] Leaves were extracted with 95% aqueous ethanol, and extract was successively fractionized with *n*-hexane, chloroform and *n*-butanol. All extracts were active against STZ-induced diabetes in rats, where positive controls were metformin and glybenclamide. In addition, four pure, known compounds that were isolated from extracts were tested and found active antidiabetic: oleolenic acid, ursolic acid, β-sitosterol and 17-triacontanol.[102] Herbal tea of leaves stems and flowers (combined) was prepared and administered to diabetic (alloxan-induced) rats. It had clear antidiabetic and hypolipidemic activities.[103] Ethanolic seed was supplied to diabetic rats (STZ-induced) and significant increase in blood glucose, as well as lower levels of blood lipids,were observed.[104] Saponin-rich fraction was obtained by extraction with 70% aqueous ethanol and 1-butanol, successively. This fraction has anti-obesity activity in high fat diet fed rats.[113] Powdered seeds were orally administered to high doses of fructose-fed female rats. Hypolipidemic effect was recorded.[137,138] Triton-induced hyperlipidemia in rats was treated with separately with aqueous and ethanolic leaves extracts. The alcoholic extract had significant effect, while the aqueous extract had none.[139]
Antioxidant, anti-inflammatory and related activities	Whole plant was extracted with methanol and extract was fractionized with several organic solvents. Saponin-rich fraction was found active against FCA-induced arthritis. FCA is mycobacteria.[76] Leaves were defatted with petroleum ether and extracted with water. The aqueous extract was active against formaldehyde-induced arthritis.[77] Seeds were extracted sequentially with chloroform, petroleum ether, acetone, methanol and water. All extracts showed antioxidant activity (DPPH), where methanolic extract had highest capacity.[91] Ethanolic seed extract was supplied to diabetic rats (STZ-induced) and significant decrease in the levels of superoxide dismutase and glutathione (GSH) peroxidase and increase in the levels of vitamin E, catalase, and reduced GSH were observed.[104] Ethanolic leaves extract was tested on carrageenan-induced hind paw edema and cotton pellet granuloma models in rats. In both cases, notable anti-inflammatory activity was recorded.[106] Roots ethanolic extract had anti-inflammatory activity in rats, that was observed in two tests: carrageenan-induced paw edema and cotton pellet granuloma.[107] Leaves and whole plants were separately extracted with water, and both extracts had anti-inflammatory activity in carrageenan-induced paw edema in rats.[108] Leaves were extracted with 80% aqueous ethanol, and extract had activity against inflammatory cytokines TNF-a and IL-5 in the lungs of mice.[109] In this important report, gel was prepared (procedure is provided) using aqueous roots extract. The gel was used to treat patients with chronic periodontitis and proved strong activity.[110] Methanolic extracts of leaves and roots were prepared and had high antioxidant activity (DPPH, ascorbic acid standard).[114] Stems were successively extracted with *n*-hexane, chloroform, methanol and water. Antioxidant was tested (DPPH) and methanolic extract had highest capacity. Oddly enough, authors report that extracts were tested against 4 bacteria species, and only *n*-hexane fraction was active against one species.[115] Leaves were extracted with 50% aqueous ethanol, and extract had high antioxidant activity (DPPH, NO radical inhibition).[116] Roots and flowers were extracted separately and sequentially with petroleum ether, benzene, chloroform, ethyl acetate, ethanolwater. General chemical composition of extracts was determined as well as antioxidant capacity (3 methods).[117] Leaves and stems were separately extracted with water, and extracts showed notable antioxidant (DPPH) capacity.[118] Ethanolic leaves extract was prepared, analyzed for general chemical composition, and tested for antioxidant capacity (phosphomolybdenum assay) was determined.[119] This study reports a comparison between the antioxidant capacity of *A. aspera* and *Cyathulaprostrata* that grow in Sri-Lanka. For both species, aqueous extract of whole plant was prepared, general chemical composition was determined, and antioxidant capacity was tested by four methods.[120] Whole plant was separately extracted with dichloromethane, ethyl acetate, methanol and water. All extracts were analyzed for detailed chemical composition, yet, no new compounds are reported. All extracts were tested for antioxidant capacity (4 methods).[121] Leaf aqueous extract was orally administered to rats, resulting reduction in liver lipid peroxidation and prothyroidic activity.[122]
Brain related activities	Aerial parts were extracted with methanol and theextract had CNS depressant activity tested by three methods.[73] Leaves were extracted with methanol and theextract showed anxiolytic activity. Authors refer this activity to the presence of alkaloids in the extract.[75] Roots were extracted with 95 % aqueous methanol and extract (oral administration) was found neuroprotective in mice (pentobarbital sleeping test, open field test).[112] Extracts and pure natural products from the plant were tested for nootropic activity (radial arm maze, step through latency in passive shock avoidance and increased recognition index). Results indicated modulating brain glutamatergic and cholinergic neurotransmission.[127]

Cardiovascular system related activities	Leaves were extracted with 70 % aqueous methanol and extract was administered to mice. As a result, a significant increasein lymphocyte and platelet counts were recorded.[125]
Digestive system protection, hepatoprotection, nephroprotection, lung protection	Ethanolic and aqueous leaves extracts were administered to mice that had diarrhea induced by castor oil. Extracts had laxative as well as bronchodilator effects.[105] Roots were extracted with 95 % aqueous methanol and extract (oral administration) was found diuretic in mice.[112] Aqueous extract of roots prevented nucleation of calcium oxalate (urolithiasis) and preventing renal epithelial NRK-52E cells injury.[130] Leaves were extracted with petroleum ether, methanol, ethanol and water, but only ethanolic and aqueous extracts were used for *in vivo* studies. These extracts were orally administered to rats, and diuretic effect was recorded.[131] Whole plant was successively extracted with petroleum ether, chloroform, ethyl acetate, methanol and water. All extracts were tested for diuretic activity in rats, and methanolic extract was most active.[132] Aqueous extract of seeds had diuretic effect on mice and rats.[133] Leaves were extracted with 70 % aqueous ethanol and this extract had protective effect against pylorus ligation and chronic ethanol-induced ulcer in rats.[134] Whole plant was extracted with 50 % aqueous ethanol and this extract had protective effect against N-nitrosodiethylamine and CCl_4-induced hepatocarcinogenesis in rats.[135] Seeds were defatted with petroleum ether and extracted with 70 % aqueous ethanol. The extract had hepatoprotective activity against CCl_4-induced toxicity in rats.[136]
Enzyme inhibition, antivenom and related activities	Whole plant was separately extracted with dichloromethane, ethyl acetate, methanol and water. All extracts were tested for as enzyme inhibitors: AChE, BChE, α-amylase, α-glucosidase and tyrosinase.[121] Aqueous and ethanolic extracts of leaves were prepared and tested against snake (Ruselli's viper and Saw scaled vipe) in mice. This activity was tested by inhibition of venom phospholipase and procoagulant activity.[123] Aqueous extract of stems inhibited protease and phospholipase A2 from the venom of *Bitis arietans*.[124]
Insecticidal, molluscicidal, antiparasitic, herbicidal	Acetone and aqueous extracts of leaves that were collected from different areas and mixed, were prepared. These extracts had anthelmintic activity against *Caenorhabditis elegans*.[90] Various extracts and their combinations were used as herbicidal against 6 weed species. In all cases, positive results were recorded, and highest efficiency was found for fruit extract.[140] Leaves were extracted separately with acetone, chloroform, ethyl acetate, *n*-hexane and methanol. All extracts had moderate insecticidal activity against *Aedes aegypti* and *Culex quinquefasciatus*. A pure saponin that was isolated from the ethyl acetate extract, had strong activity[141] and it was identified as a compound that was isolated from *Achyranthes bidentate*, a species that is not included in this review.[142] Contrary to ref. 141, authors of this report published that leaves *n*-hexane extract had strong activity against *Aedes aegypti*.[143] Leaves and stems were separately extracted with *n*-hexane, and both extracts had significant activity against *Aedes aegypti*.[144] Aqueous extract of leaves had strong molluscicidal effect against *Biomphalari apfeifferi* and *Lymnaea Natalensis*.[145] Pure natural product (hormone) Ecdysterone (see Figure 7), that was isolated from ethyl acetate leaves extract, has strong activity against *Aedes aegypti*.[146]
Metals related activities	Methanolic leaves extract inhibited corrosion of mild steel that was exposed to industrial water medium.[147] Aqueous leaves extract was used to reduce silver ions ($AgNO_3$), to produce nanoparticles (AgNPs), which had notable larvicide against *Aedes aegypti*.[148] Aqueous leaves extract was used to reduce gold ion ($HAuCl_4$), to produce nanoparticles (AuNPs), which proved nontoxic, so authors conclude that they can be used for drug delivery.[149] Aqueous extract was used to prepare CuO nanoparticles, which had notable inhibition of cellular adhesion (*E. lenta* and *E. aerogenes*).[150]
Nutrition, toxicity	Leaves powder and their methanolic extract were fed to mice and no toxicity was recorded.[151]
Reproductive system, sex	Roots were extracted with 50 % aqueous ethanol and extract was orally administered to male rats. Results indicated reduction of sperm counts, weight of epididymis and reproductive system hormones.[152] Roots were successively extracted with petroleum ether, chloroform, ethanol and water. Chloroform and ethanolic extracts had antifertility activity in female rats.[153] Ethanolic extract of roots that was fed to pregnant female rats had 100 % combined antifertility activity (anti-implantation and abortifacient).[154] Leaves were extracted with 80 % aqueous methanol. This extract was administered to female rats, and it had combined antifertility effect, but it did not reduce reproductivity hormones.[155] Aqueous ethanol (50 %) was used to separately extract roots of *A. aspera* and *Stephania hernandifolia* (not included in this review). A composite of 1:3, respectively, was prepared and orally administered to male rats. The result was clear antifertility effect.[156,157] Roots were extracted with 50 % aqueous ethanol, resulting the isolation of 58-kDa protein. Its composition is not reported. This protein had clear antifertility activity. Gossypol was used as control antifertility agent in male mice.[158] A follow up study with the same protein, showed that it has antifertility effect on human males.[159] Similar study to references 156 and 157.[160]

Chemical composition	Selected articles that reported general chemical composition, which means, natural products families (phenolics, carbohydrates … etc.), minerals or detailed chemical composition that included known compounds, without reporting novel natural products and their characterization.[161-168] First report of the isolation and the characterization of Ecdysterone from roots methanolic extract (Figure 7) that we mentioned earlier in ref. 146.[169] 36,47-Dihydroxyhenpentacontan-4-one (Figure 7) was isolated and characterized, from methanolic shoot extract.[170] A follow up study by the same research group resulted the isolation of two long chain compounds from the methanolic shoot extract, 27-cyclohexylheptacosan-7-ol and 16-hydroxy-26-methylheptacosan-2-one.[171] Two new saponins were isolated and characterized from the methanolic extract of aerial parts (Figure 7).[172] Futher analysis of the same extract, in a follow up study by the same group, resulted the isolation and characterization of three new saponins and two known compounds that were reported as new, but actually the are not (for example, Ecdysterone).[173] New cyclic chain fatty ether (interestingly, authors classified it as cyclic chain fatty acid) was isolated from the seed petroleum ether extract (Figure 7).[174] Even though new compounds were not reported in this study, an interesting and new method was developed for the determination of oleanolic acid in this plant.[175] New derivative (glucoside) of oleanolic acid was isolated and characterized.[176] Even though new compounds were not reported in this publication, it is very detailed, presents structures of active natural products and their GCMS chromatograms. This publication can be very useful.[177] Leave methanolic extract was analyzed by column liquid chromatography, and a new compound, aromadendrene-15-olyl ferulate was isolated and characterized (Figure 7).[178] Leaves were extracted and fractionized with several solvents. Fractions were analyzed resulting a new sesquiterpene (Figure 7) and other known compounds.[179] New 6-prenyl apigenin (Figure 7) was isolated and characterized from methanolic extract of leaves. This compound is candidate for developing novel monoamine oxidase-A inhibitor.[180]

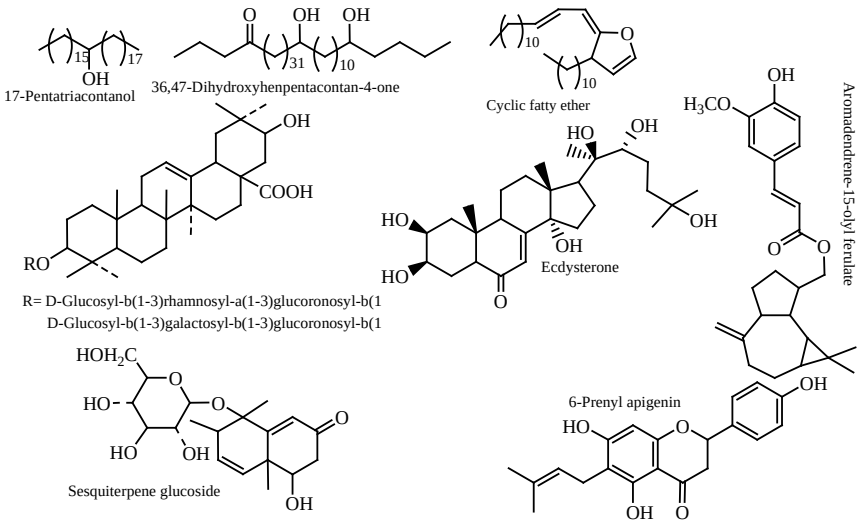


Figure 7. Active natural products isolated from *Aerva javanica*.

Table 3. Biological, medicinal and other properties of *Aerva javanica*.

Activity/Property	Major Findings/Reference
Analgesic and pain related activities	Aqueous extract of leaves had antinociceptive (acetic acid induced writhing test, hot plate injury and tail immersion method) and antipyretic (Brewer's yeast induced test) activities.[181]
Antibacterial, antifungal, antiviral and related activities	Methanolic, ethyl acetated and petroleum ether leaf extracts were prepared and tested for activity against several species of bacteria and fungi. Methanolic extract was highly active, ethyl acetate extract had moderate activity and the non-polar extract was not active. Plant name is mistakenly written *Earvajavanica* instead of *Aerva*.[182] Whole plant was separately extracted with *n*-hexane, chloroform, ethyl acetate, methanol and water. Extracts were chromatographed and known active natural products were isolated. All extracts and natural products had weak to moderate antibacterial activity. Some of these compounds were isolated from this plant for the first

	time.[183,184] Aerial parts were separately extracted with *n*-hexane, ethyl acetate, dichloromethane and methanol. All extracts were active against 5 bacteria species, where DCM extract was most active.[185] Whole plant was extracted with chloroform, ethanol and methanol. Extracts were tested against several bacteria species, and methanolic extract was most active.[186] Dried and fresh leaves were separately extracted with methanol, chloroform, petroleum ether, acetone or water. Each extract was tested against 4 bacteria species, and methanolic extract was most active.[187] Whole plant was extracted with acetone, ethanol, methanol and water, and essential oil was also prepared. All products were tested against several species of bacteria and fungi. Essential oil was most active.[188] Whole plant was extracted with 80 % aqueous ethanol, and extract was active against 6 bacteria species.[189]
Anticancer and related activities	Dried and fresh leaves were separately extracted with methanol, chloroform, petroleum ether, acetone or water. Each extract was tested against prostate and breast cancer cells, and methanolic extract was most active.[187] Whole plant was extracted with acetone, ethanol, methanol and water and essential oil was also prepared. All products were tested against human red blood cells. Ethanolic extract was the most active one.[188] Whole plant was extracted sequentially with *n*-hexane, chloroform and 80 % aqueous methanol. Extracts were tested against two human breast cancer cell lines (MCF7 and MDA-MB-231). Hydro-methanolic extract was most active.[190] Leaves were successively extracted with *n*-hexane, chloroform, ethylacetate, acetone, and methanol. Extracts were attested against human breast cancer cell line MCF7. All extracts had significant activities, where methanolic extract was most active.[191]
Antidiabetic	Leaf ethanolic extract had antihyperglycemic effect on alloxan-induced diabetes in mice.[192]
Antioxidant	Whole plant was extracted with acetone, ethanol, methanol and water, also, essential oil was prepared. All products were tested for antioxidant capacity (DPPH). Methanolic extract was most active.[188] Whole plant was extracted with 80% aqueous ethanol, and extract had high antioxidant capacity (DPPH).[189] Flowers were extracted with 50% aqueous ethanol, and extract was successively fractionized with petroleum ether, diethyl ether, ethyl acetate, benzene, acetone, and ethanol. Ethanolic and ethyl acetate fractions were used to test antioxidant (lipid peroxidation inhibition) in rats. Ethyl acetate fraction was more active.[193] Aerial parts were extracted with 70% aqueous ethanol, and antioxidant capacity (DPPH) of this extract was determined.[198]
Digestive system protection, hepatoprotection, nephroprotection, lung protection	Whole plant was extracted with 80% aqueous methanol and extract was defatted with*n*-hexane. The resulting crude solid was fractionized with water, dichloromethaneand ethyl acetate. Further fractionation and chromatography resulted the isolation of three known compounds. Fractions were tested for urease inhibition and found active, indicating anti-ulcer potential.[194] Aerial parts were extracted with 95% aqueous ethanol, and extract had activity against ethanol-induced gastric lesion in rats.[195] Whole plants was extracted sequentially with ethyl acetate and methanol. Extract had antilithiatic activity against ethylene glycol-induced hyperoxaluria in rats.[196] Whole plant aqueous and ethanolic extracts were active against castor oil induced diarrhea in rats.[197]Aerial parts were extracted with 70% aqueous ethanol, and this extract showed hepatoprotective activity against CCl_4-induced toxicity in rats.[198] The information in this publication is confusing. The title is “research paper”, which describes the hepatoprotective activity of whole plant extracts. Practically, it is written as review article.[199]
Enzyme inhibition	Flowers methanolic extract showed clear activity of the following enzymes inhibition: acetylcholinesterase (AChE), butyrylcholinesterase (BChE)and lipoxygenase (LOX).[200]
Herbicidal	Aerial parts aqueous extract had herbicidal activity against *Cyperus rotundus*.[201]
Toxicity	Aqueous infusions were prepared from aerial parts of female and male plants. These infusions were orally administered to female and male rats. At the dose of 500 mg kg^{-1} for several weeks, female rats suffered hypochromic anemia.[202]
Chemical composition	Flowers methanolic extract was analyzed and four new compounds (Ecdysteroids, Figure 8) were isolated and characterized.200Chromatographic purification of ethyl acetate soluble fraction of the methanolic extractof the floweryielded three new acylated flavone glycosides(Figure 8).[203] A follow up study of the same extract by the same group obtained Aervfuraniside(Figure 8).[204] The following publications reported general chemical composition, and did not report new compounds: essential oil (stems and leaves) composition,[205] essential oil (seeds) composition, with comparison between methods of extraction,[206] composition of whole plant ethanolic extract,[207] very detailed and very useful analysis of various extracts of all parts, including mineral composition,[208] analysis of essential oils compositions resulting from transmission of phytoplasmas.[209]

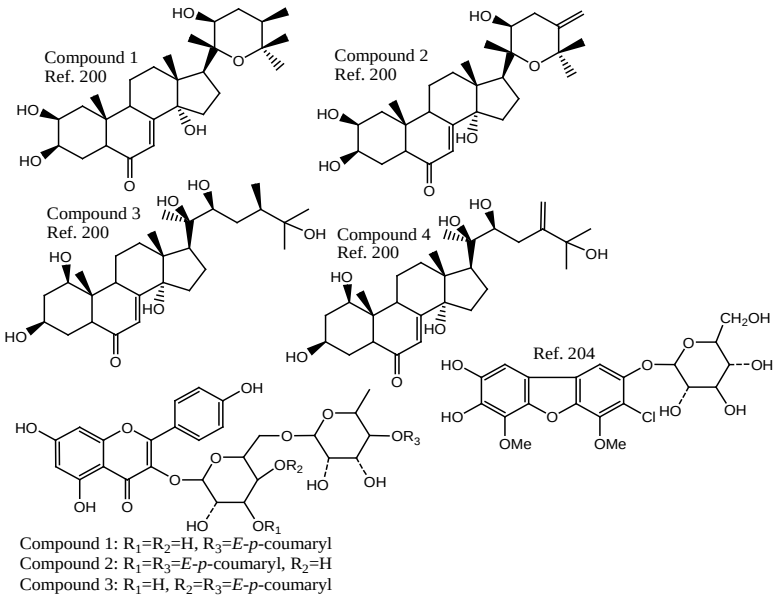


Figure 8. Active natural products isolated from *Aerva javanica*.

Table 4. Biological, medicinal and other properties of *Alternanthera pungens.*

Activity/Property	Major Findings/Reference
Analgesic and pain related activities	Whole plant ethanolic extract was prepared and tested for analgesic activity in mice by hot plate test and acetic acid-induced writhing test.[210]
Antibacterial, antifungal, antiviral and related activities	Aerial parts were separately extracted with water, acetone, ethanol and petroleum ether. All extracts were tested for antibacterial activity and ethanolic extract was most active.[211]
Antioxidant, anti-inflammatory and related activities	Aerial parts were separately extracted with water, acetone, ethanol and petroleum ether. Antioxidant capacity of all extracts were determined by DPPH method.[211] Whole plant ethanolic extract was prepared and tested for antioxidant (DPPH) and anti-inflammatory (albumin denaturation technique) activities in mice.[210] Even though a detailed NMR work is reported, but the analyzed compounds are previously known phenolics. These were tested for antioxidant capacity (Trolox test). The report includes a confusing part (Extraction and isolation), where it states that aerial parts were extracted with "boiling ethanol", and when extract was concentrated, aqueous concentrate was obtained.[212]
Diuretic, gastroprotective	Whole plant ethanolic extract have diuretic effect in rats, like the effect of Furosemide.[213] Whole plant aqueous extract acted as gastro-stimulant in rats.[214]
Antiparasitic	Whole plant was successively extracted with n-hexane, chloroform, ethyl acetate and methanol. All extracts were tested for antiparasitic (*Pheritimaposthuma*) activity, and all extracts were active except methanolic.[215]

Table 5. Biological, medicinal and other properties of *Alternanthera sessilis.*

Activity/Property	Major Findings/Reference
Allelopathy, growth promotion	Aqueous extract of leaves was tested for allelopathic activity against seed germination of Rice (*Oryza sativa*). The allelopathic effect increased with concentration and when this reached 5 %, the germination of seeds was zero. Active phenolics in this extract are chlorogenic acid, gallic acid andvanillic acid.[216] Leaves were successively extracted with petroleum ether, acetone and ethanol. The ethanolic extract was fed to *Macrobrachium rosenbergii* (Prawn) resulting growth promotion in these animals. An excellent presentation of active natural products is provided.[217]
Analgesic and pain related activities	Aerial parts methanolic extract had analgesic activity in abnormal writhing test in mice.[218] Aerial parts were extracted with 90 % aqueous ethanol. Extract had analgesic activity in mice, as prove by two tests: acetic acid induced writhing test and hot-plate test.[219] Whole plant was defatted with *n*-hexane and extracted with ethanol, and this extract had antipyretic (yeast-induced) activity.[227]
Antiallergy, skin protection, wound healing	Aerial parts were extracted with 95 % aqueous ethanol and the extract had inhibitory effect in IgE-mediated allergicresponse in RBL-2H3 cells.[220] Leaves were successively extracted with petroleum ether, chloroform, acetone, methanol and water. All extracts (methanolic highest) had wound healing activity (excision, incision) in rats.[224] Stems were extracted with 90 % aqueous ethanol and extract had wound (scratch) activity.[225]

Antibacterial, antifungal	Aerial parts were extracted with 95 % aqueous ethanol and extract was active against 6 bacteria and 3 fungi species.[222] Leaves were separately extracted with water, ethanol and acetone. Extracts and leaves juice had activity against 3 bacteria species.[223] Leaves were successively extracted with petroleum ether, chloroform, acetone, methanol and water. All extracts (chloroform highest) had weak to moderate activity against 4 bacteria species.[224] Leaves were extracted with methanol and petroleum ether, and both extracts were active against 3 bacteria and 2 fungi species.[226]
Anticancer	Aerial parts were extracted with ethanol, and extract had activity against human colon cancer cells (HT-29, 3T3).[228]
Antidiabetic, anti-obesity and related activities	Aerial parts methanolic extract had antidiabetic activity in glucose loaded mice.[218]Leaves were extracted with methanol and petroleum ether, and both extracts had antidiabetic activity (α-amylase inhibition).[226] Aerial parts were extracted with 95% aqueous ethanol, and extract was fractionized by *n*-hexane. This fraction was extracted with ethyl acetate, and the obtained extract antidiabetic activity in obese rats that had STZ-induced diabetes.[230] Leaves and callus were extracted with methanol, and extract was fractionized with several polar solvents. Extracts and fractions were tested for α-glucosidase inhibition. All showed notable activity, but callus extract was more active.[231]
Antioxidant, anti-inflammatory and related activities	Stems were extracted with 90 % aqueous ethanol, and its antioxidant capacity (DPPH) was determined.[225] Leaves were extracted with methanol and petroleum ether, and antioxidant capacity (DPPH) of both extracts was determined. Anti-inflammatory activity was proved by egg albumin test.[226] Leaves and callus were extracted with methanol, and extract was fractionized with several polar solvents. Extracts and fractions were tested antioxidant (DPPH) capacities.[231] Antioxidant capacities of ethanolic extracts of two cultivars of this plant, by three methods: DPPH, Trolox and FRAP.[232] Essential oil was extracted from aerial parts and its antioxidant capacity was determined by DPPH method.[233] Leaves were extracted with methanol and extract was fractionized with dichloromethane and *n*-hexane. Extract and fractions were tested for antioxidant capacity (DPPH).[234]
Brain related activities	Aerial parts were extracted with 90 % aqueous ethanol. Extract had stimulant activity in mice, as prove by three tests: Pentobarbitone-induced sleeping time test, open field test and hole cross test.[219] Methanolic extract of leaves had antidepressant (tail suspension and forced swimming tests) activity in mice.[229]
Cardiovascular system	Whole plant was extracted with 70 % aqueous ethanol and the extract was fractionized with water and dichloromethane. Extract and fractions had hypotensive effect in rabbits. Extract had higher activity than fractions[221]
Digestive system protection, hepatoprotection, nephroprotection, lung protection	Whole plant was extracted with 70 % aqueous ethanol and the extract was fractionized with water and dichloromethane. Extract and fractions had anti-asthmatic and anti-diarrheal effect in rabbits. Extract had higher activity than fractions[221] Aqueous extract of leaves had strong activity against castor oil-induced diarrhea in mice.[53] Ethanolic extract of aerial parts was active against damages in mice caused by three hepatotoxines: carbon tetrachloride acetaminophen and galactosamine.[235] Whole plant methanolic extract was active against damages in mice caused by carbon tetrachloride.[236]
Metals related activities	Aqueous extract of leaves was used as a reductant in the production of silver nanoparticles (AgNP's) from $AgNO_3$ solution. These AgNPs have antibacterial and antioxidant activities.[237] Young plants found active chromium ($Cr_2O_7^{-2}$) phytoremediator in,[238] domestic sewage,[240] PCB-contaminated soil (with an addition of Bentonite),[241] ions ($Cd^{+2}>Cr^{+3}>Pb^{+2}$). Antioxidant enzymes concentrations increased in different parts of the plant after absorbing the metal ions.[242]
Nutrition, toxicity	Leaves were analyzed for nutrients and antinutrients. Authors concluded that its safe and recommended to eat it.[243]
Chemical composition	Leaves were extracted with petroleum ether, resulting the isolation and characterization of a new natural product that authors symbolized with PDHC (Figure 9). Detailed structures of known compounds are also presented.[226] New saponin from methanolic extract of leaves(Figure 9).[244] Analysis of leaves ethanolic extract afforded new ionone (Figure 9).[245] Novel (plant defense) peptides were isolated from leaves aqueous extract.[246]The following references reported chemical compositions (some are very detailed) of known natural products.[233,234,247-250] Special method for detection and quantification of gallic acid in the plant.[251] Very extensive work was invested in this research, especially in spectroscopic characterization of the reported compound. Authors did not claim novelty, but the presentation of the work ("isolation and characterization") can mislead readers. Anyhow, this compound was isolated and characterized on year earlier.[252,253] Detailed work, including some useful chromatograms.[254]

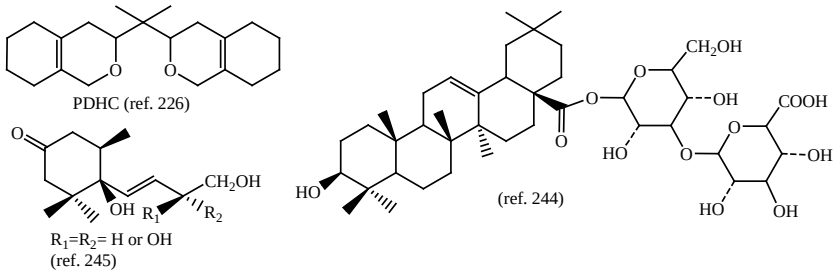


Figure 9. Active natural products isolated from *Alternanthera sessilis.*

Table 6. Biological, medicinal and other properties of *Amaranthus cruentus.*

Activity/Property	Major Findings/Reference
Allelopathy	Tomato (*Lycopersicon esculentum*) was planted in soil that was brought from a field where *A. cruentus* was growing, shewed weak germination and growing compared to control.[257] Allelopathy of *A. cruentus* was clearly temperature-dependent, when its influence was tested by growing factors of several vegetables that were planted with *A. cruentus*. Influence was not uniform for all tested vegetables.[258] Aqueous extract of seeds had allelopathic effect on seedlings of garden cress (*Lepidium sativum*).[269]
Antihyperlipidemic	Seeds were defatted with *n*-hexane and hydrolyzed with pH=11 solution. Proteins contained in this hydrolysate, had inhibition activity of HMG-CoA reductase, suggesting possible hypocholesterolemic effect.[265]
Antioxidant	Seeds were extracted with methanol and the antioxidant capacity of this extract was determined by three methods (FRAP, DPPH and ABTS).[259] High fructose diet resulted in oxidative stress in rats. When co-administered with seeds, indications of decreasing malondialdehyde in plasma and increasing activities of antioxidant enzymes were recorded.[260] Aerial parts were extracted with 20 % aqueous acetone and the extract was fractionized with water. Antioxidant capacities of extract and fraction were determined by FRAP and DPPH methods.[261]
Blood related activities	Seed were separately extracted with *n*-hexane, ethanol and 70 % aqueous ethanol. All extracts had strong haemagglutinating properties.[262] Ethanolic extract of leaves had protective activity (aided in restoring the levels of red blood cells, white blood cells and hemoglobin) against phenylhydrazine-induced toxicity in rats.[263] Ethanolic leaves extract had hematopoietic effect on cyclophosphamide-induced toxicity in rats.[264]
Enzyme inhibition	Aerial parts were extracted with 20 % aqueous acetone, and extract was fractionized with water. Extract and fraction had xanthine oxidase inhibitory activity.[261]
Metals related activities	Analysis of seed samples that were collected from wild growing plants (USA), indicated high concentrations (accumulation) of toxic metal ions: As^{+3}, Cr^{+3} and Pb^{+2}.[266]
Nutrition, toxicity	Major nutritional components of seeds flour and its protein concentrate were determined as phenolics, mineral, fatty acids and carbohydrates.[267] Dichloromethane extracts of seeds was found rich in saponin and toxic for hamsters.[268]
Chemical composition	Young methanolic extract of leaveswas analyzed resulting isolation and characterization of (*E*)-caffeoylisocitric acid (Figure 10). Its enzymatic synthesis is presented.[270] Novel pectinic polysaccharides were isolated and characterized from the methanolic extract of aerial parts.[271] The following publications presented interested information about chemical composition of the plant but did not report new natural products, HPLC method for isolation of betalains (Figure 6),[272] proteins and fibers,[273] HPLC method for analysis of phenolic acids and flavonoids in the seeds[274] and isolation of betacyanins (Figure 6) from the flowers.[275]

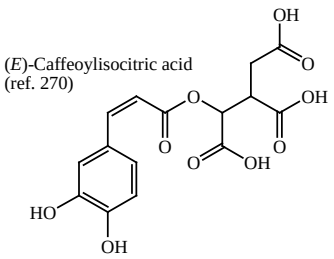


Figure 10. Active natural products isolated from *Amaranthus cruentus.*

Table 7. Biological, medicinal and other properties of *Amaranthus graecizans.*

Activity/Property	Major Findings/Reference
Analgesic	Whole plant was extracted with 90 % aqueous methanol. This extract had analgesic activity tested by three methods (hot plate, tail immersion, acetic acid induced writhing) in mice.[276]
Antibacterial	Whole plant was extracted with chloroform, ethanol and methanol. Extracts were tested against several bacteria species and the methanolic extract was most active.[186]
Antioxidant, anti-inflammatory	Whole plant was extracted with 90 % aqueous methanol. This extract had anti-inflammatory activity tested by carrageenan-induced paw edema method.[276] Whole plant was extracted with methanol and extract was fractionized with water, *n*-hexane, chloroform, ethyl acetate and n-butanol. The antioxidant capacities of extract and fractions were determined by four methods: DPPH, FRAP, FTC and phosphomolybdenum. General chemical composition was determined in this study.[277]
Hepatoprotection	Whole plant was extracted with 90 % aqueous methanol, and extract was active against isoniazid and rifampicin-induced hepatotoxicity.[278]
Enzyme inhibition	Whole plant was extracted with 90 % aqueous methanol, and extract had cholinesterase inhibition activity.[276]
Chemical composition	Aerial parts were extracted with 10 % aqueous ethanol and the general chemical composition of extract was determined.[279]

Table 8. Biological, medicinal and other properties of *Amaranthus retroflexus.*

Activity/Property	Major Findings/Reference
Allelopathy	Aqueous extract of seeds had allelopathic effect on seedlings of garden cress (*Lepidium sativum*).[269] Leaves, stems and roots were collectively extracted with water, and this extract had allelopathic effect on Barley.[287] Whole plant aqueous extract had allelopathic effect on cucumber, alfalfa, common bean and bread wheat.[288] A follow up study by the same research group that tested the allelopathic effects of aqueous extracts on cucumber and wheat, but in this case, plant organs were extracted separately.[289] Plant powder had allelopathic effect on germination of maize.[290]
Allergy	Allergens were isolated from aqueous extract of pollen, and they were tested in human patients.[291] An allergen named Polcalcin was isolated from the aqueous extract of pollen. It can be produced in *E. coli*.[292]
Antibacterial	Leaves and flowers were combinedly extracted with 70 % aqueous ethanol and extract was active against 7 bacteria species.[293]
Antioxidant, anti-inflammatory and related activities	Leaves and flowers were combinedly extracted with 70 % aqueous ethanol and the antioxidant capacity of this extract was tested by DPPH method.[293] Leaves were extracted with 70 % aqueous ethanol, and this extract had high antioxidant capacity (DPPH).[294] Leaves were extracted with 10% aqueous methanol and 10 known nerolidol derivatives (structures are presented) were isolated and tested for their antioxidant capacities (DPPH).[295]
Metals related activities	Plant was found good phytoremediator of soil contaminated with Cr^{+3}, Cd^{+2}, Cu^{+2} and Ni^{+2}.[296] Lead and zinc ions were successfully removed from wastewater, especially after treating the plants with growth promoter, citric acid.[297] Aqueous extract of leaves was used to reduce silver ions ($AgNO_3$ solution), to prepare silver nanoparticle, AgNPs, which had antifungal activity.[298]
Toxicity	Leaves were extracted with methanol-acetone-water (ratio is not indicated) and this extract was toxic only to renal cell culture.[299] Following cases of poisoning cases (renal) of livestock in Australia, aerial parts methanolic extract was prepared and analyzed. The major toxic ingredients were mainly quaternary ammonium and polyhydroxylated amines. New compounds were not reported.[300]
Chemical composition	Leaves were extracted with 10 % aqueous methanol and the extract was chromatographed, resulting the isolation and characterization of 7 new compounds that were identified as nerolidol derivatives (Figure 11).[301] A follow up study by the same research group afforded 4 new compounds from the same family, nerolidol glucoside derivatives.[302] An outstanding and comprehensive analysis of the chemical composition of the plant including a new natural product, a sphingolipid (Figure 11), has been reported.[303] Detailed composition of volatile compounds was analyzed from gases released by the plant itself, or from whole plant aqueous extract, that was subjected to vacuum distillation. New compounds were not reported.[304] Comprehensive analysis of water-soluble compounds, with special focus on carbohydrates, organic acids and phenolics was reported.[305]

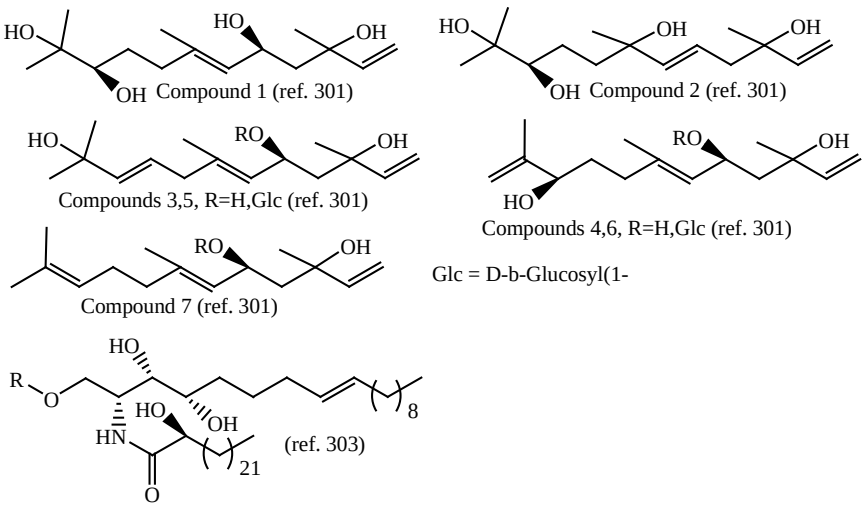


Figure 11. Active natural products isolated from *Amaranthus retroflexus.*

Table 9. Biological, medicinal and other properties of *Amaranthus spinosus.*

Activity/Property	Major Findings/Reference
Allelopathy	Aqueous extract of leaves had allelopathic effect on the growth of mustard (*Brassica campestris*) and rice (*Oryza sativa*). This activity was also observed by inhibition of peroxidase, catalase and α-amylase activity.[306]
Allergy	Pollen was isolated from flowers and extracted with water. This extract was analyzed for proteins, and some of them had allergenic and antigenic activities.[307]
Analgesic and pain related activities	Whole plant was successively extracted with petroleum ether, ethyl acetate and methanol. Extracts had analgesic activity in mice, that was detected in two tests: acetic acid induced writhing andradiant heat tail-flick.[308] Whole plant was extracted with 50 % aqueous ethanol, and this extract had analgesic activity in rats, shown by four methods, formalin-induced pain, acetic acid-induced writhing, hot plate injury and tail immersion.[309] Leaves were separately extracted with ethyl acetate, chloroform, *n*-hexane, *n*-butanol and water. Ethyl acetate extract had highest analgesic activity in several (mentioned above) tests, in rats.[310] Leaves were extracted with methanol and extract had analgesic activity (mice) proved by the four methods.[318] Methanolic leaves extract had analgesic activity in three tests (mentioned above) in mice.[334]
Antibacterial, antifungal	Leaves were extracted with 80% aqueous methanol, and extract had activity against few bacteria species. General chemical composition has been presented.[311,312] Leaves were extracted successively with petroleum ether, diethyl ether, methanol and water. All extracts were active against five fungi species.[314] Whole plant was extracted with methanol and extract was active against rust disease. Very partial general chemical composition is presented.[315]
Anticancer	Whole plant was extracted with methanol and extract was fractioned with chloroform, ethyl acetate and *n*-hexane. From the chloroform fraction, a fatty acid was isolated, and it had strong activity against HepG2 humanliver cancer cells.[316] Strangely enough, this acid is presented by authors in the title of the article as "A Novel Tetraenoic Fatty Acid". But the same three authors, published the same acid (14E,18E,22E,26E)-methyl nonacosa-14,18,22,26-tetraenoate) as "A new ester of fatty acid", one year earlier (see ref. 317).
Antidiabetic	Whole plant was extracted with methanol and extract was fractioned with chloroform, ethyl acetate and *n*-hexane. From the chloroform fraction, a new fatty acid was isolated and characterized (Figure 12). It had α-glucosidase inhibition activity.[317]
Antioxidant, anti-inflammatory	Whole plant was extracted with 50% aqueous ethanol, and this extract had anti-inflammatory (carrageenan-induced) activity in rats.[309] Leaves were separately extracted with ethyl acetate, chloroform, *n*-hexane, *n*-butanol and water. Ethyl acetate extract had highest antioxidant capacity (DPPH, H_2O_2). It had also anti-inflammatory activity against inflammations that resulted from analgesic activity tests, in rats.[310] Leaves were extracted with 80 % aqueous methanol and antioxidant (DDPH) capacity of extract was determined.[311] Leaves were extracted with methanol and extract had anti-inflammatory activity in mice, tested by carrageenan-induced inflammation.[318] Roots were successively extracted with petroleum ether, ethyl acetate and methanol. The antioxidant capacity of the three extracts was determined (FRAP, DPPH), and ethyl acetate was highest.[319] Ethyl acetate leaves extract had moderate antioxidant capacity (DPPH).[320] Antioxidant capacity of methanolic extract of leaveswas determined by four methods. Antipyretic activity of extract was tested by Brewer's yeast test in rats.[321] In this comprehensive work, leaves were extracted with 80% aqueous methanol and distilled for

	essential oil. Both products were analyzed for chemical composition, and their antioxidant capacities were determined (DPPH, H_2O_2 and enzymatic assay). Detailed presentation of chemical composition is provided.[322] Methanolic extract of seeds had high antioxidant capacity (DPPH, H_2O_2).[333] Antioxidant capacity of leaves was determined by two methods (DPPH, $ABTS^+$). General chemical composition has been presented.[335]
Brain related activities	Leaves were defatted with petroleum ether and extracted with 95% aqueous ethanol. Extract had antianxiety activity which was induced in rats by several methods.[323] An earlier study by the same group, where whole plant was extracted with methanol and extract was tested for antidepressant activity, that was induced in rats by several methods. In both studies, acute toxicity and general chemical composition were presented.[324]
Cardiovascular system related activities	Leaves were extracted with 70 % aqueous methanol. When the extract was administered to rats, adverse effects of fat increasing in the plasma of rats were recorded. But when administered with ascorbic acid, a synergetic effect was observed.[325] Whole plant aqueous extract had toxicity only in high doses in rats, but its cardioprotective effect was weak and temporary.[326]
Digestive system protection, hepatoprotection, nephroprotection, lung protection	Leaves were extracted with methanol and extract had gastroprotective (gastric erosion assay) and antidiarrheal (castor oil–induced diarrhea) activities in mice.[318] Whole plant was extracted with 50 % aqueous ethanol. This extract had activity against castor oil-induced diarrhea and ethanol-induced gastric ulcer, in mice.[327] Leaves were extracted with petroleum ether, chloroform, ethanol and water. All extracts had anti-ulcer (pylorus ligation) activity in rats, where ethanolic extract was more active than others.[328] Whole plant was extracted with 70 % aqueous methanol and extract was fractionized by ethyl acetated and water. Three animal species were administered with carbachol and treated with extract and fractions. These had bronchodilator andgut modulatoryactivities, where extract was more active than fractions.[329] Whole plant aqueous extract had diuretic activity in rats.[330,331] Whole plants was extracted with 50 % aqueous ethanol and this extract had activity against d-galactosamine/LPS-induced hepaticfailure.[332]Seeds methanolic extract had activity against hepatotoxicity associated with deltamethrin in rats.[333]
Insecticidal	Whole plant was extracted with 70% aqueous ethanol. This extract combined with the same extract of *Andrographis paniculate* were active against*Plasmodium berghei*-infected mice.[336]
Metals related activities	Leaves ethanolic extract was used to reduce Au^{+3} ions (H_4AuCl_3) to prepare gold nanoparticles, AuNP's.[337] Aqueous leaves extract was used to prepare FeO-NPs from $FeCl_3$ solution.[338]
Nutrition, toxicity	Aerial parts were successively extracted with *n*-hexane, chloroform, ethanol and water. Ethanolic extract showed toxicity in brine shrimp lethality test. Partial general chemical composition is presented. Interestingly, it is reported that none of these extracts had antibacterial activity.[313] Leaves were fed to *Clarias gariepinus* (African catfish species) as a potential protein source.[339] Consumption of aqueous extract of leaves by postpartum mothers, increased prolactin and breast milk.[340] Single report of poisoning as a result of consumption of the plant by sheep in Brazil. Various adverse physical damages were observed, but the major adverse effect was renal insufficiency.[341]
Reproductive system, sex	Roots were extracted with acetone, and extract was co-administered to male rats with acetone seeds extract of *Dolichosbiflorus*. Various adverse effects of on sex organ and enzymes were recorded.[342] Methanolic extract of leaves was co-administered with *Abrusprecatorius* extract (70 % aqueous methanol) to male rats, resulting increasing of infertility.[343] Whole plant ethanolic extract was orally administered to female rats, resulting contraceptive and abortifacient activities.[344]
Chemical composition	Analysis of whole plant methanolic extract (*n*-butanol fraction) afforded new natural product, Spinoside (Figure 12).[345] The following reports presented general chemical composition or known compounds, but they also presented uniqueness or special interest. Betacyanins and phenolics,[346] Very detailed composition with (or without) tables,[347-354] isolation of α-spinasterol from stem extract,[355] identification and quantification of quercetin in leaves extract,[356] isolation of mucilages from leaves[357] have been reported

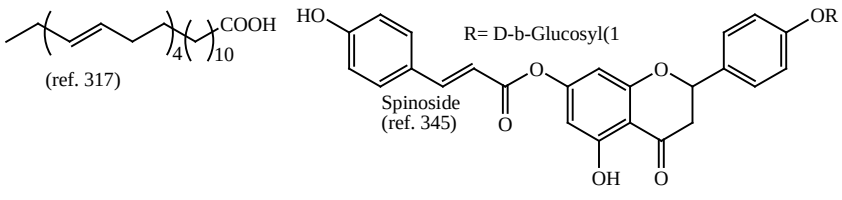


Figure 12. Active natural products isolated from *Amaranthus spinosus.*

Table 10. Biological, medicinal and other properties of *Amaranthus viridis.*

Activity/Property	Major Findings/Reference
Analgesic and pain related activities	Methanolic whole plant extract had analgesic activity in three tests (mentioned above) in mice.[334] Whole plant methanolic extract of whole plant was had antinociceptive activity tested by acetic acid-induced writhing test, hot plate test and tail immersion test in mice. Antipyretic activity was tested by yeast-induced pyrexia method in rats.[365] Whole plant methanolic extract had antinociceptive effect against acetic acid-induced gastric pain in mice.[367]
Wound healing	Methanolic extract of leaves had wound healing activity (excision, incision, dead space) in diabetic rats.[366]
Antibacterial, antifungal	Whole plant was extracted with chloroform, ethanol and methanol. Extracts were tested against several bacteria species, and methanolic extract was most active.[186] Aerial parts ethanolic extract had activity against 5 bacteria and 5 fungi species.[358] Seeds (in the title it is indicated as leaves) methanolic extract was prepared and tested against 5 bacteria species. A GC-MS analysis is presented.[359] Extract of leaves alkaloids was found active against several bacteria species.[360] Seeds, leaves or aerial parts, were separately extracted with organic solvents, and extracts were active against some bacteria species.[361-363] Leaves were separately extracted with dichloromethane, ethyl acetate and ethanol. All extracts were active against two fungi species.[364] Analysis of seed extract (70 % aqueous methanol) afforded a new lectin that was active against two fungi species.[368]
Anticancer and related activities	Analysis of seed s extract (70 % aqueous methanol) afforded a new lectin that was active against HB98 and P388D1 murine cancer cell lines.[368] Leaves and stems were combinedly extracted with 50 % aqueous ethanol. Extract had activity against 3 human leukemic cell lines. General chemical composition is presented.[369] Leaves were extracted with *n*-hexane, chloroform, methanol and water. Methanolic extract had antigenotoxic activity.[377]
Antidiabetic and related activities	Whole plant methanolic extract had antihyperglycemic effect in glucose-loaded mice.[367] Whole plant was extracted with 75 % aqueous ethanol and the extract had activity against STZ-induced diabetes in rats.[370] Whole plant or methanolic extract of leaves had activity against alloxan/STZ-induced diabetes in rats, and antihyperlipidemic activity.[371,372]
Antioxidant, anti-inflammatory and related activities	Antioxidant capacity of methanolic extract of leaves was determined by two methods (DPPH and $ABTS^{+}$). General chemical composition is presented.[335] Various parts, were separately extracted with organic solvents, and extracts were tested for antioxidant capacities (DPPH).[361-363,374,375] Leaves and stems were combinedly extracted with 50 % aqueous ethanol, and the antioxidant (DPPH) capacity of extract was determined.[369] Whole plant methanolic extract had activity against lipid peroxidation in rats.[371] Leaves were analyzed for nutrient and mineral contents, extracted with methanol, and the antioxidant capacity of this extract was determined (DPPH).[373] Alkaloid-rich leaves extract had activity against H_2O_2 damage in human erythrocytes.[376] Leaves were extracted with *n*-hexane, chloroform, methanol and water. Methanolic extract had highest antioxidant capacity (5 methods).[377] Leaves, stems and seeds were extracted with methanol and the antioxidant capacity of each extract was determined by 5 methods. Anti-inflammatory activity was tested by hyaluronidase and lipoxygenase inhibition.[378]
Neuroprotection	Aqueous extract of leaveshad activity against cyclophosphamide-induced neuro-endocrine dysfunctiontoxicity in rats.[384]
Cardiovascular system related activities	Methanolic extract of leaves had hypocholesterolemic and anti-atherosclerotic effects in rabbits. Detailed HPLC analysis of extract is presented.[379] Leaves or whole plant methanolic extract had protective effect against isoproterenol toxicity in rats.[380,381]
Hepatoprotection, nephroprotection	Aquous extract of roots had activity against ethylene glycol-induced urolithiasis in rats.[382] Whole plant methanolic extract had activity against paracetamol liver toxicity in rats. Antioxidant biomarkers concentrations are reported.[383]
Enzyme inhibition	Leaves were extracted with *n*-hexane, chloroform, methanol and water. Methanolic extract had tyrosinase inhibition activity.[377] Leaves, stems and seeds were extracted with methanol and each extract had xanthine oxidase inhibition activity.[378] Phenolics rich aqueous extract of leaves, from cultivated plants, had trypsin inhibition activity.[385]
Metals related activities	Supplementation of FYM (farmyard manure) to cultivated plants, enhanced their ability as Cd^{+2} accumulator.[389] Uptake of Ni^{+2} inhibits growth of cultivated plants.[390] Plants have high tolerance to metal (Cd^{+2}, Cr^{+3}) soil contaminations.[391] Risk assessment of metals (Cd^{+2}, Ni^{+2}, Pb^{+2}) accumulation in plants, that grow in contaminated soil and can be consumed by humans as food, been reported.[392] Aqueous extract of leaves/twigs reduced Ag^{+} ($AgNO_3$) for the preparation of silver nanoparticles, AgNPs, which had antibacterial sctivity.[393,394]
Nutrition, toxicity	Starch from this plant was modified (functional groups) for the purpose of using it as fat replacement.[395,396] Aqueous extract of leaves was not toxic to rats.[397]

Reproductive system	Aqueous extract of leaves had activity against cyclophosphamide-induced reproductive system toxicity in rats.[384] Roots powder had notable anti-menorrhagia in humanfemales aged between 16 - 45 years sufferingfrom excessive and or irregular vaginal bleeding.[386] Aqueous extract of roots had abortifacient effect in female rats.[387] Methanolic extract of leaves had estrogenic activity in female rats.[388]
Chemical composition	In addition to general chemical composition that was presented in previous cited publications, two more interesting articles did the same.[398,399] First isolation and characterization of Amasterol, an ecdysone precursor and a growth inhibitor (Figure 13).[400]

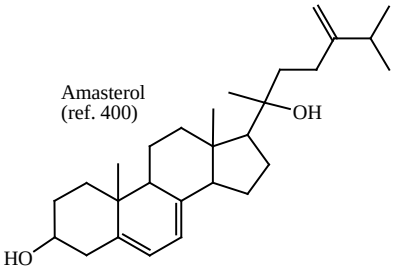


Figure 13. Active natural products isolated from *Amaranthus viridis.*

One of these notable attempts used the combination of Murashige and Skoog medium and indole acetic acid, as growth promoters. This research was performed for the aim of enhancement of active compounds production.[406]Another interesting cultivation used this plant to protect Cowpea (*Vigna unguiculata*) and Mung bean (*Vigna radiata*) crops from root rot fungi.[407]

Alternanthera pungens was very limitedly studied and most of its chemical and medicinal properties were not published (Table 4). Even its general chemical composition is still unknown and to the best of our knowledge, isolation of novel natural products from this plant has never been published.

On the contrary, the second representative of the same genus, *A. sessillis* has been well investigated and most of its properties are known and so is its chemical composition (Table 5, Figure 9). Some interesting natural products were isolated from that plant. But some of these cited reports seem confusing when the information that they include are compared. Lalitha Sree *et al*. state that leaves of this plant are highly nutritional, and it is safe to consume them.[243] Singh and her colleagues go even beyond that: they consider it a famine food plant and report its cultivation under different growth promoting conditions.[408] But Gayathri *et al*. reported three years earlier that aqueous extract of aerial parts was found hepatotoxic in mice.[409] Finally, it is important to include into toxicity considerations not only the location of the plant harvest and soil contamination levels , but seasonal variations in the possibly toxic contents of the plant also.[410]

All other 11 plants of the *Amaranthaceae* family, that grow wild in Israel and Palestine, are of the genus *Amaranthus*. Many published articles present various aspects and properties of this genus, and we presented some of these publications earlier in this article. But some of these reports may need further examination.

One of these outstanding reports was published by Noori and her colleagues.[411]They analyzed aerial parts (excluding stem) of 7 *Amaranthus* (5 of them are included in this review article) species in Iran, for flavonoid content. Even though they did not report novel compounds, this work is very detailed, comprehensive and can be very useful for interested researchers and scholars. An early review article by Suma *et al*. focuses on the allelopathy of some *Amaranthus* species.[412] It's a useful publication, but it needs updating and despite including a section of allelochemicals, no structures are presented, and it is very brief. Finally, an important work was published by Srivastava, about the nutritional potential of some cultivated wild *Amaranthus* plants.[413] The importance of this work emerges from the reported ability to cultivate these plants and to partially control their nutritional values.

The cultivation of *Amaranthus cruentus* drew notable attention from researchers and many works were published about this issue. Marin and his colleagues studied the influence of various cultivation parameters on seeds production due to their high nutritional value.[414] Kornarzynski and his colleagues reported growth promotion of this plant by electromagnetic stimulation to enhance the production of pigments (chlorophylls and carotenoids) in leaves.[415] Hlinkova and her colleagues grew this plant for two consecutive years and discovered high content of fatty acids (seeds) with notable unsaturation index (UI).[416]

As we mentioned earlier, *Amaranthus palmeri* also has not been investigated much. Its general chemical composition and its allelopathic effect on some domestic plants are partially known. Since in general it is considered a weed, its remarkable resistance to herbicides (see Figure 4 and ref. 58), like all *Amaranthus* plants, was studied.[417] Authors report that the plant has multiple resistance for 4 herbicides.

Amaranthus retroflexus is one of the most widespread *Amaranthus* plants in the reviewed region (Figure 1). It has been sufficiently studied (Table 8, Figure 11) and a remarkable number of very interesting, new natural products were isolated from this plant. In addition to the cited literature above, a special report about its chemical composition, was published by Woo.[418] This report indicated the very early scientific interest in this plant and its usefulness lies in the good graphical presentations of the chemical contents. The plant is mostly considered a weed and its resistance to herbicides is well known. Francischini *et al*. studied the resistance of this plant to acetolactate-synthase inhibitors, such as trifloxysulfuron-sodium and pyrithiobac-sodium (Figure 14),[419] and Wang *et al*. studied its resistance to thifensulfuronmethyland fomesafen (Figure 14).[420]

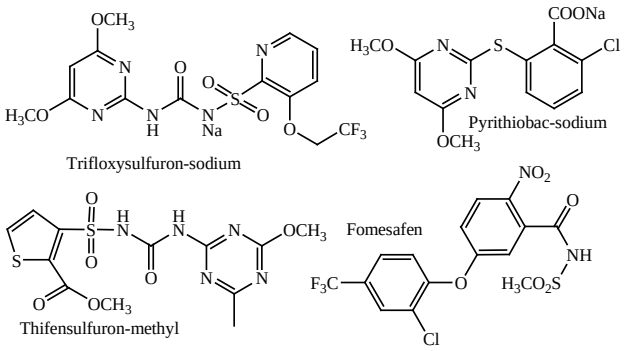


Figure 14. Herbicides that *A. retroflexus* showed resistance to (ref. 419, 420).

The toxicity of this plant goes way beyond allelopathy. An interesting study that was published by Dinu and her colleagues showed that the 50 % aqueous ethanol extract of leaves had toxic activity against mice, *Daphnia magna* (plankton) and *Triticum aestivum* (common wheat).[421] So, in addition to attempts of combating this plant with herbicides, some controlled cultivation trials were published, that aim to find the best method of preventing seeds germination,[422] including using growth promoters.[423]

The case of *Amaranthus rudis* is not quite understandable in terms of the lack of published studies about it. Its relatively not very common in the reviewed region as it grows only in the Northern parts of it but worldwide and especially in North America it is very widespread weed. This is probably the reason that the only publication, we found about it, is a study of its control by herbicides, in maize fields.[424]

Amaranthus spinosus is the most studied plant of the *Amaranthus* genus so far. Its medicinal properties and chemical composition (Table 9, Figure 12) are well known, especially the biologically active long chain alcohols. Its allelopathic effects are also known,[306,417] and so like other plants of this genus, several studies were performed about its control as a weed. One of these studies was carried out by Syahri and his colleagues where they tried a biocontrol method ofcontrolling *A. spinosus* using Mango leaf extract.[425] It should be noticed that the title of this publication stated that a "bioactive compound" was used, but actually its an extract not a pure compound.

Amaranthus viridis was also extensively (properties but very limited chemical composition) studied, but oddly enough, there are no significant reports about is allelopathy (Table 10, Figure 13). In many countries it is an invasive harmful plant to the local domestic and wild vegetation.[426] And like other plants of this genus, it has remarkable resistance to herbicides.[427] But despite that, in some regions in the world, it is cultivated mainly as a protein source.[428]

To conclude this part, we will cite two interesting reports related to *Amaranthus viridis*. First is the publication of Ratnasooriya and his colleagues about the lack of diuretic activity of hot water extract of whole plant of *Amaranthus viridis* L. in rats.[429] This work does not look obvious since generally such investigations are done to clarify, opposing, previous reports or to contradict unreliable reports. To the best of our knowledge, there are no publications that report diuretic activity of this plant, save in traditional medicine.[25]

Second, two new interesting natural products have been isolated and characterized, from *Chaetomium globosum*, a fungal endophyte isolated from *A. viridis* leaves (Figure 15).[430]

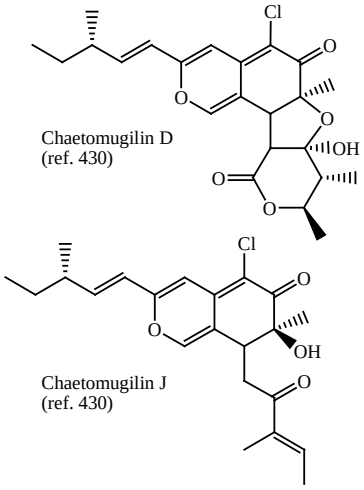


Figure 15. Novel compounds from *Chaetomium globosum*, a fungal endophyte isolated from *A. viridis* leaves.

CONCLUSIONS AND FUTURE VISION

(1) Plants of the *Amaranthaceae* plants of Israel and Palestine, possess great properties. They contain unique natural products with special structural sub-units.

(2) Medicinal potential and properties of the plants is far from being fully explored. Most of the unique natural products isolated from these plants have not been studied yet for medicinal activities and their synthetic analogues have not been prepared and studied. Some of the species of this family have either limited studies or not at all.

(3) A very thorough study for the medicinal potential of these plants is needed. Efforts are needed to isolate new natural products from all the plants of this family. It is important to test the medicinal potential of these natural products. It is highly important to prepare synthetic analogues of these natural products and intensify the research of biocontrol of some of the species.

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I grew up in an agricultural family, and most local *Amaranthaceae* plants are very common in our fields and gardens. We have always known their allelopathic effects, especially that of *Amaranthus retroflexus* (Table 8). We unrooted them when they grew close to crops, but we highly esteemed them as food for our livestock. When I started the literature search for this article, a young plant of *A. retroflexus* started growing in our garden. So, I planted very young plant of Chile pepper (*Capsicum annuum*, *Solanaceae*) near it. Both plants grew very well, the plant of *A. retroflexus* started blossoming, but the pepper plant, despite reaching impressive size, was not flowering. I added flowering promoter to both plants, and *A. retroflexus* flowered more rapidly. The pepper plants were very green but no flowers or fruits. When *A. retroflexus* was about 100 cm high, I unrooted it. Within a week, the pepper plants were flowering so impressively and now (second week of August), they are heavily loaded with fruits.

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DEVELOPMENT OF PROMISING CATHODE MATERIALS BASED ON MODIFIED SPINELS FOR Li-ION BATTERIES

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Keywords: Iron-modified lithium manganese spinal, solid phase synthesis, X-ray structural determination.

An iron-modified lithium manganese spinel, $LiFe_xNi_{0.5-x}Mn_{1.5}O_4$, where $0 \leq x \leq 0.4$, has been developed as a promising cathode material for Li-ion batteries. Conditions for obtaining single-phase cubic spinels from Li_2CO_3, Mn_2O_3, Ni_2O_3 and $Fe_2O_{3\ as}$ starting materials have been optimized.

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INTRODUCTION

Modern development in the field of chemical energy and power sources is associated with elaboration of various new materials. Application of these allows to decrease weight and dimensions of power sources, increase their energy capacity, capability and resourcefulness. Lithium-ion batteries (LIB) are now ubiquitous. Recently they found application in electric and hybrid vehicles.[1]

Lithium rich compounds represent a promising cathode material of Li-ion accumulators due to their valuable electrochemical properties and represent cathode material of the next generation high-performance lithium-ion batteries.[2,3] These compounds are of great interest mostly because of the high capacity exceeding 250 mAh g^{-1}. However, a number of disadvantages, such as voltage drop caused by unwanted phase transformations during cycling, as well as low operational performances still limit their application. Improved cycling stability can be achieved by cathode materials doping (modification). Regarding costs and raw materials, Fe-Mn-based systems are economically attractive cathodes for LIB containing Fe as a cheap promising alternative to commercial $LiCoO_2$ and $LiMn_2O_4$.

The goal of the present work was to develop promising cathode material based on Fe modified Li-manganese spinel $LiMn_2O_4$, including optimalization of preparation conditions for $LiFe_xNi_{0.5-x}Mn_{1.5}O_4$ type single-phase, homogeneous, nanostructured cubic spinels as cathode materials for LIBs.

EXPERIMENTAL

The properties of the synthesized samples were studied using a Paulik-Paulik-Erdey type derivatograph (MOM, Hungary) with simultaneous recording of temperature (T) and weight loss (TG) curves, as well as the corresponding differential curves (DTG) and (DTA) at heating rate of 10˚ min^{-1}. X-ray diffraction patterns of the synthesized samples were recorded on DRON-3M type diffractometer with Cu-K_α radiation in the range $2\theta = 10^\circ$- 60°. The detector speed was 2° min^{-1}. Chemical analyses of the samples were implemented by atomic absorption method with Perkin-Elmer AAnalyst 200 atomic absorption spectrometer. Three methods were tested to obtain single phase $LiFe_xNi_{0.5-x}Mn_{1.5}O_4$ ($0 \leq x \leq 0,4$) samples:

Method 1. Initially, the Li_2CO_3, Mn_2O_3, Ni_2O_3 and Fe_2O_3, were mixed in a corundum crucible in necessary amounts to obtain samples of given composition, and the mixture was placed in a cold electric furnace. After heating to 700 °C, the crucible was cooled, the heat-treated mixture was thoroughly mixed and again placed into the furnace for 1 h at 700 ˚C. The mixing process was repeated, and the mixture was placed again into the oven for 1 h at 700 °C. The $LiFe_{0.3}Ni_{0.2}Mn_{1.5}O_4$ (sample No. 3**)** and $LiFe_{0.4}Ni_{0.1}Mn_{1.5}O_4$ **(**sample No. 4) were prepared in this way.

Method 2. A crucible with carefully mixed starting components was placed into an electric furnace. The sample was heated for 5 h at 700 °C and then cooled in the open air to room temperature. As a result, samples No. 2 and No. 5 with composition $LiFe_{0.3}Ni_{0.2}Mn_{1.5}O_4$ and $LiFe_{0.4}Ni_{0.1}Mn_{1.5}O_4$, respectively, were obtained.

Method 3. (Melting-saturation method) At the first stage of synthesis, the mixture of initial reagents was heated at 180 °C for 2.5 h, then the heating was followed at 700 °C for 5 h. In this case sample No.1, $LiFe_{0.3}Ni_{0.2}Mn_{1.5}O_4$, was obtained.

RESULTS

The results X-ray diffraction phase analysis studies are presented in Table 1.

The sample No. 1, $LiFe_{0.3}Ni_{0.2}Mn_{1.5}O_4$, obtained by melting-saturation method fits to the lithium manganese spinel $LiMn_2O_4$ (ASTM-736) card. Splitting of peaks 241 and 237 could be observed due to doping elements in the structure. $LiFe_{0.3}Ni_{0.2}Mn_{1.5}O_4$ (No. 2) and $LiFe_{0.3}Ni_{0.2}Mn_{1.5}O_4$ (No. 3) obtained by continuous and stepwise heat treatment at 700 °C (methods 2 and 1), respectively, are single phase spinels.

Table 1. Results of x-ray phase and x-ray structural studies of synthesized cathode materials of given composition for Li - ion batteries.

Sample 1 $LiFe_{0.3}Ni_{0.2}Mn_{1.5}O_4$		**Sample 2** $LiFe_{0.3}Ni_{0.2}Mn_{1.5}O_4$		**Sample 3** $LiFe_{0.3}Ni_{0.2}Mn_{1.5}O_4$		**Sample 4** $LiFe_{0.4}Ni_{0.1}Mn_{1.5}O_4$		**Sample 5** $LiFe_{0.4}Ni_{0.1}Mn_{1.5}O$	
d_o/n	I/I_0	d_o/n	I/I_0	d_o/n	I/I_0	d_o/n	I/I_0	d_o/n	I/I_0
4.73	36	4.73	53	4.73	38	4.67	55	4.64	92
-	-	-	-	-	-	2.71	5	-	-
-	-	-	-	-	-	2.59	30	-	-
2.48	100	2.48	100	2.48	100	2.46	92	2.46	89
2.41	10	-	-	-	-	-	-	-	-
2.37	18	2.37	20	2.37	21	2.35	18	2.35	24
-	-	-	-	-	-	2.08	26	-	-
2.06	77	2.06	67	2.06	74	2.04	100	2.04	100
1.88	11	1.88	9	1.88	9	1.87	18	1.87	16
-	-	1.60	18	-	-	-	-	-	-
1.58	23	1.58	22	1.58	19	1.56	26	1.56	32
a=0.824 nm		*a*=0.824 nm		*a*=0.824 nm		*a*=0.816 nm		*a*=0.816 nm	

$LiFe_{0.3}Ni_{0.2}Mn_{1.5}O_4$ (No. 2) and $LiFe_{0.3}Ni_{0.2}Mn_{1.5}O_4$ (No. 3) obtained by continuous and stepwise heat treatment at 700 °C (methods 2 and 1), respectively, are single phase spinels. Sample No. 4, $LiFe_{0.4}Ni_{0.1}Mn_{1.5}O_4$, obtained by method 1, mainly contains $LiMn_2O_4$, and in addition, the rudiments of $NiMn_2O_4$ (ASTM-1-1110) can also observed. Sample No. 5, $LiFe_{0.4}Ni_{0.1}Mn_{1.5}O_4$, obtained by method 2, is a single-phase spinel, other phases could not be detected.

CONCLUSION

Several $LiFe_xNi_{0.5-x}Mn_{1.5}O_4$, where $0 \leq x \leq 0.4$ composites as promising cathode materials for Li-ion batteries have been prepared via solid-phase synthesis methods.

The conditions to obtain single-phase samples of cubic spinels from Li_2CO_3, Mn_2O_3, Ni_2O_3 and Fe_2O_3 have been optimized.

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SYNTHESIS, THERMAL STABILITY AND KINETIC STUDIES OF COPPER(II) AND COBALT(II) COMPLEXES DERIVED FROM 4-AMINOBENZOHYDRAZIDE AND 2-MERCAPTOBENZOTHIAZOLE

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Keywords: Co(II), Cu(II) complexes, XRD, thermogravimetry, thermal stability.

Complexes of divalent transition metal ions Cu(II) and Co(II) of the formula [M(ABZH)(MBTH)$Cl_2(H_2O)_2$], (M= Cu(II) and Co(II), ABZH=4-Aminobenzohydrazide (L_1) and MBTH = 2-mercaptobenzthiazole (L_2)) have been synthesized and characterized. The structure of the two compounds has been assigned based on elemental analysis, electronic spectral, FT-IR, magnetic measurements and XRD. The thermal properties of copper(II) and cobalt(II) metal complexes in dynamic air have been analyzed via thermogravimetry (TG) and differential thermogravimetry(DTG). The kinetic analyses of the thermal decomposition for the two compounds were calculated by the Coats-Redfern and Horowitz-Metzger methods. The obtained kinetic parameters display the kinetic compensation effect.

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INTRODUCTION

The coordination complexes comprise of a central ion or atom, which is usually metallic, and a surrounding array of ions or bound molecules, that are in turn known as complexing agents or ligands.[1,2] Many transition metals for example, copper(II) and cobalt(II) form coordination compounds. The name coordination indicates the coordinate covalent bonds between the ligands and the central ion or atom in the complexes. Cu(II), Co(II) and other transition metals mainly occur in solution as coordination compounds.[3] This class of complexes is useful in a wide variety of ways such as in bio-inorganic chemistry, analysis, homogeneous catalysis and many other applications. Copper and cobalt are metals with very high thermal and electrical conductivity, form complex ions, alloys, and has natural properties that destroy a wide range of microorganisms and they are used many applications.[4-6] Chemistry of heterocyclic complexes is a developing field of biology and chemistry because of many applications of the organic complexes of heterocyclic rings in medicine, pharmacy, agriculture and other fields. Anthranilic acid (4-aminobenzoic acid) is a compound, in which carboxyl group and amino are bounded to aromatic ring and its derivatives are known to have biological activity, additionally it has many applications such as used in dyes, corrosion inhibitors and for the synthesis of compounds, fluorescent and radio protective properties.[7-9] Moreover, in recent years, 4-aminobenzoic acid have attracted interest as ligand in transition metal compounds, which is apparent by many publications.[10,11] 2-Mercaptobenzothiazoles have been used as bactericide, fungicide and herbicide in agriculture, as antimicrobial agents[12,13] and also having interesting biological activities, it finds an important role in industrial and pharmaceutical applications.[14-16]

Stability of complexes in aqueous solution are indicated by its Gibbs free energy, standard electrode potential, rate constant or activation energy for substitution reactions and bond dissociation energy. The thermodynamic stability of compounds indicates its propensity to exist under equilibrium conditions. Although there are large number of studies of thermal analysis on Schiff base metal compounds, few papers have been published on calculation of the thermodynamic and kinetic parameters of their decomposition.[17,18]

EXPERIMENTAL

Material and methods

High purity 4-aminobenzoic acid, 2-mercaptobenzthiazole and hydrazine hydrate were supplied by Merck and Sigma Aldrich. $CuCl_2.2H_2O$ and $CoCl_2.6H_2O$ were of AR grade.

Synthesis of 4-aminobenzohydrazide(ABZH) ligand (1)

4-Aminobenzoic acid (1.4 g, 1mmol) was dissolved in distilled water (30 mL) in a 250 mL conical flask, then 0.5 ml of hydrazine hydrate was added to conical flask with stirring and the mixture was refluxed for 14 h. After cooling of the mixture, the white product was filtrated, washed with ethanol and dried under vacuum at room temperature overnight. M.p.: 218 °C. The FT-IR spectral data displayed absorption at (1628 cm^{-1}, for $\nu_{C=O}$), (3034 cm^{-1}, for ν_{C-H}, aromatic), (1560 cm^{-1}, for $\nu_{C=C,Ar}$) and (3428-3236 cm^{-1} for ν_{NHNH2}).

Synthesis of copper(II) and cobalt(II) complexes

Synthesis of the mixed ligand complexes of Cu(II) and Co(II) with 4-aminobenzohydrazide (**L_1**) and 2-mercaptobenzthiazole (**L_2**) follows the same procedure.

Table 1. Pysical properties of the complexes.

Compound	Mol. formula (M.Wt)	Color	Found (Calcd. %)				Mp. °C
			C	H	N	S	
[Cu(ABZH)(MBTH)$Cl_2(H_2O)_2$]	$C_{14}H_{18}N_4S_2CuCl_2O_3$	Light	35.75	3.92	11.83	14.02	252
	488.92	brown	34.39	3.71	11.46	13.11	
[Co(ABZH)(MBTH)$Cl_2(H_2O)_2$]	$C_{14}H_{18}N_4S_2CoCl_2O_3$	Dark	35.04	3.98	11.95	13.78	226
	484.30	green	34.71	3.75	11.57	13.23	

Synthesis of [Cu(ABZH)(MBTH)$Cl_2(H_2O)_2$] is typical. An ethanolic solution (20 mL) of **L_1** (1mmol) was added to a hot ethanolic solution (15 mL) of $CuCl_2.2H_2O$ (1.74 g, 1mmol) and to it an ethanolic solution (20 mL) of **L_2** (1.70 g, 1mmol) was added dropwise. The resultant product was stirred for 30 min and filtered. Light-brown precipitate was collected, washed with ethanol, and then dried over P_2O_5.

Physical measurements for complexes

Analysis of carbon, hydrogen, nitrogen and sulphur were carried out by using Analyischer Funktions test. Details of physical measurements have been reported earlier.[19]

RESULTS AND DISCUSSION

The 4-aminobenzohydrazide ligand was synthesized by the substitution reaction of 4-aminobenzoic acid and hydrazine hydrate, in presence of the ethanol as a solvent**.** The prepared two complexes were found to react in molar ratio; 1:1:1, metal:ABZH:MBTH. The copper(II) and cobalt(II) complexes are air stable. The syntheses of the two compounds are supported by the elemental analysis and melting points (Table 1).

FT-IR results

The Fourier-transform infrared spectroscopy recorded absorption at (1628 cm^{-1}, for $\nu_{C=O}$), (3034 cm^{-1}, for $\nu_{C\text{-}H,Ar}$), (1560 cm^{-1}, for $\nu_{C=C,Ar}$.) and (3428-3236 cm^{-1} for ν_{NHNH2}) (Figure 1). The FT-IR spectrum for 4-aminobenzohydrazide displays the stretching vibration at 3210-3400 cm^{-1} for asymmetric and symmetric ($NHNH_2$) and evanescence band at 1685 cm^{-1}, which belong to stretching vibration, of CO group of ester.[20] The MBTH ligand consists of three centers capable of chelation either to the two sulfur atoms or to one of the sulfurs and the nitrogen atom and appears to be in the range 3148-3170 cm^{-1}. Absorption shown at 764, 766 cm^{-1} and 1634, 1638 cm^{-1} for $\nu_{C\text{-}S}$ and $\nu_{C=N}$ by cobalt (II) and copper(II) compounds, respectively, indicated that the metal ions are coordinated to one amino and the sulfur centre.[21] Furthermore, the bands found in the region of 3196-3204 cm^{-1} are due to the ν_{OH} stretching vibrations of the coordinated H_2O for both the complexes. M-O and M-N bonding are demonstrated by the presence of a band at 539-548 cm^{-1} and 436-442 cm^{-1} regions, respectively.

UV spectra and magnetic measurements

The UV spectra of the cobalt(II) and copper(II) complexes were determined in DMSO solution. The band observed in the case of two ternary compounds of 4-aminobenzohydrazide and 2-mercaptobenzthiazole the region of 238-242 nm may be assigned to a ($\pi\rightarrow\pi^*$) transition due to molecular orbital energy levels originating, in the ABZH ligand. For the cobalt(II) and copper(II) compounds another band is recorded in the region of 325-329 nm and has been ascribed to an intra-ligand transition for the MBTH.

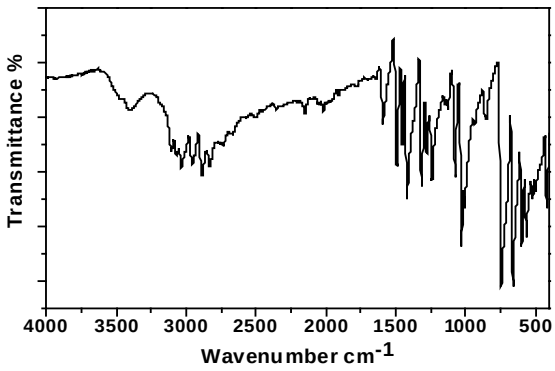

Figure 1. FT-IR spectrum of the Cu(II) complex.

In Co(II) compound a *d-d* band was observed in the 505 nm. The magnetic moment value for this complex was found to be 4.23 BM, which is in agreement with the octahedral environment around Co(II) ion.[22] The magnetic moment value of 1.87 B.M for the Cu(II) compound indicates a octacoordination around copper(II) and a *d-d* transition band showed at 475 nm.[23] The suggested structures for ABZH mixed ligand compounds are shown in Figure 2 and 3.

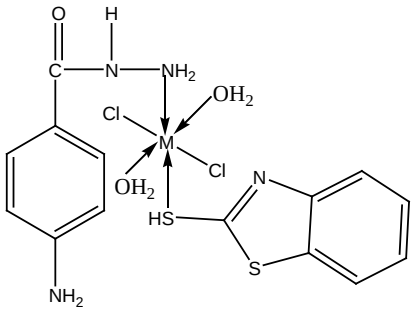

Figure 2. Structure of the two complexes; M= Cu(II) or Co(II).

The thermal decomposition details of the copper(II) and cobalt(II) complexes are presented in Table 2. The two compounds are thermally stable and their, thermal decompositions are multi-stage processes. The compounds were subjected to a TG analysis from (50-700 °C) in dynamic air.

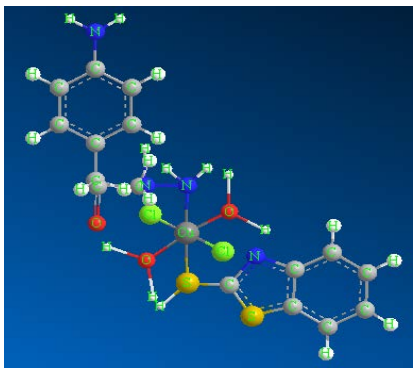

Figure 3. A proposed view of coordination round Cu(II).

The thermogravimetry (TG, DTG and DTA) curves of the Cu(II) complex are given in Figure 4. They showed that the thermal decomposition of the compound involves four stages. The first stage is a dehydration process happening in the temperature range of 48 to 145 ºC. The mass loss (calcd. 7.36 %, found 7.19 %) indicates a loss of $2H_2O$. For this step (DTG minimum at 89 ºC) an endothermic peak is showed in the DTA curve at 92 ºC.

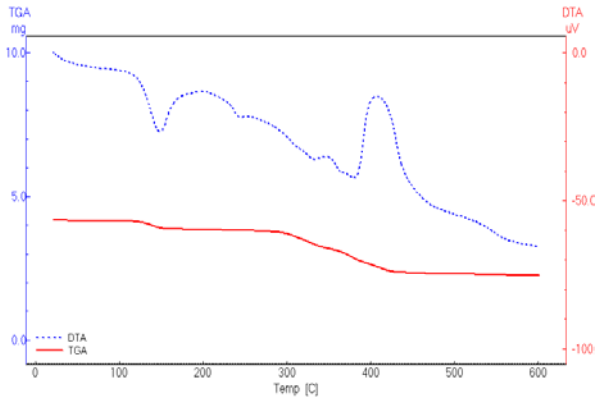

Figure 4. TG, DTG and DTA of the Copper(II) complex.

The second, third and fourth steps (147-700 ºC) represents a mass loss of 77.62 % and appears in the DTG curve as three peaks at 182, 347 and 438 ºC with the corresponding three exothermic peaks in DTA curve at 184, 349 and 440 ºC. At about 700 ºC, the final stable residue is copper oxide. CuO. The theoretical mass loss should be 16.26 %, the found one was 15.94 %.

A four-steps decomposition was observed in the thermo-gravimetric curve of the Co(II) complex. This occurs in the temperature ranges 45-123, 125-250, 252-410 and 412-700 ºC. The first step in the TG curve shows a loss amounting of 7.44 % corresponds to the release of the $2H_2O$ molecules. For this step a differential thermogravimetry (DTG) peak at 85 ºC and an exothermic peak at the position at 87 ºC in DTA trace were recorded. The 2nd, 3rd and 4th steps agree to the decomposition of the rest of ligands. It is manifested on the DTG curve as three peaks at 174, 390 and 496 ºC and the DTA trace furnishes an exothermic DTA effect at 176, 392 and 498 ºC. The final stable residue is CoO (calcd.15.47 %, found 14.89 %).

Kinetic analysis for the compounds

Non-isothermal kinetic studies, of the two compounds were accomplished applying two different procedures, the Coats-Redfern[24] and the Horowitz-Metzger[25] methods (Figures 5-10). The kinetic parameters were calculated given by the two equations and are listed in Table 3.

Table 2. Thermal decomposition data for two complexes.

Complex	Step	TG/DTG			Mass loss, %
		T_i	T_m	T_f	
1	1st	48	89	145	7.36
	2nd	147	182	243	14.50
	3rd	245	347	380	30.12
	4th	382	438	700	31.92
2	1st	45	85	123	7.44
	2nd	125	174	250	13.63
	3rd	252	390	410	31.20
	4th	412	496	700	32.54

Table 3. Kinetic parameters for the two compounds.

Metal	Step	Coats-Redfern equation			
		r	*n*	*E*	*Z*
Cu(II)	1st	0.9984	0.00	52.15	10.70×10^2
		0.9979	0.33	57.00	11.45×10^2
		0.9977	0.50	60.01	12.06×10^2
		0.9976	0.66	62.26	12.52×10^2
		0.9971	1.00	67.86	13.65×10^2
		0.9955	2.00	86.53	17.51×10^2
Co(II)	1st	0.9995	0.00	34.23	6.91×10^2
		1.0000	0.33	50.40	10.29×10^2
		0.9998	0.50	60.86	12.23×10^2
		0.9997	0.66	71.32	14.35×10^2
		0.9987	1.00	97.94	19.72×10^2
		0.9957	2.00	116.49	23.42×10^2

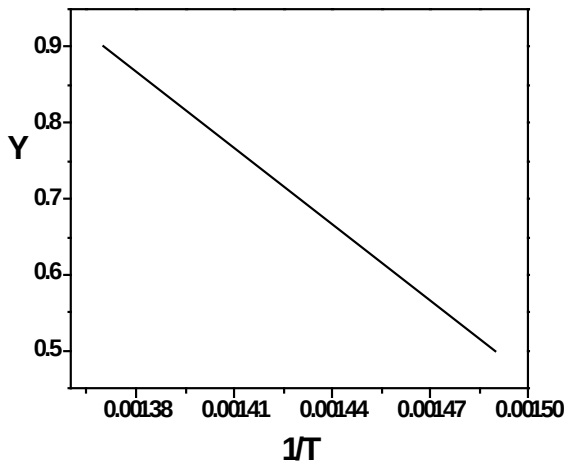

Figure 5. Coats-Redfern plots for $[Co(ABZH)(MBTH)Cl_2(H_2O)_2]$.

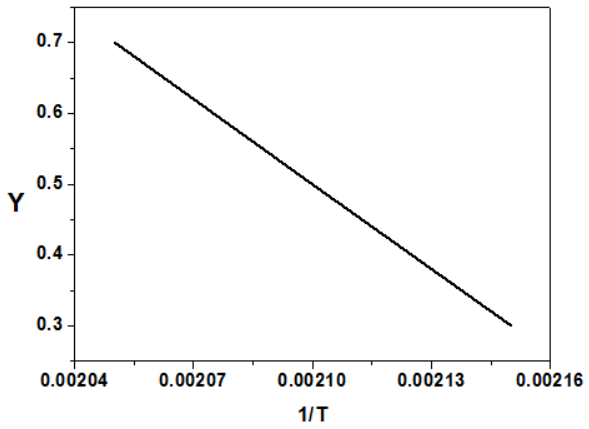

Figure 6. Horowitz-Metzger plots for [Co(ABZH)(MBTH)Cl_2 $(H_2O)_2$].

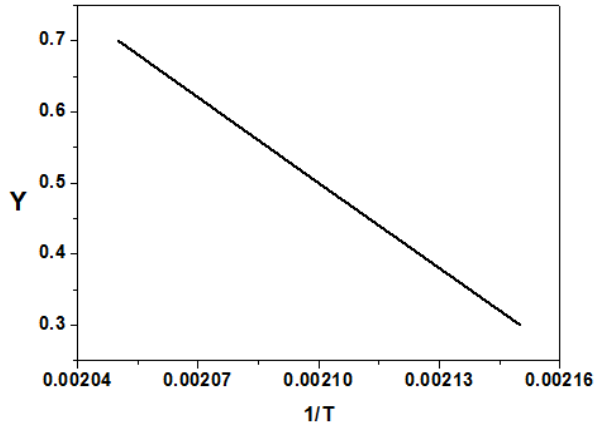

Figure 7. Coats-Redfern plots for [Cu(ABZH)(MBTH)$Cl_2(H_2O)_2$].

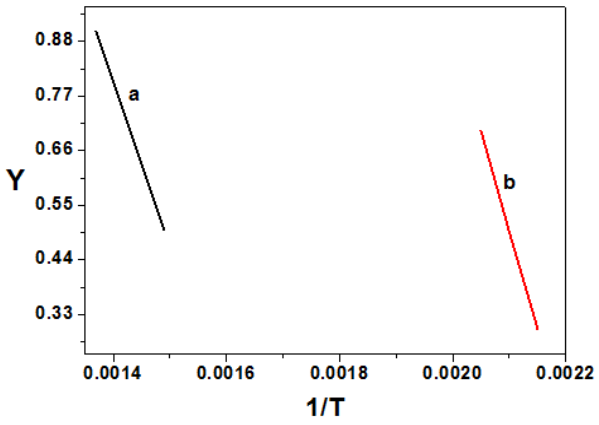

Figure 8. Horowitz-Metzger plots for the compound [Cu(ABZH)(MBTH)$Cl_2(H_2O)_2$].

Thermodynamic parameters for the compounds

The activation variables ΔH^*, ΔS^* and ΔG^*, for the decomposition steps of the two compounds are listed in Table 4. Negative ΔS^* numbers of the both steps of decomposition of the compounds suggest that the activated compound is more highly ordered by than the reactants and the reaction rates are low than normal.[26] The more ordered nature is due to the polarization of bonds in the activated complex, which happens to be charge transfer electronic transition (CTET).[27] The difference in of ΔG^* and ΔH^*

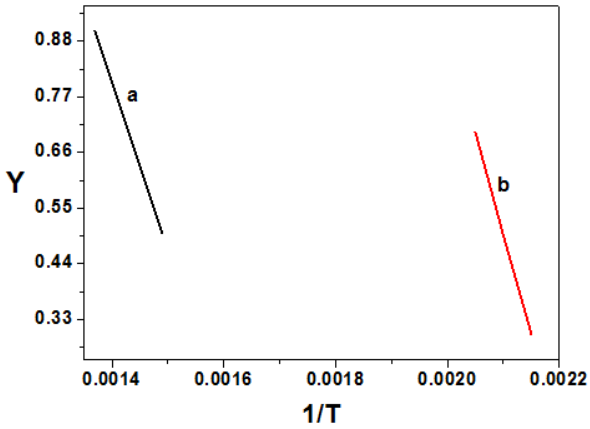

Figure 9. Coats-Redfern plots for (a) the Co(II) complex and (b) the Cu(II) complex.

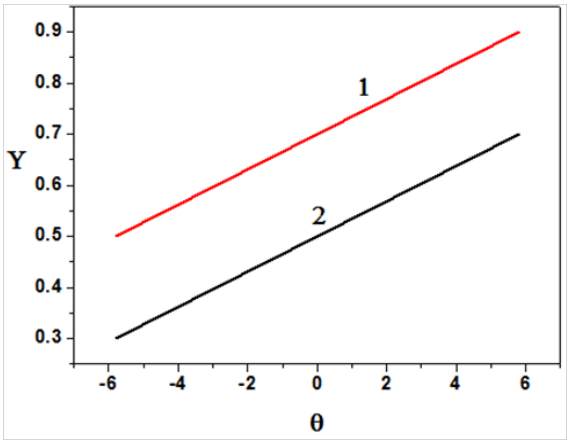

Figure 10. Horowitz-Metzger plots for (1) the Co(II) complex and (2) the Cu(II) complex.

of the two complexes indicate to the effect of the suggested structure of the Cu(II) or Co(II) complexes on their thermal stability.[28] The positive numbers of ΔG^* indicate the decomposition reaction is not spontaneous. The stability of metal complexes is decided by two different considerations such as thermodynamic and kinetic stabilities.

Table 4. Thermodynamic parameters for the compounds.

Metal	Step	ΔS^*	ΔH^*	ΔG^*
Cu(II)	1st	-190.69	48.24	137.86
		-190.12	53.09	142.44
		-189.69	56.10	145.25
		-189.38	58.35	147.35
		-188.66	63.95	152.62
		-186.59	82.62	170.31
Co(II)	1st	-197.31	28.63	161.41
		-194.00	55.80	175.36
		-192.56	55.26	184.85
		-191.23	65.72	194.42
		-188.59	92.34	219.26
		-187.16	110.89	236.84

ΔH^*, ΔG^* are in kJ mol^{-1} and ΔS^* in kJ mol^{-1} K^{-1}

Decomposition rate and stabilities of the two complexes

The decomposition rates of the two compounds in dynamic air have been deduced from plotting α (fraction decomposition) against temperature of decomposition for

the first step as depicted in Figure 11. Taking the temperature of maximum decomposition rate (DTG maximum temperature) as a criterion, the stabilities of the complexes could be correlated. Accordingly, in the following are the decomposition rate and the stability orders of the two compounds (the decomposition rate is based on the temperature of the inflection point and the stability order on the initial temperature of the first step of the anhydrous compounds).

Co(II) complex (685°C) > Cu(II) complex(475°C) (Decomposition rate).

Cu(II) complex (450°C) > Co(II) (650°C) (sequence of stability).

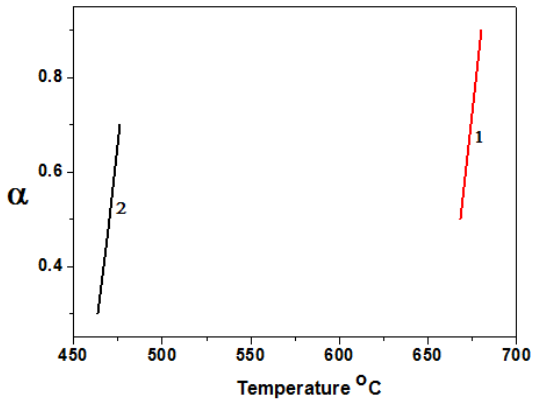

Figure 11. Fraction decomposed (α) and temperature plots of the (1) Cobalt(II) and(2) Copper(II)complexes.

The steepness of the curves (α against temperature) indicates that the copper(II) and cobalt(II) compounds decompose by different decomposition rates depending on the respective metal ion. The observed differences in the thermal stability of the two compounds for the same ligand may be ascribed also to the nature of the central metal ion. The effective electric field strength *F** of the metal ion may affect the stabilities of the compounds. *F** can be calculated from the relation

$$F^* = Z_{eff}/r_c^2 \qquad (1)$$

where Z_{eff} and r_c are effective charge and ionic radius of the cation present, respectively.[29,30] Increase of *F** of the metal ion leads to an increase in thermal stability of the compounds. For their mixed ligand complexes with 4-aminobenzohydrazide and 2-mercaptobenzthiazole in dynamic air, the *F** values run in the direction Cu(II) complex > Co(II) complex which, is in good correspond with the Irving-Williams series.[29,30]

Kinetic compensation effect

The kinetic compensation effect (KCE), means that the reduction in rate, which is predictable from an increase in activation energy does not show for the given set of reactions. KCE, which was noted in many non iso-thermal methods is seen to be valid here. It was recorded that for the particular process, the value of energy (*E*) conforms to a linear relationship to ln *Z* (Eqn. 2), where *E* = energy, *a* and *b* are constants.

$$\ln Z = aE + b \qquad (2)$$

The application of this equation to the Co(II) and Cu(II) mixed ligand compounds are shown Figures 12 and 13.

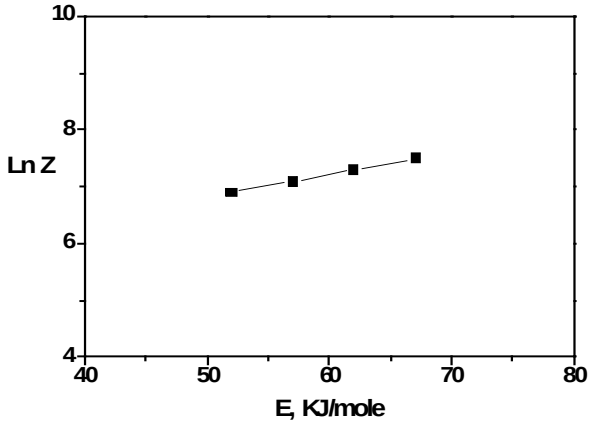

Figure 12. Kinetic compensation effect in Cu(II) complex.

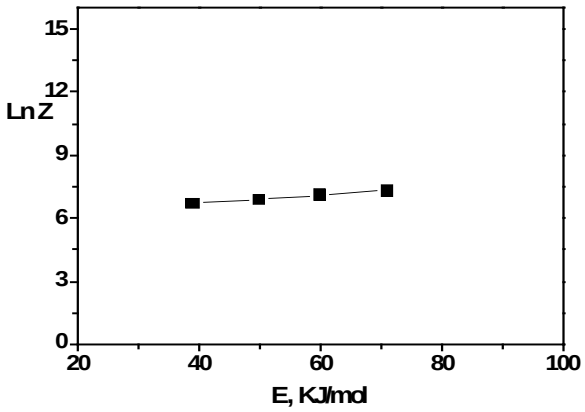

Figure 13. Kinetic compensation effect in Co(II) complex.

XRD for the copper(II) and cobalt(II) complexes

The XRD patterns were recorded for two the complexes. The crystal details for all compounds correspond to the crystal system triclinic for copper(II) complex and monoclinic system for cobalt(II) complex. XRD of compounds are shown in Figure 14 and 15.

Table 5. XRD data of the two complexes.

Parameters	Co complex	Cu complex
C.S	monoclinic	triclinic
a (Å)	7.433	6.126
b (Å)	8.528	10.745
c (Å)	3.675	5.981
α (°)	90.00	82.31
β (°)	99.28	107.34
γ (°)	90.00	102.58
V, (Å^3)	229.9	365.4

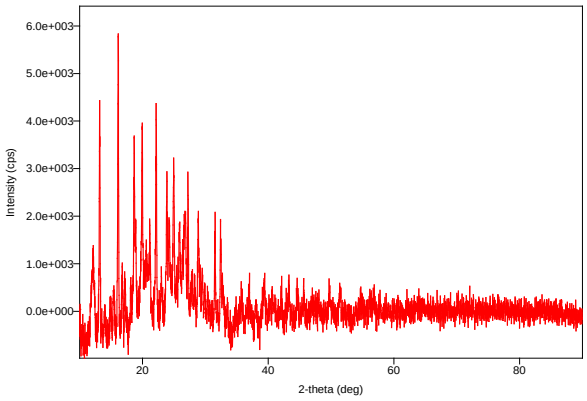

Figure 14. XRD of Cu(II) complex.

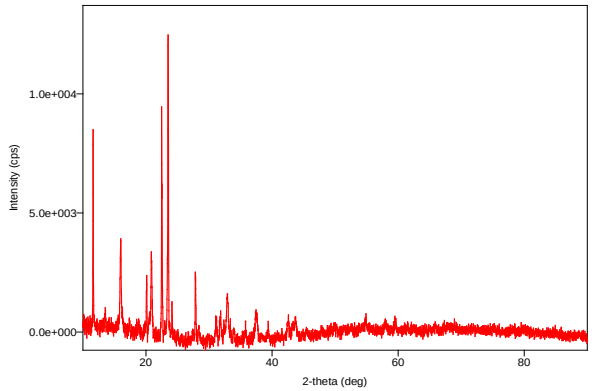

Figure 15. XRD of Co(II) complex,

Scherrer's equation (eqn. 2) was used to appreciate the particle size, of the two compounds.

$$D = K\lambda/\beta\cos\theta \qquad (3)$$

The elementary cell parameters for the Cu and Co-compounds are listed in Table 5.

CONCLUSION

In this article we report on the kinetics, of the thermal decompositionand the accompanying compensation effect; for a Cu(II) and Co(II), ABZH and MBTH mixed ligand complexes. Also, it is supposed that dehydration of the compounds including water happen within an active reaction interface. The (KCE) is excellent for the thermal decomposition of the two compounds indicating the effect of the change of compound mass on the evaluated values of activation energy and preexponential factor. The copper(II) and cobalt(II) complexes are found to possess a triclinic and monoclinic crystal system, respectively.

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SYNTHESIS, MOLECULAR DOCKING AND ANTI-INFLAMMATORY ACTIVITY 2,4-DIMETHYL-*N*-(2-ARYL)-3-FURAMIDES

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Keywords: Furamides, acylation, molecular docking, anti-inflammatory activity.

2,4-Dimethyl-*N*-aryl-3-furamides were synthesized by the reaction of 2,4-dimethyl-furan-3-carbonyl chloride with aromatic amines in dry dioxane in the presence of triethylamine. The structures of the obtained substances were confirmed by ^{1}H NMR spectroscopy and elemental analysis. The synthesized compounds were preselected via molecular docking to be tested for their anti-inflammatory activity. The anti-inflammatory effect of the prepared compounds was investigated applying the carrageenan-induced paw edema model. The results have shown that the some novel furamides demonstrated considerable anti-inflammatory effect.

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INTRODUCTION

Inflammation is a protective attempt by the organism to remove the injurious stimuli and to initiate the healing. This process may vary from a localized to a generalized response characterized by the accumulation of fluids and leukocytes leading to edema and pain.[1] The non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most common therapeutic groups of agents used worldwide for the treatment of inflammation. However, NSAIDs have high incidence of serious side effects.[2] Although drug treatment has been improved to some extent yet, it is still a challenge for the pharmaceutical chemists to explore the more effective and potent therapeutic agents to treat inflammation and reduce the signs and symptoms of acute inflammation and chronic inflammatory diseases.[3]

Furan derivatives are an important class of heterocyclic compounds that possess important biological properties. During last few decades a considerable amount of attention has been focussed on synthesis of furan derivatives and screening them for different pharmacological activities. Amides of furan-3-carboxic acids are also promising compounds with a broad spectrum of biological activity. Fenfuram, furcarbanil and methfuroxam are used as agrochemical fungicides. About of the activity of analogues of these drugs was reported in the works.[4] Furan-3-carboxamides exhibit antiproliferative[5] activities also. They are inhibitors of carboxylesterase,[6] glycosidase,[7] β-galactosidase[7] and HCV NS5B Polymerase.[8]

In a previous work[9] we have described the synthesis and anti-inflammatory activities of some 2,5-dimethyl-3-furan-3-carboxamides and 5-aryl-2-methyl-3-furan-3-carboxamides. In this article which is the part of our project on of biologically active heterocycles[10-23] we describe synthesis, molecular docking and anti-inflammatory activities of 2,4-dimethyl-*N*-(2-aryl)-3-furamides.

EXPERIMENTAL

All chemicals were of analytical grade and commercially available. All reagents and solvents were used without further purification and drying. Ibuprofen was purchased from a medical store.

All the melting points were determined in an open capillary and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Mercury 400 (400 MHz for ^{1}H) instrument with TMS or deuterated solvent as an internal reference. Satisfactory elemental analyses were obtained for new compounds (C±0.17, H±0.21, N±0.19).

Syntheses

Ethyl 2,4-dimethyl-3-furoate (3)

To a solution of 6.5 g (0.05 mol) of ethyl acetoacetate (**1**), in 100 mL of 0.5 M alcoholic solution of sodium ethoxide, was added a solution of 9.05 g (0.05 mol) of dimethyl-2-propynylsulfonium bromide in 100 mL of ethanol. The mixture was refluxed for 6-7 h and the ethanol was distilled off in a water bath. To the residue was added 200 mL of ether and the suspension was filtered. The ether was distilled off from the filtrate under atmospheric pressure. The residue was distilled at 130–132 ºC/20 Torr.

2,4-Dimethyl-3-furoic acid (4)

To a solution of 8.5 g (0.05 mol) of **3** in 30 mL of alcohol was added a solution of 4.5 g (0.08 mol) of potassium hydroxide in 20 mL of alcohol. The mixture was refluxed for 30 min, then dissolved in an equal amount of water and

acidified with diluted (1:1) hydrochloric acid. The precipitate was filtered off, washed with water and recrystallized. Yield 82 %, m.p. 119–120 °C (m.p. [d1] 118–119 °C).[24]

2,4-Dimethyl-3-furoyl chloride(5)

A mixture of 2.8 g (0.02 mol) of **4** and 3 mL of thionyl chloride in 50 mL of dry benzene was refluxed until complete dissolution of the acid. After cooling, the benzene was distilled off and the residue was distilled in vacuum at 115–118 ºC /20 Torr.

General procedure for preparation of 2,4-dimethyl-N-(2-aryl)-3-furamides (7a-n)

To a mixture of 0.01 mol of corresponding amine **6a-n** and 0.12 mL of triethylamine in 10 mL of dry dioxane a solution of 1.58 g (0.01 mol) of **5** in 10 mL of dry dioxane was added with stirring. The reaction mixture was left overnight and then was poured into water. The formed precipitate was filtered and recrystallized from alcohol.

2,4-Dimethyl-N-(2-methylphenyl)-3-furamide (7a)

Yield 83 %, m.p. 131–132 °C. ^{1}H NMR (400 MHz, DMSO) δ = 9.02 (s, 1H, NH), 7.45 (d, *J* = 8.1 Hz, 1H, C_6H_4), 7.26 – 7.04 (m, 4H, C_6H_4 + 5-H_{furane}), 2.46 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.12 (s, 3H, CH_3). Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.45; H, 6.64; N, 6.02.

2,4-Dimethyl-N-(3-methylphenyl)-3-furamide (7b)

Yield 84 %, m.p. 104–105 °C. ^{1}H NMR (400 MHz, DMSO) δ = 9.56 (s, 1H, NH), 7.50 (s, 1H, C_6H_4), 7.43 (d, *J* = 8.1 Hz, 1H, C_6H_4), 7.19 (s, 1H, 5-H_{furane}), 7.13 (t, *J* = 7.8 Hz, 1H, C_6H_4), 6.83 (d, *J* = 7.7 Hz, 1H, C_6H_4), 2.40 (s, 3H, CH_3), 2.32 (s, 1H, CH_3), 2.07 (s, 3H, CH_3). Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.21; H, 6.60; N, 6.22.

2,4-Dimethyl-N-(4-methylphenyl)-3-furamide (7c)

Yield 90 %, m.p. 115–116 °C.^{1}H NMR (400 MHz, DMSO) δ = 9.55 (s, 1H, NH), 7.53 (d, *J* = 8.0 Hz, 2H, C_6H_4), 7.19 (s, 1H, 5-H_{furane}), 7.06 (d, *J* = 8.4 Hz, 1H, C_6H_4), 2.40 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.07 (s, 3H, CH_3). Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.43; H, 6.51; N, 6.03.

N-(4-isopropylphenyl)-2,4-dimethyl-3-furamide (7d)

Yield 89 %, m.p. 192–194 °C. ^{1}H NMR (400 MHz, DMSO) δ = 9.56 (s, 1H, NH), 7.55 (d, *J* = 8.5 Hz, 2H, C_6H_4), 7.19 (s, 1H, 5-H_{furane}), 7.10 (d, *J* = 8.4 Hz, 2H, C_6H_4), 2.91 – 2.80 (m, 1H, CH), 2.40 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 1.22 (d, *J* = 6.9 Hz, 6H, 2 CH_3). Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.78; H, 7.36; N, 5.56.

***N*-(3,4-dimethylphenyl)-2,4-dimethyl-3-furamide (7e)**

Yield 82 %, m.p. 119–120 °C. ^{1}H NMR (400 MHz, DMSO) δ = 9.46 (s, 1H, NH), 7.42 (s, 1H, C_6H_3), 7.35 (d, *J* = 8.2 Hz, 1H, C_6H_3), 7.18 (s, 1H, 5-H_{furane}), 6.99 (d, *J* = 8.1 Hz, 1H, C_6H_3), 2.40 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.07 (s, 3H, CH_3). Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.91; H, 7.12; N, 5.85.

N-(3,5-dimethylphenyl)-2,4-dimethyl-3-furamide (7f)

Yield92 %, m.p. 164–165 °C.^{1}H NMR (400 MHz, DMSO) δ = 9.46 (s, 1H, NH), 7.27 (s, 2H, C_6H_3), 7.19 (s, 1H, 5-H_{furane}), 6.65 (s, 1H, C_6H_3), 2.39 (s, 3H, CH_3), 2.27 (s, 6H, 2*CH_3), 2.07 (s, 3H, CH_3). Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.94; H, 7.02; N, 5.68.

N-(3-chlorophenyl)-2,4-dimethyl-3-furamide (7g)

Yield 91 %, m.p. 77–78 °C.^{1}H NMR (400 MHz, DMSO) δ 9.54 (s, 1H, NH), 7.89 (t, *J* = 2.0 Hz, 1H, C_6H_4), 7.64 – 7.58 (m, 1H, C_6H_4), 7.25 (t, *J* = 8.1 Hz, 1H, C_6H_4), 7.03 – 6.98 (m, 1H, C_6H_4), 6.59 (s, 1H, 5-H_{furane}), 2.51 (s, 3H, CH_3), 2.28 (s, 3H, CH_3). Anal. Calcd. for $C_{13}H_{12}ClNO_2$: C, 62.53; H, 4.84; N, 5.61. Found: C, 62.65; H, 4.73; N, 5.75

N-(4-chlorophenyl)-2,4-dimethyl-3-furamide (7h)

Yield 87 %, m.p. 152–153 °C.^{1}H NMR (400 MHz, DMSO) δ = 9.80 (s, 1H, NH), 7.69 (d, *J* = 8.9 Hz, 2H, C_6H_4), 7.26 (d, *J* = 8.8 Hz, 2H, C_6H_4), 7.21 (s, 1H, 5-H_{furane}), 2.49 (s, 3H, CH_3), 2.40 (s, 3H, CH_3). Anal. Calcd. for $C_{13}H_{12}ClNO_2$: C, 62.53; H, 4.84; N, 5.61. Found: C, 62.65; H, 4.91; N, 5.54.

N-(3,4-dichlorophenyl)-2,4-dimethyl-3-furamide (7i)

Yield 85 %, m.p. 151–152 °C. ^{1}H NMR (400 MHz, DMSO) δ = 9.93 (s, 1H, NH), 8.02 (d, *J* = 2.4 Hz, 1H, C_6H_3), 7.59 (dd, *J* = 8.8, 2.4 Hz, 1H, C_6H_3), 7.42 (d, *J* = 8.8 Hz, 1H, C_6H_3), 7.22 (s, 1H, 5-H_{furane}), 2.40 (s, 3H, CH_3), 2.07 (s, 3H, CH_3). Anal. Calcd. for $C_{13}H_{11}Cl_2NO_2$: C, 54.95; H, 3.90; N, 4.93. Found: C, 55.06; H, 3.81; N, 5.04.

N-(4-bromophenyl)-2,4-dimethyl-3-furamide (7j)

Yield 89%, m.p. 158–159°C. ^{1}H NMR (400 MHz, DMSO) δ = 9.80 (s, 1H, NH), 7.64 (d, *J* = 8.8 Hz, 2H, C_6H_4), 7.39 (d, *J* = 7.3 Hz, 1H, C_6H_4), 7.21 (s, 1H, 5-H_{furane}), 2.40 (s, 3H, CH_3), 2.07 (s, 3H, CH_3). Anal. Calcd. for $C_{13}H_{12}BrNO_2$: C, 53.08; H, 4.11; N, 4.76. Found: C, 53.19; H, 4.02; N, 4.84.

N-(4-methoxyphenyl)-2,4-dimethyl-3-furamide (7k)

Yield 95 %, m.p. 123–124 °C °C. ^{1}H NMR (400 MHz, DMSO) δ = 9.50 (s, 1H, NH), 7.56 (d, *J* = 8.7 Hz, 2H, C_6H_4), 7.18 (s, 1H, 5-H_{furane}), 6.81 (d, *J* = 8.3 Hz, 2H, C_6H_4), 3.74 (s, 3H, CH_3O), 2.40 (s, 3H, CH_3), 2.07 (s, 3H, CH_3).

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.65; H, 6.08; N, 5.83.

N-(4-ethoxyphenyl)-2,4-dimethyl-3-furamide (7l)

Yield 90 %, m.p. 159–160 °C. ^{1}H NMR (400 MHz, DMSO) δ = 9.45 (s, 1H, NH), 7.54 (d, *J* = 8.9 Hz, 2H, C_6H_4), 7.18 (s, 1H, 5-H_{furane}), 6.79 (d, *J* = 8.8 Hz, 2H, C_6H_4), 3.99 (q, *J* = 6.9 Hz, 2H $\underline{CH_2}CH_3$), 2.40 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 1.36 (t, *J* = 6.9 Hz, 3H, $CH_2\underline{CH_3}$). Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.57; H, 6.52; N, 5.56.

N-[4-(acetylamino)phenyl]-2,4-dimethyl-3-furamide (7m)

Yield 84 %, m.p. 191–192 °C. ^{1}H NMR (400 MHz, DMSO) δ = 9.71 (s, 1H, NH), 9.58 (s, 1H, NH), 7.55 (d, *J* = 8.9 Hz, 2H, C_6H_4), 7.46 (d, *J* = 8.8 Hz, 2H, C_6H_4), 7.19 (s, 1H, 5-H_{furane}), 2.40 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.01 (s, 3H, CH_3). Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.27; H, 6.01; N, 10.18.

Methyl 2-[(2,4-dimethyl-3-furoyl)amino]-4,5-dimethoxybenzoate (7n)

Yield 87 %, m.p. 146–147 °C. ^{1}H NMR (400 MHz, DMSO) δ = 11.11 (s, 1H, NH), 8.44 (s, 1H, C_6H_2), 7.41 (s, 1H. C_6H_2), 7.24 (s, 1H, 5-H_{furane}), 3.90 (s, 3H, CH_3O), 3.86 (s, 3H, CH_3O), 3.79 (d, J s, 3H, CH_3O), 2.51 (s, 3H, CH_3), 2.18 (s, 3H, CH_3). Anal. Calcd. for $C_{17}H_{19}NO_6$: C, 61.25; H, 5.75; N, 4.20. Found: C, 61.34; H, 5.69; N, 4.31.

Molecular docking

Molecular docking was conducted with the OpenEye Scientific Software program as a computer based approach to the search of molecules with affinity to certain biotargets. Other software used included Fred Receptor, Vida, Omega 2 and Hybrid programs.

Pharmacology

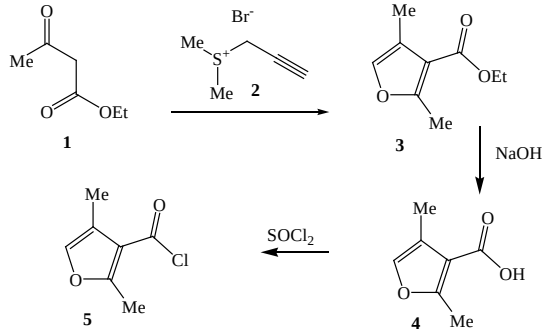
Anti-inflammatory activity[25] was evaluated using the carrageenan-induced rat paw edema method in Wistar rats (weight 180–220 g). The experiments were carried out in accordance with the requirements of the European convention for the protection of vertebrate animals used for experimental and other scientific purposes. The experimental protocol was approved by the DanyloHalytskyLviv National Medical University ethics committee, constituted by the Ministry of Health of Ukraine. Animals were divided into 16 groups comprising five rats per group. One group was kept as the control and the remaining 15 groups (test groups) were used to determine the anti-inflammatory activity elicited by Ibuprofen and the 14 compounds. Rats were kept in the animal house under standard conditions of light and temperature on a standard diet prior to the experiment. The standard drug, Ibuprofen (50 mg kg^{-1} body weight) and the test compounds (50 mg kg^{-1} body weight) were dissolved in DMSO and administered through an intraperitoneal route. DMSO was injected into the control group. At 30 min later, 0.1 mL of a 2 % carrageenan solution in saline was injected in the sub-plantar region of the right hind paw of each rat. At 4 h after the carrageenan injection, the volume of paw edema (in mL) was measured using a water plethysmometer and decrease in paw edema was compared between the control group and the test groups. Results of decreased paw edema were expressed as the mean ± standard deviation and compared statistically with the control group using Student's t-test. A level of $p<0.05$ was considered to be significant. The inflammatory reaction inhibition was expressed as a percent reduction of paw volume and was calculated using Eqn. (1),

$$\%\,(\text{inhibition}) = \frac{V_{\text{control}} - V}{V_{\text{control}}} \times 100 \qquad (1)$$

where $V_{control}$ is the increase in paw volume in control group; *V* is the increase in paw volume in animals injected with the test substances

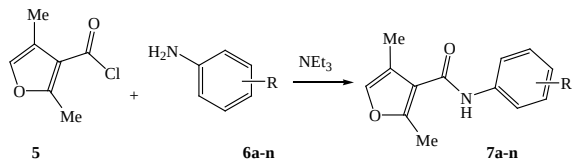
RESULTS AND DISCUSSION

The starting material, **5**, was prepared according scheme 1. In the first stage, **2** was reacted with an acetoacetic ester **1** to form ethyl 2,4-dimethyl-3-furoate **3** which was hydrolyzed with an aqueous solution of sodium hydroxide. Next 2,4-dimethyl-3-furoyl chloride **5** was prepared by the reaction of acid **4** with thionyl chloride.



Scheme 1. Synthesis 2,4-dimethyl-3-furoyl chloride.

The target 2,4-dimethyl-*N*-aryl-3-furamides **7a-n** were synthesized by the reaction of 2,4-dimethyl-furan-3-carbonyl chloride **5** with aromatic amines **6a-n** in dry dioxane in the presence of triethylamine (Scheme 2). Yields of the reaction products were 84–92 %.

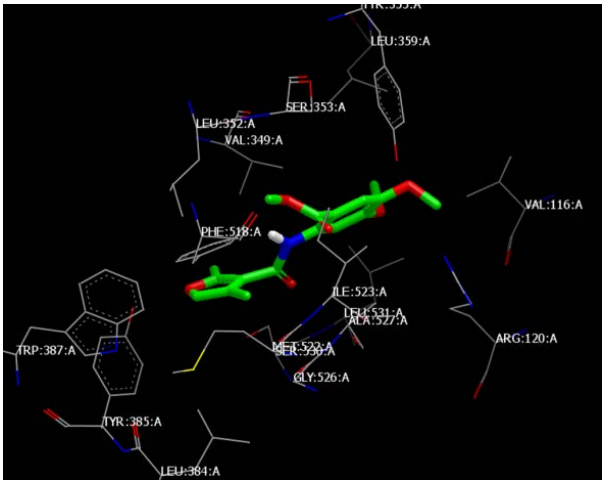


6, **7**: R = 2-CH_3(**a**), 3-CH_3(**b**), 4-CH_3(**c**), 4-$CH(CH_3)_2$(**d**), 3,4-$(CH_3)_2$(**e**), 3,5-$(CH_3)_2$(**f**), 3-Cl(**g**), 4-Cl(**h**), 3,4-Cl_2(**i**), 4-Br(**j**), 4-CH_3O(**k**), 4-C_2H_5O(**l**), 4-$CH_3C(O)NH$(**m**), 2-CO_2CH_3-4,5-$(CH_3O)_2$(**n**)

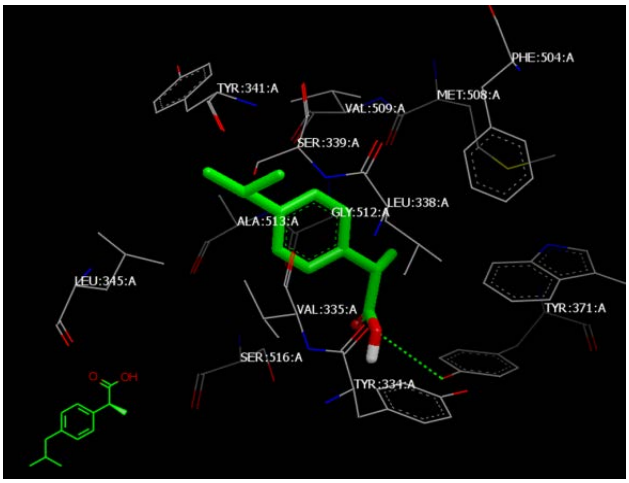
Scheme 2. Synthesis 2,4-dimethyl-*N*-aryl-3-furamides.

Table 1. Values of the Chemgauss 4 score of 2,4-dimethyl-N-(2-aryl)-3-furamides derivatives and reference compounds.

Compound ID or reference compound	Chemgauss 4 score		Compound ID or reference compound	Chemgauss 4 score	
	1HT5 (COX-1)	3MQE (COX-2)		1HT5 (COX-1)	3MQE(COX-2)
7a	-9.003030	-10.270514	Aspirin	-7.977182	-8.933105
7b	-8.843842	-10.332836	Diclofenac	-8.298965	-10.573636
7c	-8.943698	-10.325527	Etoricoxib	0.489733	-9.833312
7d	-9.316087	-10.865539	Flurbiprofen	-12.727644	-12.073698
7e	-7.995869	-11.244852	Ibuprofen	-12.126113	-10.477378
7f	-7.564784	-10.768264	Indomethacin	-8.843241	-11.326180
7g	-7.970945	-10.427266	Isoxicam	-7.356161	-9.013797
7h	-9.477314	-10.019304	Ketoprofen	-10.003001	-11.834192
7i	-7.862546	-10.936769	Ketorolac	-9.982499	-12.177383
7j	-9.574938	-10.233967	Lumiracoxib	-10.311695	-12.314234
7k	-8.871384	-10.072598	Meloxicam	-6.610479	-9.254274
7l	-8.582786	-10.723902	Parecoxib	-8.273745	-11.163197
7m	-7.314748	-9.674338			
7n	-9.126192	-11.325491			



(a)



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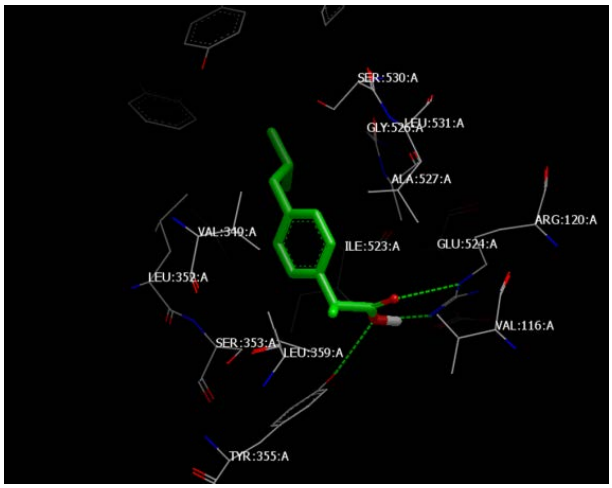
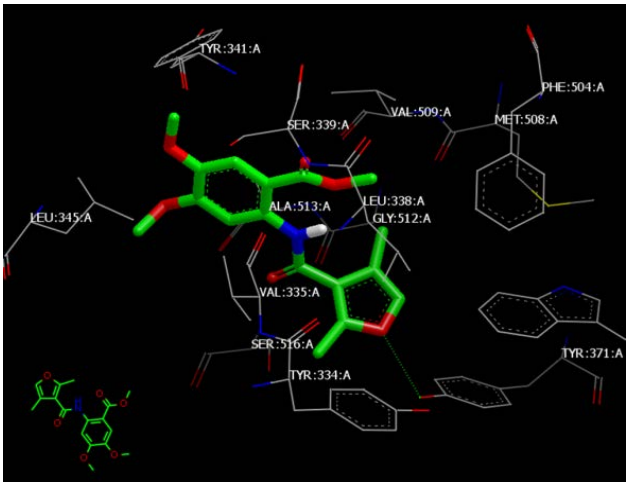


(c)



(d)

Figure. Compound **7n** docked in the active site of COX-1 (**a**) and COX-2 (**b**) in comparison with inhibitor Ibuprofen (**c** and **d**) docked in the active site of COX-1 and COX-2 correspondingly.

The structures of the obtained compounds were confirmed by ^{1}H NMR spectroscopy and elemental analysis. All these new compounds gave spectroscopic data in accordance with the proposed structures.

Molecular docking

Chrystallographic models of COX-1 and COX-2 (1HT5 and 3MQE correspondingly) were obtained from Protein Data Bank (www.rcsb.org). As research objects: 2,4-dimethyl-N-(2-aryl)-3-furamides derivatives, common NSAIDs (aspirin, mefenamic acid, diclofenac, ibuprofen, indomethacin, ketoprofen, ketorolac and others) and well-known selective COX-2 inhibitors, such as parecoxib, lumiracoxib, etoricoxib and others, were chosen. To estimate *in silico* COX-2-compound and COX-1-compound binding scoring function values were calculated. Chemgauss 4 scoring function ranking allowed us to select compounds, which could prospectively be selective COX-2 inhibitors. Make Receptor program allows to extract the active sites (biotarget) of COX-2 and COX-1 from crystallographic models for molecular docking.

Molecular docking studies included generation of R-, S- and cys-trans isomers of ligands and them conformers using program were generated via Omega 2 with Flipper parameter. Further program Hybrid that uses elements of ligand based design to enhance performance. Typically, the protein structure is determined with X-ray crystallography in the presence of a known binding ligand (or bound ligand). The Hybrid program uses the information present in both the structure of the protein and the bound ligand to enhance docking performance.

Values of the scoring function (Chemgauss 4) were obtained as a result. Ranking property of the scoring function allowed to analyze the results easily (table 1).

Ranking and analysis of the molecular docking results were obtained using the selected compounds and crystallographic model of COX-2 and COX-1 with scoring function (Chemgauss 4). Results allowed us to select compounds, which could prospectively be COX inhibitors at the level of Ibuprofen for future (in-depth) pharmacological studies for further evaluation of in vitro anti-inflammatory activity. The interactions between COX-1 and COX-2 active site and the most active compound **7n** in comparison with Ibuprofen (non-selective inhibitor of COX-1&2) is shown in Figure. Moreover, it should be noted that results predicted via docking correlate quite well with that obtained in the in vitro assay. The selected "lead" compound **7n** based on the *in vitro* screening results was also predicted to be the most active in the docking studies.

Pharmacology

Carrageenan-induced paw edema is a well-known animal model of acute inflammation, and is the most widely used in the search for new anti-inflammatory drugs. In vivo studies of novel 2,4-dimethyl-*N*-aryl-3-furamides were performed for anti-inflammatory activity. The results of the anti-inflammatory activity of the synthesized compounds and Ibuprofen are shown in Table 2.

The synthesized compounds induce various anti-inflammatory activity – from almost complete absence to a pronounced anti-inflammatory effect. Evaluation indicated that 11 compounds (**7a**, **7b**, **7c**, **7d**, **7e**, **7f**, **7g**, **7j**, **7k**, **7l**, **7m**) showed no significant decrease in carrageenan-induced rat paw edema, as their inhibition rates were only 7.2-35.6%, as compared to the control group. The anti-inflammatory effect for compounds **7h** and **7i** is approximately equivalent to that of the reference drug. However, the anti-inflammatory activity of the for compound **7n** gave the result at the level of 45.4 % inhibition indicating the methyl 2-[(2,4-dimethyl-3-furoyl)amino]-4,5-dimethoxybenzoate were more potent than Ibuprofen.

Table 2. Anti-inflammatoryeffect of 2,4-dimethyl-*N*-aryl-3-furamides on carrageenan-induced rat paw edema (mL) in vivo evaluation, % protection from inflammation.

Compound ID	Paw edema volume (mL)±SEM*	% Inhibition	Activity relative to Ibuprofen, %
Control	2.20 ± 0.050	-	-
7a	1.71± 0.040	22.3	55.5
7b	1.93± 0.045	12.1	30.1
7c	1.84± 0.045	16.2	40.3
7d	2.04 ± 0.050	7.2	17.9
7e	1.58 ± 0.040	28.3	70.4
7f	1.90 ± 0.045	13.5	33.6
7g	1.42± 0.035	35.6	88.6
7h	1.31± 0.035	40.5	100.8
7i	1.29± 0.035	41.2	102.5
7j	1.51± 0.035	31.2	77.6
7k	1.86± 0.045	15.6	38.8
7l	1.65 ± 0.040	25.1	62.4
7m	1.71 ± 0.040	22.3	55.5
7n	1.20 ± 0.030	45.4	112.9
Ibuprofen	1.32 ± 0.035	40.2	100

CONCLUSION

In summary, we have presented an efficient approach of the synthesis of 2,4-dimethyl-*N*-(2-aryl)-3-furamides.The synthesized compounds were preselected via molecular docking for further testing of their anti-inflammatory activity in vitro. During the study of synthesized substances anti-inflammatory effect in the carrageenan model of inflammatory oedema of white rats paws, we found three highly active compounds with a pronounced anti-inflammatory effect. Further optimization of the structure to improve biological activity is currently in progress.

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STABILIZATION OF DIOXOCHROMIUM(VI) IN THE COMPLEX WITH TETRA[BENZO]PORPHYRAZINE AND TWO OXO LIGANDS: DFT QUANTUM-CHEMICAL CONSIDERATION

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Keywords: Cr^{+6}, oxo ligand, tetra[benzo]porphyrazine, DFT method.

Based on the results of a quantum chemical consideration in the framework of DFT OPBE/TZVP and B3PW91/TZVP methods, the possibility of the self-existence of a chromium heteroligand complex with (NNNN)-donor macrocyclic ligand – tetra[benzo]porphyrazine and two oxo ligands where chromium oxidation degree is (+6), have been shown. The data on the key structural parameters and also, on multiplicity of the ground state of the given macrocyclic metal complex have also been presented.

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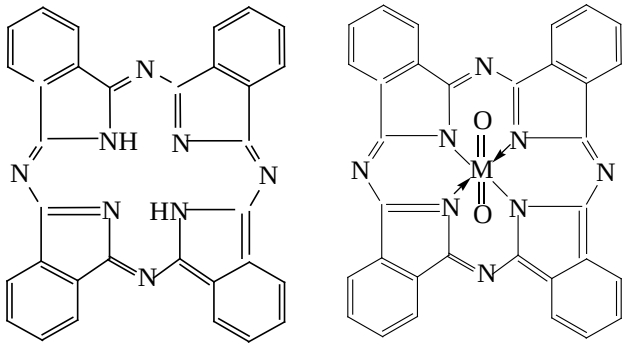
INTRODUCTION

Cr^{+6} oxidation degree is known to be highest theoretically possible oxidation degree of the given 3*d*-element, however, chromium compounds with such a degree of oxidation are represented only by chromium trioxide CrO_3 and a number of oxo anions,[1,2] in particular CrO_4^{2-}, $Cr_2O_7^{2-}$, $Cr_3O_{10}^{2-}$ and, also, by oxo-fluoro-compounds $CrOF_4$ и CrO_2F_2.[3-11] Besides, judging by the data of the review,[3] so far there is no information on either simple or coordination Cr(VI) compounds, which would contain other chemical elements besides oxygen and fluorine. Moreover, even the possibility of the existence of chromium(VI) fluoride (CrF_6) has not been confirmed. Nevertheless, there is no reason to believe that Cr(VI) complexes cannot exist, and, in this connection, it seems interesting to find such coordination compounds.

It has long been established that a (NNNN)-donor macrocyclic ligand as tetra[benzo]porphyrazine or phthalocyanine having structural formula **I** (Figure 1) capable to stabilize a wide variety of oxidation states of *d*-elements-both low and high (see, for example, review articles[12-14] and the books[15,16]). Another ligand which is capable of stabilizing high oxidation states, is the oxo anion O^{2-} [1-3,17,18]. By taking into account the aforesaid, it seems appropriate to use for Cr(VI) stabilization the combination of the given two ligands that occurs in the macrocyclic metal chelates with structural formula **II** shown in figure 1.

As it was indicated above, there is no information on such a metal complex in the current literature; nonetheless, at the present time, a possibility of its existence can be evaluated using modern quantum chemical calculation methods. In this connection, this article has been devoted to consideration of the given problem.



(I) **(II)**

Figure 1. The NNNN ligand (**I**) and complex (**II**) (M=Cr(VI))

CALCULATION METHOD

Quantum-chemical consideration of the chromium complex having formula **II** was done by using the two versions of DFT method, namely OPBE/TZVP and B3PW91/TZVP as it was done already in our earlier articles.[19,20] First of them combines the common TZVP extended triple zeta split-valence basis set[21,22] with the OPBE non-hybrid functional,[23,24] which as reported earlier,[24–28] in the case of 3*d* elements, more adequately predicts the relative energy stabilities of high-spin and low-spin states and reliably characterizes key geometric parameters of corresponding molecular structures. The other DFT calculation method combines the common TZVP and B3PW91 functional,[29,30] and according to data,[31] has minimal value of so-called "normal error" in comparison with other DFT methods. Such a conclusion is in full harmony with the data of structural parameters of macrocyclic complexes of various 3*d*-elements with phthalocyanine obtained as a result of various DFT

quantum-chemical calculations and in experiments. Calculations were done by using the Gaussian09 program package.[32] The correspondence of the found stationary points to energy minima was proved in all cases by the calculation of second derivatives of energy with respect to atom coordinates. All equilibrium structures corresponding to minima of the potential energy surfaces had only real positive frequency values. Chromium in the oxidation degree +6 has $3p^6$ electronic configuration; in this connection, spin multiplicities 1, 3 and 5 were considered in calculation. Among the structures optimized at these multiplicities, the lowest-lying structure was selected. Parameters of molecular structures with the given multiplicities were calculated by the unrestricted methods (*UOPBE* and *UB3PW91*, respectively). The standard thermodynamic parameters of formation of this complex were calculated according to procedure described in literature.[33]

RESULTS AND DISCUSSION

By judging to the data obtained by us as a result of our calculation carried out using the OPBE/TZVP as well as the B3PW91/TZVP, the chromium macrocyclic complex having structural formula **II** is capable to self-existence, at least in the gas phase. Molecular structure of the given complex obtained by B3PW91/TZVP method is shown in figure 2, molecular structure obtained by the OPBE/TZVP method, looks similarly. The calculated chemical bond lengths between atoms and bond angles for this macrocyclic metal complex presented in table 1. As it may be seen from these data, both methods used by us, give practically identical data for all structural parameters indicated above. A little difference between the results of these methods occurs only in the case of bond lengths Cr1O1 (Cr1O2). As it can be seen from figure 2, and table 1, the chromium complex under examination has in general a structure of regular tetragonal bipyramid or flattened octahedron (since here, the lengths of the Cr–O bonds are noticeably less rather than the lengths of the Cr–N bonds). CrN_4 chelate node in this macrocyclic compound has the structure of regular quadrangle (square) because the Cr–N bond lengths, distances between adjacent nitrogen atoms (N1 and N2, N2 and N3, N3 and N4, N4 and N1) absolutely identical (according to OPBE/ TZVP, 199.8 and 282.5 pm; according to B3PW91/TZVP, 199.9 and 282.7 pm, respectively), and both (NCrN) bond angles and (NNN) non-bond ones are equal to 90.0 °.

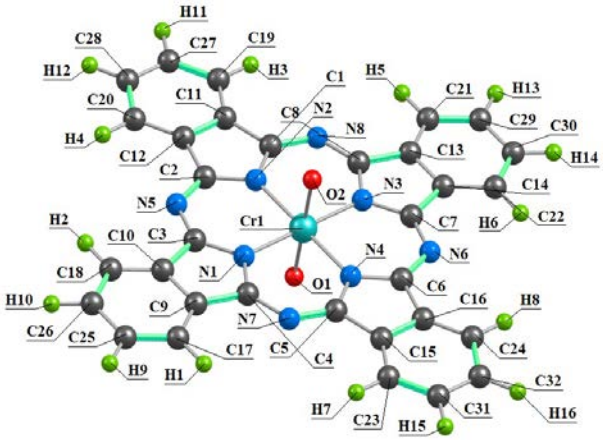


Figure 2. Structure of the complex obtained by B3PW91/TZVP method.

Table 1. Bond lengths and bond angles in the chromium complex with tetra[benzo]porphyrazine and two oxo ligands of type **II**.

Structural parameter	Calculated by DFT	
	OPBE/TZVP	B3PW91/TZVP
Cr–N bond lengths in chelate node, pm		
Cr1N1	199.8	199.9
Cr1N2	199.8	199.9
Cr1N3	199.8	199.9
Cr1N4	199.8	199.9
Bond angles in chelate node CrN_4, *deg*		
(N1Cr1N2)	90.0	90.0
(N2Cr1N3)	90.0	90.0
(N3Cr1N4)	90.0	90.0
(N4Cr1N1)	90.0	90.0
Bond angles sum (BAS), *deg*	360.0	360.0
Non-bond angles between N atoms in N_4 grouping, *deg*		
(N1N2N3)	90.0	90.0
(N2N3N4)	90.0	90.0
(N3N4N1)	90.0	90.0
(N4N1N2)	90.0	90.0
Non-bond angles sum (NBAS), *deg*	360.0	360.0
Bond angles in 6-numbered ring (Cr1N2C1N8C8N3), *deg*		
(Cr1N2C1)	125.0	124.7
(N2C1N8)	128.1	128.1
(C1N8C8)	124.0	124.4
(N8C8N3)	128.2	128.1
(C8N3Cr1)	124.7	124.7
(N3Cr1N2)	90.0	90.0
Bond angles sum (BAS^6), *deg*	720.0	720.0
Bond angles in 5-numbered ring (C2N2C1C11C12), *deg*		
(C2N2C1)	110.3	110.8
(N2C1C11)	108.6	108.3
(C1C11C12)	106.3	106.3
(C11C12C2)	106.3	106.3
(C12C2N2)	108.5	108.3
Bond angles sum (BAS^5), *deg*	540.0	540.0
C–N bond lengths in 6-numbered chelate rings, *pm*		
N1C3	135.6	135.4
N1C4	136.3	135.4
N2C1	135.6	135.4
N2C2	136.3	135.4
N7C4	132.6	132.3
N7C5	133.1	132.3
C–C bond lengths in 5-numbered ring, *pm*		
C1C11	146.9	146.8
C11C12	140.6	140.1
C12C2	146.8	146.8
Cr–O bond length, *pm*		
Cr1O1 (Cr1O2)	168.7 (168.7)	167.8 (167.8)
Bond angles between fluorine, copper and nitrogen atoms, *deg*		
O1Cr1N1 (O2Cr1N1)	90.0 (90.0)	90.0 (90.0)
O1Cr1N2 (O2Cr1N2)	90.0 (90.0)	90.0 (90.0)
O1Cr1N3 (O2Cr1N3)	90.0 (90.0)	90.0 (90.0)
O1Cr1N4 (O2Cr1N4)	90.0 (90.0)	90.0 (90.0)
Bond angles between fluorine, copper and nitrogen atoms, *deg*		
O1CrO2	180.0	180.0

As may be seen from Fig. 3, Cr atom is oriented in the center of square formed by four donor nitrogen atoms N1, N2, N3 and N4. Both four 6-membered metal-chelate rings and four 5-membered non-chelate one with one nitrogen atom and four carbon atoms adjoining to 6-membered metal-chelate rings, as in the range of bond angles in them. Besides, all they are strictly coplanar since the sum of the internal bond angles in each of the 6-membered cycles (BAS^6) is exactly 720°, in the 5-membered ones (BAS^5), is exactly 540°, which coincides with the sums of the internal angles in a flat hexagon and pentagon, respectively. The given complex has a center of symmetry and therefore for it a priori one can expect that value of the electric moment of the dipole will be zero. The data for calculating this parameter (0.00 Debye units according to both OPBE/TZVP and B3PW91/TZVP method) are in full accordance with such a forecast.

The ground state of the chromium complex considered by us, according to both calculation methods used here, is a spin triplet (M_S= 3) that is a little unusually for such an electron configuration as $3p^6$. However, according to the data obtained as a result of using these methods, the nearest excited singlet state in the case of OPBE/TZVP method has only a little higher energy (12.0 kJ mol^{-1}) whereas in the case of B3PW91/TZVP method, much more significant one (97.1 kJ mol^{-1}). By taking into account that, as it was indicated in the section Calculation Method, that OPBE/TZVP method more adequately predicts the relative energy stabilities of high-spin and low-spin states than B3PW91/TZVP method, the first value must be more reliable. Such a conclusion is favored by NBO analysis of the given complex according to which, the values of spin square operator (<S**2>) of the given compound are 2.0554 and 2.1008, respectively, that correspond of availability of namely two unpaired electrons in it and M_S= 3.

CONCLUSION

From the data presented above, it clearly follows that both variants of the DFT method, used in the given article (OPBE/TZVP and B3PW91/TZVP), quite definitely showed about the possibility of the existence of chromium complex of composition $[CrL(O)_2]$ containing double deprotonated form (L^{2-}) of tetra[benzo]porphyrazine (H_2L) and two oxo ligands (O^{2-}). In this complex, as expected, donor nitrogen atoms occupy four positions of the "equatorial plane" of the tetragonal bipyramid, oxygen atoms occupy its two axial positions (Figure 2). The Cr–N and Cr–O atom interatomic distances (Table 1) in this compound correspond in their size to single bonds chromium – nitrogen (Cr–N) and to double chromium – oxygen (Cr=O), and, hence, the oxidation degree of the given 3*d*-element in the given macrocyclic metal complex is namely +6. It should be noted in this connection that, according to our calculations of standard thermodynamic parameters $\Delta H^0_{f,\ 298}$, $S^0_{f,\ 298}$ and $\Delta G^0_{f,\ 298}$ of the complex under study using method described in[33], all they are positive (369.7 kJ mol^{-1}, 1152.4 J mol^{-1} K and 632.9 kJ mol^{-1}, respectively by OPBE/TZVP method), and, hence, the given compound cannot be obtained from simple substances formed by chemical elements containing in its composition (Cr, O, N, C and H). Nevertheless, both variants of the DFT method used by us, predict the possibility of the existence of this complex, and there is every reason to believe that this compound sooner or later will be obtained experimentally also.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest, financial or otherwise.

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SYNTHESIS OF ACETINS FROM ETHYL ACETATE VIA TRANSESTERIFICATION WITH GLYCEROL USING A SULPHONIC ACID TYPE ION-EXCHANGE RESIN

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Keywords: Bioglycerol, acetins, transesterification, ion exchange resin.

Demand for biodiesel has increased over the years as a substitute to petrol and diesel due to its environmental-friendly nature and lower cost. Glycerol being major by-product of the process constitutes 10 wt.% of the products hence conversion of glycerol to value added products such as acetins in the plant reduces the production cost of biodiesel. The present work focuses on the transesterification reaction between glycerol and ethyl acetate over heterogeneous catalyst, Amberlyst-15(wet). The batch studies were carried out and the effect of reaction parameters such as reaction time (1-7 h), glycerol to ethyl acetate molar ratio (1:3-1:12), temperature (50-70 ºC), catalyst loading (2-5 w/w%) have been studied. The maximum conversion of glycerol obtained at (G : EA) molar ratio 1:6, reaction temperature of 70 ˚C and 4 w/w% catalyst loading for 7 h was 97.71 % and the selectivity of mono-, di- and triacetins were 36.7, 60.7 and 2.51 %, respectively. This provides an eco-friendly and sustainable path for valorisation of biodiesel derived glycerol.

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INTRODUCTION

In present years due to considerable utilization of fossil fuels there is lot of ecological disturbance globally.[1] Worldwide the transportation sector is depended on fossil fuel to a major extent. The attention is consequently focused on cleaner fuels that can effortlessly replace fossil fuels i.e., biofuels. This would assist to tackle the depletion of worldwide energy reserves and environmental pollution.[2] Bio-diesel, a renewable fuel, possessing the characteristics comparable to petroleum, has gained huge interest in the current years.[3] Biodiesel which serves as a green substitute to diesel is synthesized by transesterification of vegetable oils (Soya bean oil, palm oil etc.) or animal fats with an alcohol such as methanol and ethanol.[4- 6]Though biodiesel is a greener fuel and penetrated the market internationally, it has not realized its potential due to the formation of a substantial amount of by-product i.e., glycerol.[7] Various researchers have explored different routes to give value addition to glycerol, which in turn enhances the economic value of biodiesel. Conversion of glycerol to acetins by esterification or transesterification reactions is an effective way to make use of glycerol.[8] The products obtained from the esterification or transesterification are mono-, di- and tri-acetins. These products have wide applications especially as food additives, safety plasticizers, solvents, biodegradable polyesters etc.[9, 10]

Literature review on synthesis of acetins via esterification of glycerol using acetylating agent such as acetic anhydride and acetic acid reveals that studies were made with heteropoly acids[11,12] ion exchange resin, zeolites, and mixed oxides.[13-15] Limited attempts were made for conversion of glycerol of acetins through transesterification route using homogeneous and heterogeneous acid catalysts.[16]

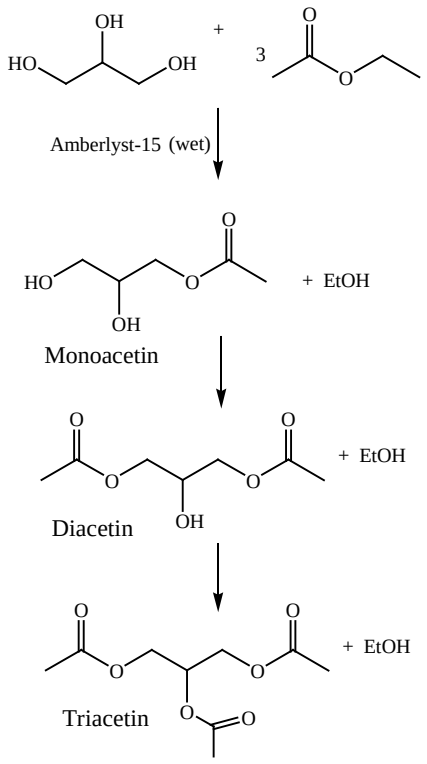

Figure 1. Transesterification of glycerol with ethyl acetate.

Homogeneous catalysts have various boundaries such as difficulty in removal from reaction mixture, non-reusability and corrosion of equipment. As per the literature in our purview this is the first work being reported for the conversion of glycerol with ethyl acetate to acetins by transesterification over Amberlyst-15 (wet). The main objective of this work is to propose a viable eco-friendly and

sustainable route to convert glycerol resulting from biodiesel production to value added products acetins using Amberlyst-15 (wet) catalyst. This article focuses on obtaining optimum operating parameters, so studies were conducted by varying parameters such as reaction time, mole ratio of reactant (glycerol: ethyl acetate), reaction temperature and catalyst loading(weight of catalyst to the weight of reaction mixture). The reusability studies were done and reported. The present work provides a path for the continuous conversion of biodiesel derived glycerol to value added products. The esterification reaction of glycerol with ethyl acetate over Amberlyst-15 (wet) is presented in Fig. 1.

EXPERIMENTAL

Materials

Glycerol (purity of 99.9 %) was supplied by Hi-Media Laboratories Pvt. Ltd., Ethyl acetate (purity of 99 %) and Amberlyst-15 (wet) was supplied by Sigma Aldrich. It is a macro-porous based ion exchange resin containing a strongly sulfonic acid group. It acts as an excellent strong acid catalyst. It has good reusability property. The significant properties of Amberlyst-15 (wet) are listed in Table 1.

Table 1. Properties of Amberlyst-15 (wet).

Appearance	Hard spherical particles
Matrix	styrene-divinylbenzene (macro reticular)
Particle size	<300 µm
Hydrogen ion capacity	4.7 meq g^{-1} by dry weight
Moisture	≤1.6%

Procedure

The experimental setup consists of a three-necked round bottomed flask equipped with an oil bath, magnetic stirrer, water-cooling condenser, thermometer and a temperature controller. When the desired temperature is reached, calculated amount of glycerol and ethyl acetate were added to the flask and the catalyst was also charged into the mixture. The amounts of glycerol and ethyl acetate to be added were calculated based on the molar ratio to be maintained for the reaction. After the addition of desired amount of catalyst into the reaction mixture the reaction time commences. Samples were collected at regular intervals. After the reaction is completed, the catalyst was removed by filtration and the reaction mixture was analysed using GC. Experiments were conducted thrice to minimize the error.

Analysis of sample

The periodically collected samples were analysed using GC (Mayura Analytical LLP Model 1100). 0.1 µL of the sample was withdrawn with a syringe and injected to the GC column equipped with capillary column (silphenylene polysiloxane, (30 m, 250 µm, 0.25 µm) with nitrogen as the carrier gas at 40 $mLmin^{-1}$ and programmed temperature of 120-150°C. The products monoacetin (MA), diacetin (DA) and triacetin (TA) were identified based on their retention times by utilizing predetermined calibration data of known pure compounds. Glycerol conversion, yield and selectivity of acetins were calculated as follows (Eqns. 1, 2 and 3), where X = MA, DA or TA.

$$\varphi_G(\%) = \frac{[G]_{\text{reacted}}}{[G]_{\text{initial}}} \times 100 \qquad (1)$$

$$Y_X(\%) = \frac{[X]_{\text{formed}}}{[G]_{\text{starting}}} \times 100 \qquad (2)$$

$$S_X(\%) = \frac{[X]_{\text{formed}}}{[G]_{\text{reacted}}} \times 100 \qquad (3)$$

where φ_G is the glycerol conversion, Y_X is the yield of X^{th} product, S_X is the selectivity for the X^{th} product, $[G]$ is the glycerol concentration.

RESULTS AND DISCUSSION

Influence of reaction time

In batch studies, the time of reaction is an important parameter as it affects the yield and selectivity of the products. In order to understand the influence of time, the studies were conducted with 1:6 mole ratio of glycerol : ethyl acetate (G : EA) at 70 °C and 4 w/w% Amberlyst-15(wet) catalyst loading for 8 h at 600 rpm. Fig. 2a depicts the variation of glycerol conversion with time. From Fig. 2a results it was evident that with increase in reaction time from 1 to 7 hours there has been significant rise in glycerol conversion from 37.36 to 97.71 %. As predicted in a series reaction, the glycerol conversion and yield of monoacetin and diacetin improved with increase in time from 1 to 7 h (Fig. 2b). The reason for longer reaction time could be due to the Amberlyst-15(wet) diffusion resistance to glycerol and further hindrance to the glycerol molecule to enter into the interior resin surface of the catalyst. With progress of reaction the movement of the reaction blend enhances with the formation of products, acetins and ethanol. These are the reasons for Amberlyst-15(wet) showing longer time in glycerol conversion of 7 hours as compared to with Amberlyst-15 (dry).[16] It can also be observed the conversion of glycerol decreased at 8 h might be due to the formation of ethanol, the reversible reaction takes place leading to the reactants. Whereas the formation of diacetin is favoured after 7 h. As this formation is not significant hence a reaction time of 7 h was chosen as optimum for further studies.

The molar ratio of reactants (G : EA) is an important parameter affecting the conversion rate. According to Le Chatelier's principle, using excess molar ratio of reactants, the conversion of equilibrium limited reaction can be enhanced. The transesterification of glycerol is equilibrium limited reaction the study of this parameter is significant.

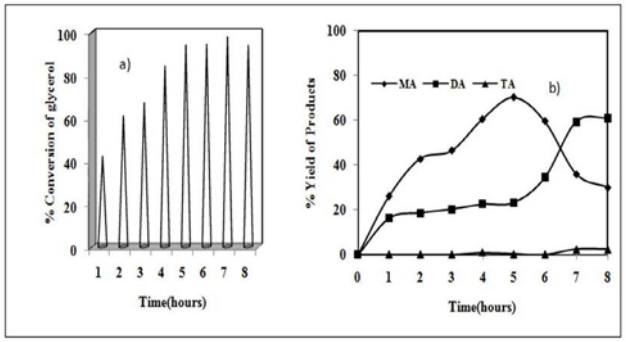

Figure 2. Influence of reaction time on **a)** glycerol conversion **b)** yield of products under optimized conditions.

Influence of molar ratio

The effect of different reactant molar ratio of (G : EA) 1:3, 1:6, 1:9, and 1:12 were studied at a reaction temperature of 70 °C, catalyst loading of 4 w/w% for 7 h at 600 rpm. Fig. 3 depicts results of the variation of glycerol conversion with molar ratio of reactants.

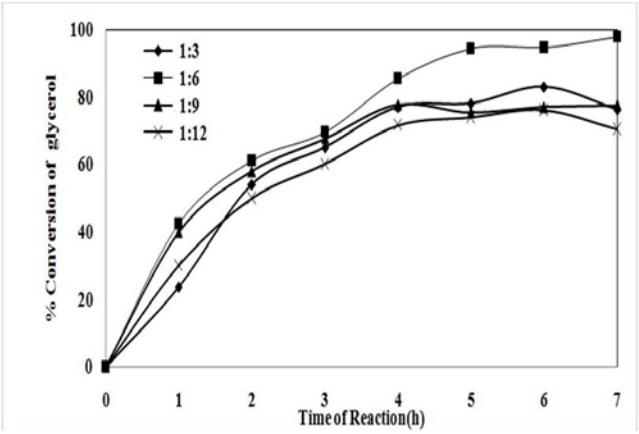

Figure 3. Influence of (G: EA) molar ratios on glycerol conversion, under optimized conditions.

The conversion of glycerol with (G : EA) molar ratio of 1:3, 1:6, 1:9, and 1:12 were 78.79, 97.7, 77.57 and 70.42 %, respectively. Fig.4 depicts the variation of acetins selectivity with molar ratio.

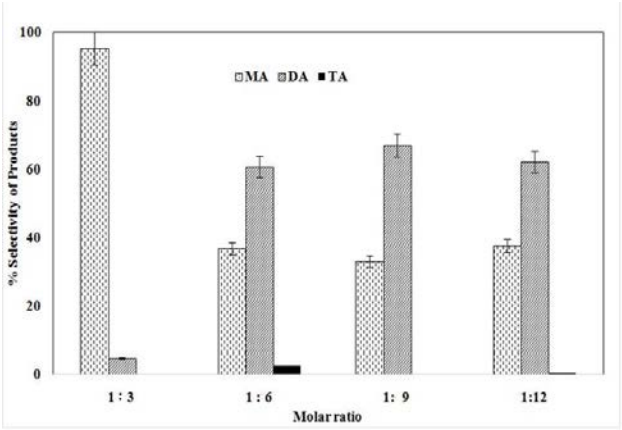

Figure 4. Influence of (G : EA) molar ratios on product selectivity under optimized conditions.

The selectivity's of products at 1:3 molar ratio were 95.3 % MA, 4.68 % DA at 1:6 were 36.7 % MA, 60.7 % DA and 2.51 % TA; at 1:9 were 32.9 % MA and 67.1 % DA; at 1:12 were 37.6 % MA, 62.2 % DA and0.25% TA. The maximum conversion of glycerol to acetins was obtained at molar ratio of 1:6. The decrease in conversion on glycerol for the molar ratio1:9 could be due to the reason that, excess ethyl acetate concentration may hinder the transesterification reaction by diluting the active reacting species i.e. glycerol leading to decrease in mass transfer of glycerol and subsequently reaction rate. Hence for further studies, molar ratio of 1:6 has been chosen as the optimum value.

Influence of reaction temperature

The experimental studies carried out at a particular temperature are useful for obtaining a rate constant. Further the studies at different temperature are useful in determining the activation energy for the reaction.[17] The reaction was carried out at (G : EA) molar ratio of 1:6, catalyst loading of 4 w/w % and at different temperatures, 50, 60 and 70 ˚C. The reaction temperatures were chosen based on the boiling point of the reactants so that the loss of reactant was avoided.

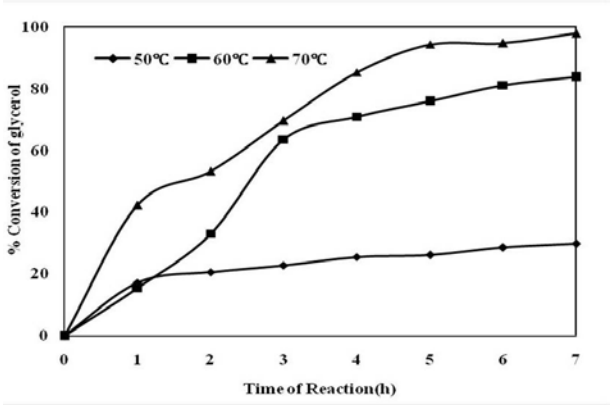

Figure 5. Influence of temperature on conversion of glycerol,under optimized conditions.

The conversion of glycerol obtained at 50, 60 and 70 ˚C were 29.81, 83.75 and 97.7 % as shown in Fig.5. The selectivity's obtained at 50 ˚C were 36.55 % MA and 63.45 % DA, at 60 ˚C were 51.11 % MA and 48.88 % DA, at 70 ˚C were 36.7 % MA, 60.7 % DA and 2.51 %, Fig. 6. Indeed, at lower temperature of 50 ˚C it was difficult for the reactants to contact the active sites of the inner and outer sites of the Amberlyst-15 (wet) resin due to the viscosity of the reaction mixture. This resistance was the main reason for low glycerol conversion at 50 ˚C. As the temperature increased, the viscosity of the glycerol is reduced and this in turn results in lower viscosity of the reaction mixture, which results in more accessibility to active sites of the resin results in higher conversion at 70 ˚C. Similar observations were reported by Shafiei et.al in their work.[18]

Influence of catalyst loading

The rate of the chemical reaction can be increased by using proper amount of the catalyst due to availability of a new low energy pathway for the conversion of reactants to products. The effect of catalyst loading on transesterification

of glycerol with ethyl acetate was studied with catalyst loading of 2, 3, 4 and 5 w/w% with (G : EA) molar ratio of 1:6 and reaction temperature of 70 °C at 600 rpm.

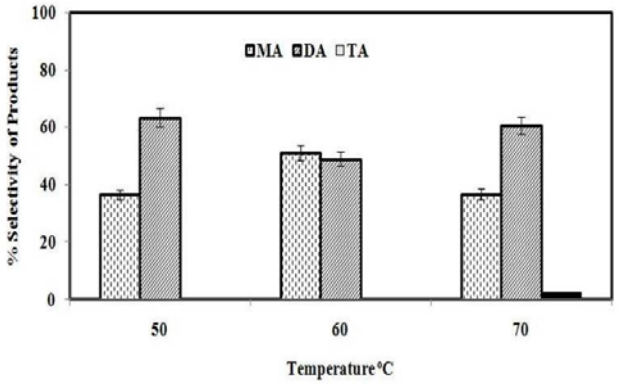

Figure 6. Effect of temperature on product selectivity under optimized conditions.

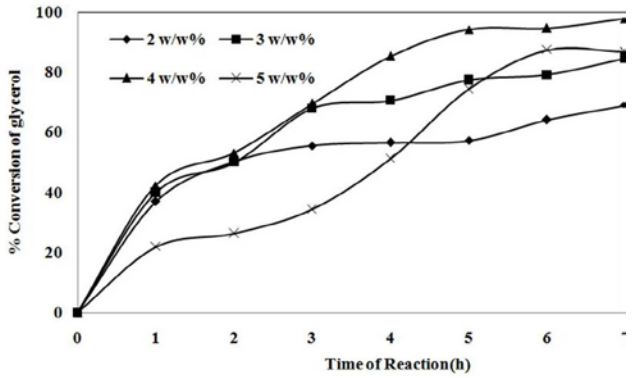

Figure 7. Influence of catalyst loading on conversion of glycerol,under optimized conditions.

The conversion of glycerol obtained with 2, 3, 4 and 5 w/w% catalyst loading were 69.08, 84.75, 97.71 and 86.91 % respectively as shown in Fig. 8. The selectivity's obtained at 2 w/w% were 51.77 % MA and 48.22 % DA, at 3 w/w% were 47.54 % MA and 52.54 % DA, at 4 w/w% were 36.7 % MA, 60.7 % DA and 2.51 % TA, at 5 w/w% were 45.46% MA, 53.63 % DA and 0.89 % TA (Fig. 8). With increase in catalyst loading from 2 to 4 w/w% the glycerol conversions was increased from 69.08 to 97.71 % and even the selectivity from monoacetin to diacetin enhanced due to the increase in active sites whereas for 5 w/w% loading the glycerol conversion dropped to 86.91 % and the selectivity declined. The reason for decline in glycerol conversion with increase in catalyst loading may be due to overloading of active sites which hinders the mass transfer phenomena, with increasing the viscosity of the reaction medium. Hence the catalyst loading greater than 4w/w% was found not effective for transesterification of glycerol with ethyl acetate to proceed forward.

Overall, it can be concluded 4 w/w% catalyst loading was appropriate to obtain the encouraging results. The selectivity towards triacetin is very low as the number of active sites on Amberlyst-15 (wet) is not enough to catalyse the triacetin and only the formation of diacetin was favourable.[19]

Comparison with literature

From literature review it was evident that very few reports are available on transesterification of glycerol with ethyl acetate to acetins. Meireles and Pereira[16] have reported various homogeneous and heterogeneous catalysts for synthesis of acetins through transesterification of glycerol with ethyl acetate. Among the studied catalysts, the homogeneous catalysts were found to be active catalyst with more selectivity towards triacetin compared to heterogeneous catalyst. It was reported complete glycerol conversion was obtained at 90 ºC, reaction time of 10 h for 1:30 molar ratio of G : EA.[16] Shafiei et al.[18] have reported synthesis of acetins through transesterification of glycerol with ethyl acetate using batch, semi batch and reactive distillation system using homogenous catalyst. They concluded that semi batch system gave 100 % glycerol conversion after 18 h of reaction time with selectivity of

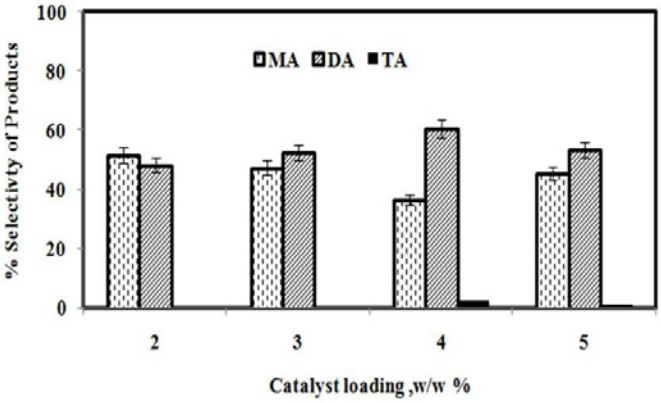

Figure 8. Influence of catalyst loading on product selectivity under optimized conditions.

Reusability of Catalyst

For industrial process to be an environmentally friendly and economical recycling of the catalyst is a significant feature. To regenerateAmberlyst-15 (wet) after a reaction of 7 h the catalyst was separated from reaction mixture by filtration, washed with methanol and n-hexane, and dried at 80 ˚C for 3 h.[20]

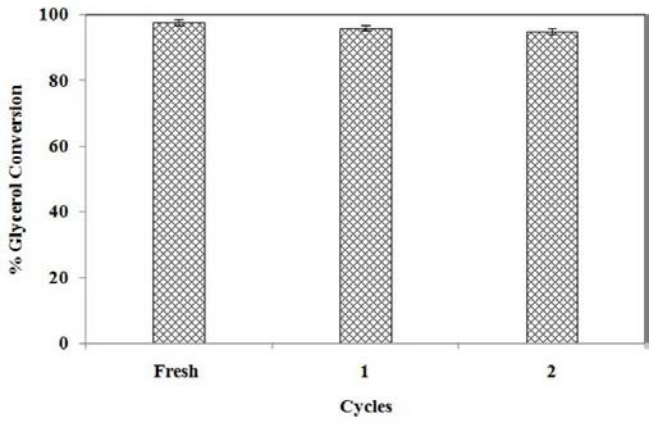

Figure 9. Reusability studies.

The reusability studies were conducted for three runs and the glycerol conversion obtained were 97.71, 95.95 and 94.89 % respectively. Fig. 9 shows that the catalyst exhibits good reusability without much significant loss in activity.

CONCLUSIONS

The environmentally economical benign route has been investigated for the conversion of biodiesel derived glycerol into fine chemicals. The maximum glycerol conversion of 97.71 % was obtained for (G : EA) molar ratio 1:6, reaction temperature of 70 ˚C and 4 w/w% catalyst loading for 7h and the selectivities of mono-, di-, tri-acetins were 36.7, 60.7 and 2.57 % respectively. Although the production of acetins via transesterification process demands longer reaction times with the use of heterogeneous catalysts Amberlyst-15(wet). It employs ethyl acetate, a reagent of lower cost and toxicity and generates by product ethanol, a low toxicity substance which acts as a raw material for other processes. Further studies can be carried out using reactive distillation as the transesterification reaction is equilibrium limited the application of reactive distillation can help in enhancing the glycerol conversion as well as yield of triacetin by removal of ethanol.

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LEAVES PEROXIDASE AND ESTERASE ISOZYMES IN SUNFLOWER CROPS EXPOSED TO SALINE ENVIRONMENT

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Keywords: Isozymes, peroxydases, esterases, leaves, salinity, sunflower.

Water deficit stress is one of the main problems determining the yield of many crop plants. The study of the effects of salinity on plant growth and development and the search for biochemical stress markers are of great importance in the selection of resistant species. Accumulation and antioxidant activities in response to salinity at different sunflower varieties constitute markers for genetic selection and improvement of plants in the face of tolerance to salinity. Electrophoretic analysis of zymograms of different sunflower varieties grown in a saline environment for 40 days revealed zymograms of peroxidases and esterases specific to varieties tolerant to the saline environment. Peroxidases activity extracted from leaves is augmented in relation to their involvement in the physiological process related to salinity tolerance. In susceptible varieties, peroxidases activity is decreased compared to normal conditions. Variability of activity and polymorphism of isozyme peroxidases and esterases in response to salinity at different sunflower varieties constitute markers for genetic selection and plant improvement in the face of salinity tolerance.

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INTRODUCTION

Salinization is one of the most important dangers for agriculture on a global scale. 23 % of 63 million irrigated arable hectares are affected by salt. With salinization and repeated drought due to climate change in the world increases poverty and results in the loss of livelihoods for many farmers.

The increase in the productivity of salt-affected land can be achieved through the use of good hauling crops associated with water management conditions, the use of appropriate fertilizers, taking into account the climate and the region concerned. The concept of developing salt-tolerant plants, even to the degree that they can be grown with seawater, captures the imagination of both the scientific and the public sector.

Shannon has defined salinity tolerance as the ability of plants to increase and reach their life cycle on a substrate that contains high concentrations of soluble salts.[1] In this habitat, the plant must meet two requirements, osmotic adaptation and acquisition of the mineral elements it needs for the growth and functioning of metabolism.

Shannon and Grieve have described plant tolerance to salinity as an ability of plants to withstand influences from high salt levels in the parts of the organs, roots and leaves without adverse consequences.[2] The plant can adapt to saline stress in different ways, excluding selective transport can absorb useful nutrient ions and re-expel Na ions.[3] The effect of water stress results in the appearance of oxidative stress, the increase of reactive oxygen species that cause degradation to cellular organizations. These oxygen drift derivatives are the superoxide free radicals (O_2), the perhydroxide radical (HO_2), the hydroxyl radical (OH), the radical peroxide (RO_2) and the radical alkyl (RO), as well as non-radical forms such as hydrogen peroxide (H_2O_2). The development of oxygenated free radicals following the stress effect of water deficit plays a central role in the senescence of the leaves.[4]

The activities of biological molecules are affected by the development of reactive forms of oxygen and leading to cell degeneration.[5] Plants adopt antioxidant systems made up of enzymes and metabolites to counter the ROS.[4] Various authors have revealed the role of ROS in signalling mechanism responsible for the expression of many defence genes (chaperone proteins, heat shock proteins, antioxidant enzymes, ascorbate peroxidase (APX), gluthation-S-transferase).[6,7] The integrity of photosynthetic activity is maintained through the action of antioxidant molecules during the water stress processes.[5] During water or saline stress, the inhibition of photosynthesis, and more precisely the leakage of electrons due to the decrease in CO_2 fixation, results in a strong accumulation of ROS.[8,9] Numerous studies show that enzymes such as superoxides dismutases (SOD), peroxydases ascorbates (APX), catalases (CAT), glutathion-Stransferases (GST) and glutathion peroxydases (GPX) accumulate in response to water stress.[5] The expression of catalases is induced by H_2O_2, that of superoxides dismutases and glutathiones reduced by various stresses including ABA, ethylene and drought.[10]

Sunflowers are part of the genus Helianthus, rich in 50 species. In particular, the species *Helianthus annuus* is present in a wide range of environments and latitudes. It may have genes to adapt to contrasting climatic conditions.[11] The present work compares the zymograms of leaves peroxidases, esterases, and activity of peroxidases extracted from hybrid sunflower leaves and population in the anti oxidative defence during ageing and during saline stress of cultivated sunflower. This work provides the genetic resources needed for the breeder to create new varieties of saline-tolerant sunflower.

Table 1. List of sunflower varieties.

Variety	ALBENA	DK3790	RECORD	ORO9
Origin	France	France	INRA Morocco	INRA Morocco
Characteristic	Hybrid	Hybrid	Population	Population
Behaviour	Moderate	salinity tolerance	Sensitive	Sensitive

EXPERIMENTAL

Plant materiel

Four varieties of sunflower provided from France and local Moroccans are selected based on agronomic characteristics, and their behaviour in the face of a saline environment presented in Table 1.

Sowing sunflower varieties

After rinsing with water with added sodium hypochlorite, sunflower seeds are germinated in separate trays containing soil and sand from the region of Rabat and maintained in a growth for a period of 40 days. Control seedlings are irrigated with tap water, and those conditioned in the saline environment are irrigated with 60 mM and 120 mM of NaCl solution. The bins are placed in places sheltered from the rain and exposed to the sun.

Extraction of crude protein fraction from sunflower leaves

0.1 g of leaves of the different control varieties and grown in a 60 mM and 120 mM NaCl environment are taken and rinsed with tap water with added NaOCl. After grunding with mortar in a buffer with pH 8.6, containing cys 0,1 mM, pvp 1% at 4°C, homogenates were filtered and centrifuged at 3500 pm for 10 min, cellular debris are eliminated and the crude fractions of total proteins contained in the supernatants are conserved at -20°C.

Analytical electrophoresis

Analytical electrophoresis was carried out in a fraction of total protein. The fraction was subjected to electrophoresis (12 % acrylamide) to separate proteins.[12] A zymogram of peroxidase activity were localised on the gels by incubating at 25 °C for 5 min in solution buffer containing acetate pH = 5 buffer and benzidine 0.05 g (acetone) made to 100 mL with distilled water. After incubation 1 % H_2O_2 (1 mL) was added for the appearance of tapes. Esterase's activity were localised on the gels by incubating them at 25 °C for 15 min in solution of buffer tris HCl pH = 7.2, containing α-naphtyl acetate 0.03g (acetone 50 %), β-naphthyl acetate and made up to 100 mL with distilled water. After rinsing with distilled water, the gels were treated for 20 min with fast blue salt at pH = 7.2 tris buffer solution salt and diluted with 100 mL of distilled water.

Assay of peroxidase activity

Peroxidase activity was determined by the described method by using guaicol as a substrate. The reaction was started by the addition of 50 µl of crude extract in 2 mL of the acetate 0.1M buffer containing 6 mM of Guaicol. The reaction was initiated by the addition of 1 mmoles solution of H_2O_2 and monitored as increase of absorbance at 470 nm.

RESULTS AND DISCUSSION

Analysis of zymogram of peroxidase

As seen in figure 1, electrophoretic analysis of peroxidase isozymes extracted from control sunflower leaves reveals peroxidase zymograms composed of 4 peroxidases pox1, pox2, pox3 and pox4 of varying color intensity.

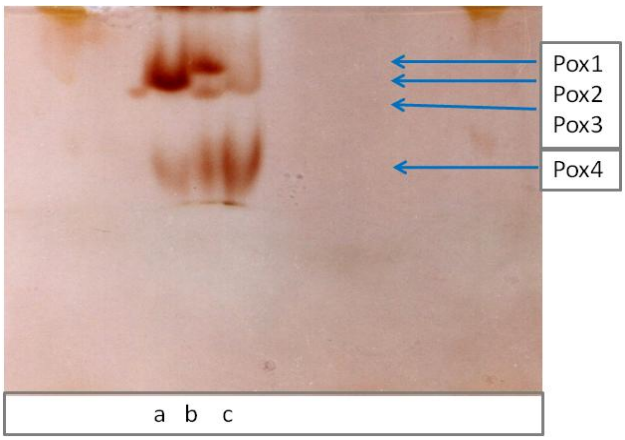

Figure 1. Zymogram of peroxydases extracted from sunflower leaves of controls varieties albena (a), DK 3790 (b) and Record (c).

The Albena variety has 2 high-intensity pox2 and pox4 isozymes, the isozymes pox1 and pox3 are absent. The variety DK 3790 presents 3 high-intensity pox1, pox3 and pox4 isozymes, isozyme pox2 is absent. The variety Record presents 2 low-intensity pox2 and pox4 isozymes, the isozymes pox1 and pox3 are absent. Isozyme pox4 is common to these three varieties. The isozymes pox1 and pox3 are specific to the DK 3790 variety. Isozymes pox2 and pox4 are common to both Albena and Record varieties. Electrophoretic analysis of peroxidase isozymes reveals a zymogram composed of Pox 1 bands under control conditions, with increasing color intensity under the conditions of NaCl 60 mM and 120 mM at the variety albena.

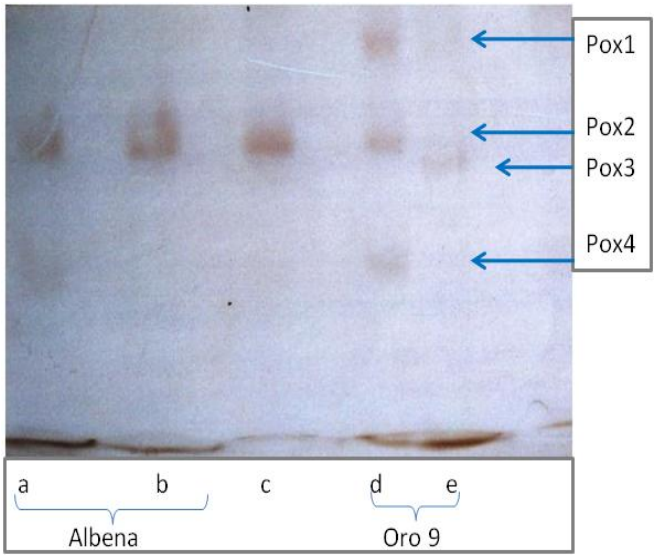

Figure 2. Zymogram of peroxidases extracted from sunflower leaves of varieties albena (sowing period November, january), Oro9 (sowing period december january) cultivated under environment of NaCl 60 mM and 120 mM.

In the variety Oro 9, 3 peroxidases Pox 1, Pox 2 and pox 4 are revealed under control conditions. Under NaCl 60 mM conditions a Pox3 peroxidase is revealed of different electrophoretic migration to that of control conditions Pox 1, pox 2 and Pox 4 are absent.

The variability of the peroxidases zymogram reveals various expressions of specific isozymes of tolerant varieties and varieties sensitive to salinity. Isozymes pox1 and pox3 may be related to the response to salinity tolerance in the DK3790 variety. This hybrid variety has a higher salinity tolerance than the Record population variety.[13] In saline environment conditions, the expression of isozymes is revealed in sunflower varieties in relation to their involvement in the physiological process related to salinity tolerance. Peroxidases have been detected in all organs of the plant and at different stages of development. [14,15] In the cultivars varieties of safflower, four guaiacol peroxidases were identified in the leaves of tolerant varieties and two in saline stress sensitive varieties.[16]

Peroxidases may be involved in changes in the plant wall by incorporating other compounds such as flavonoids, hydroxycoumarines, according to a physiological process or in response to stress.[17,18] Ascorbate peroxidases has a higher affinity for H_2O_2 and reduces it to H_2O in chloroplasts, cytosol, mitochondria and peroxisomes as well as in the aplastic space.[19] Peroxidases are involved in the polymerization of the precursors of lignin. Lignin is a polymer responsible for rendering the plant stronger and more rigid and making the cell walls hydrophobic. [20]

Analysis of activity of peroxidase

Activity of Peroxidases extracted from the sunflower leaves are 15.2 and 0.96 EU Kg^{-1} of fresh weight respectively in the controlled sunflower leaves Record and DK 3790 varieties (Table 2). Under the 60 mM environmental conditions peroxidase activity is 2.2 EU g^{-1} fresh weight of the variety DK 3790. Peroxidases activity is 12.4 and 3.2 respectively in the Record and DK 3790 varieties in the NaCl 120 mM environment. Peroxidase activity is increased a factor (F) of 3.33 in the DK 3790 variety grown in the NaCl 120 mM environment compared to control conditions. In the Record variety, activity is reduced by a factor (F) of 1.22 compared to the normal environment. The DK3790 variety reveals a higher anti-oxidative action compared to the Record variety caused by the effect of the saline environment. Salt stress has an effect on plant metabolism depending on the genotype and the intensity of the salt stress. The activity of superoxide dismutase (SOD), catalase (CAT), guaiacol peroxidase (GPX), and ascorbate peroxidase (APX) in the corn variety 'Lluteño' was significantly greater than in 'Jubilee' under the effect of saline stresses.[21] The work of Hiraga S et al[22] has revealed the variability of amino acids sequences of plant isozymes associated with their variable expression in various physiological processes. The change in the structure of the cell wall in transgenic potato seeds grown under saline stress conditions is affected by the increase in peroxidase activity.[23]

Salicylic acid treatment enhances peroxidase activity in the leaves of the cassava variety tolerant to this environment.[24]

Analysis of zymogram of esterases

Electrophoretic analysis of esterases isozymes (Figure 3) reveals the zymogram composed of the bands est1 of high intensity, est2 and est3 of low intensity in the albena variety, 4 isozymes est1 est2 of high intensity and 2 isozymes of low intensity est3 and est5 in the variety DK 3790, 3 isozymes est1 est2 of high intensity, est4 of high intensity in the variety Record. Isozyme est1 is common to albena, Dk3790 and record varieties. Isozyme est2 is of higher intensity in the Record variety compared to the albena and Dk3790 varieties. Isozyme est3 is specific to the varieties albena and Dk 3790. Isozyme is4 is specific to the record variety. Isozyme is5 is specific to the DK3790 variety.

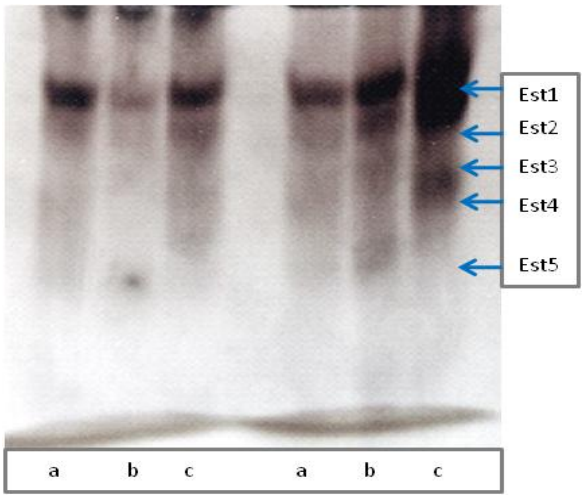

Figure 3. Zymogram of esterases extracted from controlled sunflower leaves of varieties albena (a), DK 3790 (b) and Record (c).

Table 2. Variation in activity (EU g^{-1} of fresh weight) of peroxidases extracted from the leaves of the sunflower varieties DK3790 and Record grown under normal conditions and those of the salty environment NaCl 60 Mm and 120 Mm.

Variety	Sowing period	Stress duration	Growth duration	Witness	60 Mm	120 mM
Record	June-July	33 days	50 days	15.2	-	12.4
DK3790	March-April	35 days	50 days	0.96	2.2	3.2

Electrophoretic analysis of esterases isozymes extracted from the control sheets of the DK 3790 variety reveals the zymogram composed of 2 esterases est1, est3. In the environmental conditions 60 mM, 3 isozymes est1, est 2 and est3 are expressed. The intensity of revelation est2 is increased. Under stress conditions 120 mM, 3 isozymes est1, est2 and est3 are expressed; the est2 is of increased intensity of revelation. The variability of esterous polymorphism reveals a correlation between isozyme expression and increased salinity in the environment. In the DK 3790 variety tolerant to the soil, in the saline environment conditions 60 mM and 120 mM, 3 esterases are of higher intensity of revelation compared to control conditions. The expression of est2 esterase is increased and is related to the response to salinity in the variety DK3790. Other work by Dasgupta et al.[25] has revealed the expression of specific esterases of mangroves conditioned to the saline environment. Nine different esterous isoenzymes were detected in seed embryos sprouted in 105 mM NaCl, while only five of them were detected in untreated seed embryos.[26] Amouri et al. showed quantitative and qualitative variations in esterase isoenzymes between two varieties, tolerant and sensitive of medicago during the germ process and during saline stress.[27]

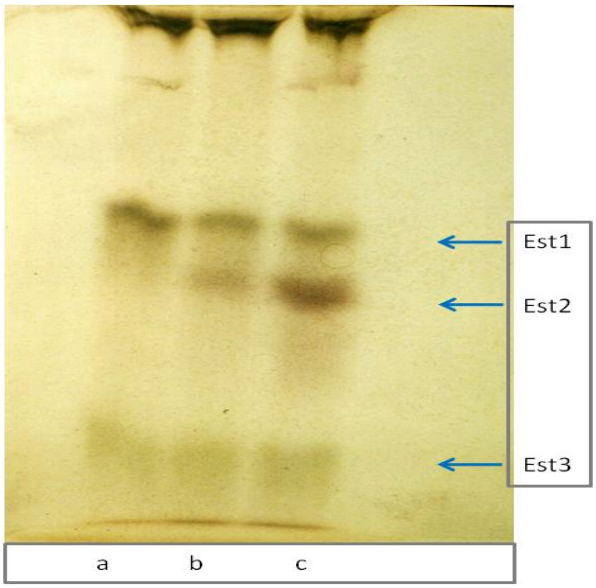

Figure 4. Zymogram of esterase extracted from sunflower leaves of varieties DK 3790 cultivated under normal and salin stress. a – absence of NaCl b –NaCl 60 mM c-NaCl 120 mM.

CONCLUSION

This work reveals the expression of specific peroxidase and esterase isozymes in the leaves of sunflower varieties tolerant to the saline environment. The activity of peroxidases extracted from the leaves is increased in the salinity-tolerant variety. The number of esterous isozymes is higher in sunflower varieties that are tolerant to the saline environment compared to susceptible varieties. The enzymatic activity of peroxidases could be biochemical markers of the adaptation of sunflowers in the conditions of the saline environment. Further work on the study of purification and isolated peroxidases will identify tissue and cell location and correlation with precise structure and function.

Further research is needed to better identify the factors of the conditions culture factors, regional variation and seasonal temperatures enzyme purification.

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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF TRANSITION METAL COMPLEXES OF 4-[(2-HYDROXY-4-METHOXYPHENYL)METHYLENEAMINO]-2,4-DIHYDRO-3*H*-1,2,4-TRIAZOLE-3-THIONE

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Keywords: SNO donor; triazole ligand; transition metal complexes, antimicrobial effect.

A novel nitrogen containing 4-[(2-hydroxy-4-methoxyphenyl)methyleneamino]-2,4-dihydro-3*H*-1,2,4-triazole-3-thione ligand **(H_2L)** was synthesized by using an equimolar ratio of 4-amino-1,2,4-triazole-3-thione and 2-hydroxy-4-methoxybenzaldehyde. A series of Mn(II), Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) complexes was synthesized by using the ligand. The synthesized ligand and transition metal complexes were characterized by IR, ^{1}H NMR, ^{13}C NMR, Mass spectrometry, UV, XRD and TGA investigation methods. Spectral data suggests that the ligand acts as a tridentate SNO donor. Further, the synthesized H_2L ligand and their metal complexes were screened for antimicrobial activity. The results of biological activities showed that the metal complexes have higher antifungal as well as antibacterial activity as compared to the parent H_2L ligand against the tested microbes.

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INTRODUCTION

Schiff base and their metal complexes play an important role in the biological systems due to their ability to bind to biologically active sites. 1,2,4-triazole derivatives show various pharmaceutical potential[1-6] including antitubercular[7,8] antimicrobial,[9] antifungal[10,11] anticancer,[12] cytotoxic[13] and antioxidant[14] activities. Due to multidentate nature, they are chelate-forming ligands and can form various transition metal complexes.[15] Various triazole moieties containing drugs such as vorozole, anastrozole and letrozole (Figure 1) are commercially available in the market.[16]

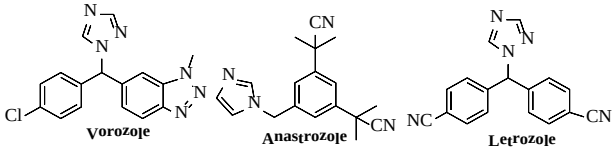


Figure 1. Some commercially marketed azole drugs

Schiff bases derived from vanillin are well-known in the literature for a wide range of biological activities.[17-19] An important benefit of using 2-hydroxy-4-methoxy benzaldehyde instead of vanillin is the availability of chelating position of -OH group, which can easily deprotonate and bind to metal ions.

In many cases, triazole moiety containing a ligand having a sulfur, oxygen and nitrogen atoms bind to the metal ion and enhance the biological activity as compared to parent moiety. In the present work, we synthesized tridentate (S,N,O) i. e. 2,4-dihydro-4-[(2-hydroxy-4-methoxy-phenyl)methylene]-amino-3*H*-1,2,4-triazole-3-thione ligand (H_2L) and its transition metal complexes which were screened for antifungal and antibacterial potential.

EXPERIMENTAL

All the used chemicals were AR grade and purchased from Spectrochem or SD Fine Ltd. and used without purification. The 4-amino-1,2,4-triazole-3-thione was prepared according to the literature method.[20] ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 on Bruker NMR, IR spectra on Perkin IR spectrometer, UV analyses were performed on a Shimadzu UV-VIS instrument and TGA results were obtained on a Shimadzu thermogravimetric analyzer. XRD measurements were done on a Philips Bragg--Brentano parafocusing goniometer (CuK_α) at 298 K.

Synthesis of 4-amino-1, 2, 4-triazole-3-thione (3a)

A thiocarbohydrazide (**2**) (20.12g, 0.2 mol) was mixed with 20 mL of 98-100% formic acid (**1**) and the contents were refluxed for 10-20 minutes. The solution was cooled to room temperature to get a white crystalline solid, which was recovered by filtration followed by crystallization from ethanol to afford the pure 4-amino-1, 2, 4-triazole-3-thione (**3a**) (Scheme 1). Yield: 76 %, M. P.= 166 ℃.

Synthesis of 4-[(2-hydroxy-4-methoxyphenyl)methyleneamino]-2,4-dihydro-3*H*-1,2,4-triazole-3-thione, ligand (H_2L) (5a)

An equimolar mixture of 2-hydroxy-4-methoxy benzaldehyde (**4**) (0.116g, 0.001 mol) and 4-amino-1,2,4-triazole-3-thione (**3a**) (0.152g, 0.001 mole) in 3 mL glacial acetic acid was refluxed for 3 hours. After completion of reaction, the reaction mass was poured on crushed ice and filtered off to get 2,4-Dihydro-4-[(2-hydroxy-4-methoxyphenyl)methyleneamino]-3H-1,2,4-triazole-3-thione as a yellow coloured solid which was crystallized from absolute ethanol (Scheme 2).

The physical and analytical data of the synthesized compound are reported in Table 1.

Spectral data of ligand (H_2L)

Yield: 80 %, M. P.: 259-260 ℃; IR (KBr): cm^{-1} 1608.52 ν (HC=N), 2758ν (-SH), 3232ν (-OH); ^{1}H NMR **(**200 MHz, DMSO-d_6**)** δ ppm 3.39 (s, 3H,-OCH_3); 5.98 - 6.17 (m,2H, Ar-H); 6.92 (d, *J* = 8.08 Hz, 1H, Ar-H); 7.92 (s, 1H, -N=CH-N); 9.13 (d, *J* = 2.53 Hz,1H, Ar-H); 10.26 (s, 1H, -OH); 13.29 (br. S, 1H, SH); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm 164.16 (s, quat, Ar), 162.71 (s, quat, Ar), 160.46 (s, quat, triazole), 158.94 (-HC=N), 137.58 (s, triazole), 130.91 (s, Ar), 110.81 (s, Ar), 107.37 (s, Ar), 101.13 (s, Ar), 55.52 (s, OCH_3); LCMS: m/z (%): 251.1 (M+H).

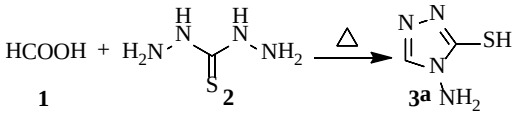
General procedure for preparation of metal complexes (6a-6f)

A methanolic solution of metal salt was added dropwise to a boiling methanolic solution of ligand H_2L in an equimolar ratio (1:1) with constant stirring. The p^H of the reaction mixture was adjusted to 7.5 to 8.5 by adding 10 % ethanolic ammonia solution and the contents were refluxed for about 7-8 hr.

The precipitated solid metal complex was filtered and washed several times with absolute methanol and dried (Scheme 3).

RESULTS AND DISCUSSIONS

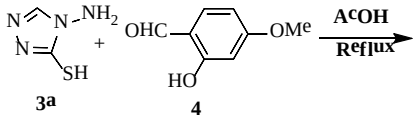
Synthesis of triazole ring was performed by reacting thiocarbohydrazide (**2)** with 98-100% formic acid (**1**) under reflux for 10-20 minutes. The yield of 4-amino-1, 2, 4-triazole-3-thione (**3a**) (Scheme 1) was found to be 76 %.



1 2 3a

Scheme 1. Synthesis of 4-amino-1,2,4-triazole-3-thione

An equimolar mixture of 2-hydroxy-4-methoxy benzaldehyde (**4**) and 4-amino-1,2,4-triazole-3-thione (**3a**) in acetic acid under 3 h reflux resulted in 4-[(2-hydroxy-4-methoxyphenyl)methyleneamino]-2,4-dihydro-3H-1,2,4-triazole-3-thione as yellow solid (Scheme 2). The physical and analytical data of the synthesized ligand is reported in Table 1.



3a 4

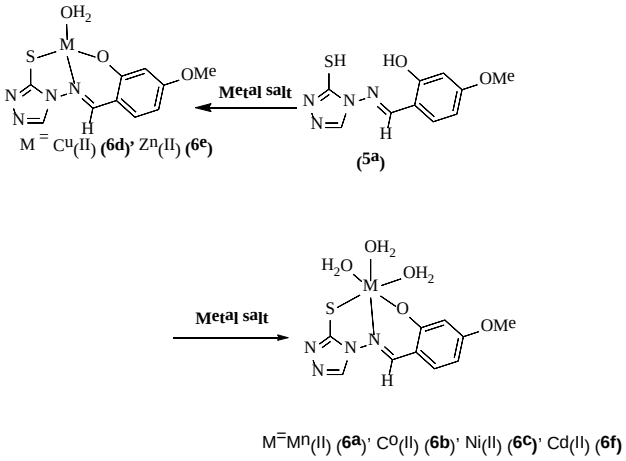
5a

Scheme 2. Synthesis of Schiff base ligand H_2L

Table 1. Physical and analytical data of the synthesized compounds

Compounds	Mol. Formula (Formula weight)	Melting point, °C	Color	Elemental analysis found (calculated)%				
				% C	% H	% N)	% S	% M
Ligand (H_2L) (**5a**)	$C_{10}H_{10}N_4O_2S$ (250.05)	259-260	Pale yellow	47.87 (47.99)	4.09 (4.03)	22.44 (22.39)	12.79 (12.81)	-
[Mn(L)(H_2O)$_3$] (**6a**)	$C_{10}H_{14}MnN_4O_5S$ (357.24)	dec	Bright yellow	33.75 (33.62)	3.99 (3.95)	15.59 (15.68)	8.92 (8.98)	15.31 (15.38)
[Co(L)(H_2O)$_3$] (**6b**)	$C_{10}H_{14}CoN_4O_5S$ (361.24)	dec	Brown	33.16 (33.25)	3.80 (3.91)	15.64 (15.51)	8.79 (8.88)	16.22 (16.31)
[Ni(L)(H_2O)$_3$] (**6c**)	$C_{10}H_{14}N_4NiO_5S$ (360.00)	dec	Brownish	33.26 (33.27)	3.80 (3.91)	15.59 (15.52)	8.79 (8.88)	16.40 (16.26)
[Cu(L)(H_2O)] (**6d**)	$C_{10}H_{10}CuN_4O_3S$ (329.82)	dec	Light green	36.49 (36.42)	3.10 (3.06)	16.80 (16.99)	9.80 (9.72)	19.15 (19.27)
[Zn(L)(H_2O)] (**6e**)	$C_{10}H_{10}N_4O_3SZn$ (330.00)	dec	Yellow	36.29 (36.21)	3.15 (3.04)	16.81 (16.89)	9.55 (9.67)	19.60 (19.72)
[Cd(L)(H_2O)$_3$] (**6f**)	$C_{10}H_{14}CdN_4O_5S$ (414.71)	dec	Cream yellow	28.89 (28.96)	3.52 (3.40)	13.42 (13.51)	7.65 (7.73)	27.20 (27.11)

Refluxing methanolic solutions of the metal salt and ligand H_2L in an equimolar ratio (1:1) for 7-8 h followed by adjusting the pH of the reaction mixture to 7.5-8.5 by adding 10 % ethanolic ammonia solution resulted in solid metal complexes (Scheme 3).



Scheme 3. Synthesis of metal complexes (**6a-6f**)

Physical and analytical data of the synthesized metal complexes is given in Table 1. The analogous reaction with iron(II) salts resulted in a complex mixture containing an iron(II) and two iron(III) complexes as detected by Mössbauer. Efforts to grow single crystals were unsuccessful. The synthesized complexes were proved to be X-ray amorphous except Mn(II), Zn(II) and Cd(II) complexes. These complexes look like to be monoclinic, and the lattice constants could not be determined exactly because of small particle size and wide bands of compounds.

^{1}H NMR spectra

In the ^{1}H NMR spectrum of the ligand, the azomethine (-CH=N-) proton appearing as a singlet at 9.14 δ ppm was shifted to δ 9.18 ppm in Zn complex. The signal for azomethine proton in zinc complex was observed slightly downfield, which is due to the transfer of electrons from azomethine nitrogen to zinc metal. There is formation of a coordination bond between azomethine nitrogen and zinc (Zn←N) [21]. The characteristic proton signal of triazole (-SH) and phenolic (-OH) disappeared in Zn complex, indicating that $-S^-$,$-O^-$ bindings form during complex formation. The coordinated water peak appeared at δ 3.04 ppm in the spectrum of Zn complex.

Mass spectra

The LCMS spectrum of ligand (H_2L) showed a peak at 251.1 amu corresponding to M+H confirming the suggested formula ($C_{10}H_{10}N_4O_2S$). The mass spectrum of metal complexes displayed peaks at 361.0 and 331.2 amu for nickel(II) and zinc(II) complexes, respectively, corresponding to the molecular ion peak (M+H). The molecular ion peaks of metal complexes confirm the proposed molecular formula $C_{10}H_{14}N_4NiO_5S$ for nickel and $C_{10}H_{10}N_4O_3SZn$ for zinc complex. The mass spectra of metal complexes reveal the evidence of equimolar ratio of metal and ligand (1:1) as presented in Scheme 3.

UV-Visible spectra

Electronic spectra of the synthesized metal complexes were recorded in DMSO solvent at room temperature. The results can be seen in Table 3. The bands found for d^{10} metal-containing complexes (Zn(II), Cd(II) may contain only CT and ligand n⟶π* bands, while ligand absorptions may correspond to n⟶π* and π ⟶π* transitions.[23-25]

Table 3. UV data for the synthesized metal complexes

Sample	Absorption maxima, λ_{max}, nm
Ligand (H_2L) (**5a**)	400, 325
[Mn(L)(H_2O)$_3$] (**6a**)	406, 279
[Co(L)(H_2O)$_3$] (**6b**)	552, 404
[Ni(L)(H_2O)$_3$] (**6c**)	800, 613, 394
[Cu(L)(H_2O)] (**6d**)	612, 432
[Zn(L)(H_2O)] (**6e**)	402
[Cd(L)(H_2O)$_3$] (**6f**)	516, 389

As can be seen from Table 3, the geometry around Zn(II) and Cd(II) might be different, probably due to the difference in coordination numbers of central ions in these complexes. The UV-Vis intensities of octahedral Mn(II) complexes are very low as a consequence of their doubly forbidden nature and easily be masked by the bands of the organic ligand. Over the ligand bands, the d-d bands of octahedral Co(II) and Ni(II) complexes could be detected (Table 3). The visible range bands at 552 for Co(II) and at 800 and 613 for Ni(II) probably belongs to the $^4T_{1g}\rightarrow{}^4T_{1g}(P)$ and the $^3A_{2g}\rightarrow{}^1E_g$ and $^3A_{2g}\rightarrow{}^3T^{1g}$ transitions, respectively. As usual, the distorted tetrahedral Cu(II) complex has only one broadband in the visible region.

IR spectra and bonding modes

Infrared spectroscopy gives information regarding the type of functional groups (-SH, -OH, -N=CH-) attached to the corresponding metal ions. IR spectrum of ligand displays a band corresponding to -N=CH- linkage at 1598 cm^{-1}, which confirms the formation of Schiff base. Similarly, the band observed around 1608 cm^{-1} corresponds to the same -N=CH- linkage coordinated to the metals.[26-28] It is supported by the appearance of metal-nitrogen ν(M-N) bands between 441 and 466 cm^{-1}. In the IR spectra of ligand and complexes, a broad band at 2758 and 1109 cm^{-1} arise due the ν(S-H) and ν(C=S), respectively, while in the complexes, an ionic nature C-S band appears at 720 cm^{-1}.[27]

The broad band in the spectra of complexes in the 3310-3330 cm^{-1} region indicates the presence of coordinated water. The broad band observed at 3232 cm^{-1} corresponds to -O-H stretching mode in the ligand, which disappears in the complexes indicating deprotonation of phenolic-OH during the complex formation. In IR spectra, -S-H stretching vibration was absent in metal complex due to deprotonation of thiol group and thiol sulfur coordinated to the metal ion.[29] Some selected IR spectral data are summarized in Table 4.

Table 4. Important IR spectral bands and their assignment

Compound	ν(HC=N)	ν(–OH)	ν(M-N)	ν(M–O)
5a	1609	3237	-	-
6a	1592	3390 (br.)	435	490
6b	1594	3345 (br.)	470	580
6c	1597	3361 (br.)	451	550
6d	1595	3450 (br.)	460	530
6e	1594	3370	447	569
6f	1592	3300 (br.)	490	553

From the IR data of the ligand and the corresponding metal complexes, it is clear that the ligand acts as a tridentate ligand. The coordinating atoms are the azomethine nitrogen, the thiol-sulfur and phenolate oxygen.

On the basis of the above spectral observations, we conclude that the ligand coordinates dinegative and tridentate around the metal ions.

Thermogravimetric analysis

Thermal data was recorded in the temperature range between 25-1000 ^{o}C under N_2 and the results are summarized in Table 5. The primary decomposition intermediates were proved to be X-ray amorphous, based on the mass loss, these are expected to be the apropriate oxides of the central metal ions.

Table 5. Thermogravimetric analysis of the synthesized complexes

Sample	Temperature range, °C (Peak temp.)	Mass loss, %
Mn(II) **6a**	54-150	7.11
	350-400	17.13
	575-600	18.66
Co(II) **6b**	60-150	9
	310-350	27.23
	440-535	12
Ni(II) **6c**	67-150	11
	323-385	51
Cu(II) **6d**	60-155	6.37
	232-250	11
	332-350	10
Zn(II) **6e**	200-212	4.53 (5.42)
	339-382	29.82
	457-660	35.26
Cd(II) **6f**	71-170	11
	335-370	22
	423-500	18

Antimicrobial study

The synthesized compounds (ligand and metal complexes) were explored for antifungal and antibacterial activities. These activities were performed on Petri-plate containing 30 mL potato dextrose agar and nutrient agar medium. The plates were incubated for 24-48 h and 20-24 h culture of fungal and bacterial strains, respectively and the results were measured in terms of zone of inhibition in mm. Two fungal (*Aspergillus niger*, *Alternaria alternata*) and one bacterial (*S. Aureus*) species at 250 ppm concentration were used for studying antimicrobial activities. Results were compared with the standard drug i. e. carbendazim for fungal and streptomycin for bacterial as positive control reference drugs (Table 6).

The results of antifungal activity suggested that among the tested compounds, only the cobalt complex was active against *Aspergillus niger* and copper, cadmium complexes against *Alternaria alternate* comparable with the standard drug.

Table 6. Results of antimicrobial activity of the synthesized compounds

Compounds	Zone of Inhibition Diameter in mm		
	Antifungal		Antibacterial
	A. Niger	***Alternaria A.***	***S. Aureus***
Ligand (H_2L)	17	5	10
6a	13	12	15
6b	21	15	15
6c	14	11	16
6d	17	40	17
6e	14	25	15
6f	13	45	20
*AF	**24**	**26**	-
*AB	**-**	**-**	**40**

*AF = Carbendazim, *AB = Streptomycin

The antibacterial screening performed against *Streptococcus Aureus* indicates that all complexes were less potent than the standard drug - streptomycin. Selected images for the antimicrobial activity are shown in Figure 5.

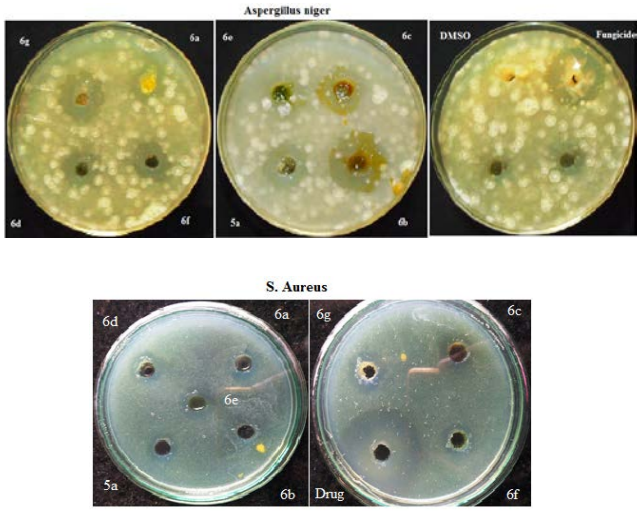


Figure 5. Selected images for the antimicrobial activity

CONCLUSION

The synthesized ligand acts as tridentate around the central metal(II) ions. On the basis of different techniques, the complexes of Mn(II), Co(II), Ni(II) and Cd(II) showed octahedral geometry, but Cu(II) complex exhibits square planar and Zn(II) form tetrahedral geometry. Results of antimicrobial activity indicate that the metal complexes show greater activity than the parent ligand. The ligand and metal complexes showed very less activity against *S. aureus*, which could be due to azomethine linkage and hetero atoms present in these compounds.

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