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GRT Golden Research Thoughts

DESIGN, SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF S-TRIAZINE DERIVATIVES

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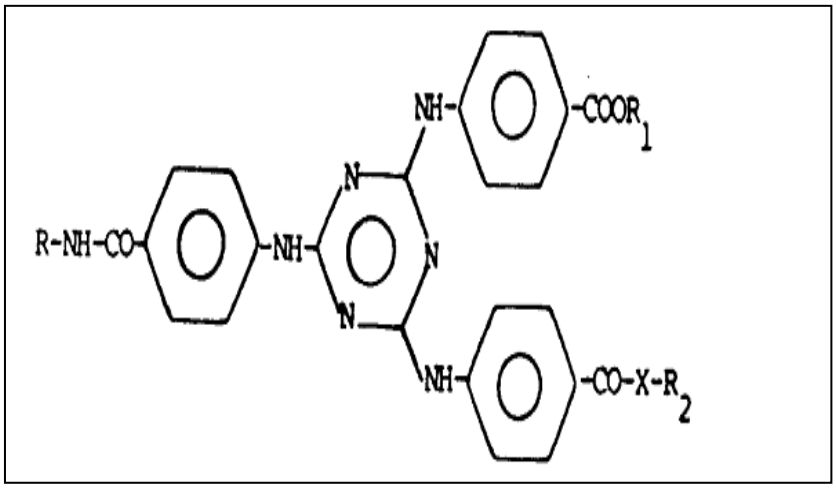
ABSTRACT

A series of 1, 3, 5-triazines derivatives were designed, synthesized and evaluated their biological activity. The preliminary investigation showed that most compounds displayed well to excellent potency against selected micro organism. The QSRRs are statistical models which quantify the relationship between the structure of a molecule and its chromatographic retention parameters in different kinds of chromatography. The application of QSRR allows the prediction of the retention of a new solute, identification of the most informative structural descriptors, and elucidation of the molecular mechanisms of separation in a given chromatographic system, evaluation of complex Physico-chemical properties of solutes and estimation of biological activities. The structure of the novel compounds were elucidated on the basis of IR, ^{1}H-NMR and elemental analysis.

KEYWORDS:*s-triazine, Lipiph ilicity, antimicrobial activity.*

INTRODUCTION

Significant progress has been achieved by combinational therapy to combat microbial infections still antimicrobial resistance appears to be a major concerns to the public health and scientific community's world wide. Further, infection spread by various pathogens fail to response the treatment resulting in prolonged illness and greater risk of death and need for an effective therapy which tends to screen the newly synthesized derivatives against the representative strains of bacteria and fungi. 1, 3, 5-triazines are amongst the oldest known organic molecules; originally they were called the symmetric triazines usually abbreviated as S- or Syn-triazines. Some of the substituted 1,3,5-striazine have reported to possess interested biological activities. A wide range of 1,3,5-triazines exhibit selective herbicidal properties, Simazine and atrazines are the organic compounds containing striazine skeleton are most important herbicides.[1] Triazines derivative Altretamine and triethylene melamine (TEM) shown activity against leukemia. Compounds contain 1,3,5-triazine as a lead moiety possessing a wide spectrum of biological activities such as anti-cancer[2-6], antiviral [7], bactericidal [8-10], fungicidal[11-12], antimalarial agents[13-14] and antituberculosis [15]. In addition, the interest in 1,3,4-



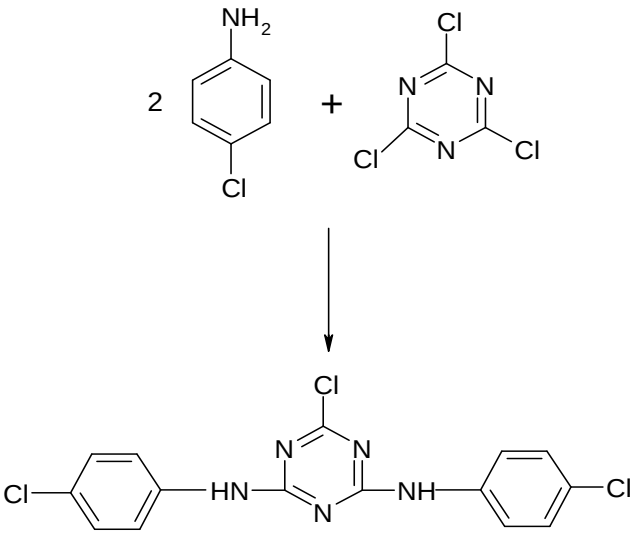
oxadiazole also one of important heterocyclic compound show significant biological activity such as antibacterial and fungicidal.[16-18]

MATERIAL AND METHODS

All chemicals and solvents procured were of analytical grade and used directly without further purification. All melting points were determined in PMP-DM scientific melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed using silica gel-G coated Al-plates (0.5 mm thickness, Merck, Germany) using appropriate mobile phase system and spots were visualized under UV and Iodine chamber. 1H NMR spectra were recorded on a Bruker Avance-II 400 MHz spectrophotometer (Bruker Bioscience, USA) using DMSO as a solvent and TMS as internal standard (chemical shifts in ∂ ppm). Infra Red spectra were recorded on FT Shimadzu spectrophotometer (Shimadzu, Tokyo, Japan) using KBr pallets. Elemental analyses were carried out on Heraeus Rapid Analyser (Heraeus, Germany) and functions were within 0.4% of the theoretical value.

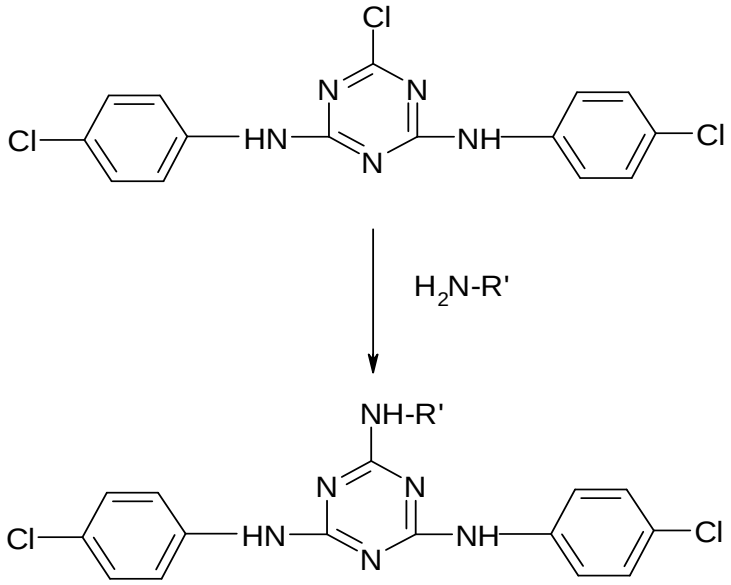
Synthesis of 2'-chloro 4', 6'-bis-(chloroaniline)-s-triazine

Cynuric chloride (9.3 gm) was dissolved in 50 ml acetone and cooled at 0^{o}C to it p-chloroaniline (10 gm) was added at low temperature followed by sodium hydroxide in water the temperature was raised to 45-50^{o}C further stirred for 2 hours poured into ice cooled water filtered and dried.



Synthesis of 4', 6'-bis-(chloroaniline)-2'-aryl-amine-s-triazine

2'-Chloro-4', 6'-bis-(chloro-aniline)-s-triazine (2.95 gm) was dissolved 50 ml dioxane and selected 1.69 gm of amine and sodium hydroxide 0.1 gm in 25 ml water were added. The constants were refluxed on the water bath for 3 hours and poured in to ice cooled water.



Compd	a	b	c	d	e	f
R'	2-toluidine	3-toluidine	4-toluidine	2-chloro aniline	3-chloro aniline	4-chloro aniline

The separated compound was filtered washed with water and dried, the amines were taken as o-toluidine, m- toluidine, p- toluidine , o-chloro aniline, m-chloro aniline and p-chloro aniline.

RESULTS AND DISCUSSION

The molecular formula of these compounds was calculated from their elemental analysis and mass spectrum. The structure of synthesized s-triazine have been confirmed by elemental analysis, IR and ^{1}H-NMR spectral data studies. The antibacterial and antifungal activities of compounds (a to f) were assayed in vitro against selected bacteria: *Escherichia coli, E. Scherichia coli, Staphyloi aures , Sligelly and* and *fungi Aspergillus niger, Aspergillus Purasities, Tricroderm uridue, Chrysoporium Sps.* The minimal inhibitory concentration (MIC) values of compounds a to f were determined using the filter paper disc diffusion method (antibacterial and antifungal activity). Streptomycin and griseofulvin, used as the standard for the antibacterial and antifungal activity, respectively, showed MIC values in the range 1.25–3.25 µg mL-1 for all the bacterial strain and 6.25–12.5 µg mL-1 for all fungal strain. All standards were also screened under similar condition for comparison.

4, 6'- bis-(chloro aniline)-2-(2-toluidine)-s-triazine (a) : Yield 89% , m. p. 215^{0}C. Anal. Cald for $C_{21}H_{18}N_6Cl_2$: C 58.20 %,H 4.18 %,N 19.65 % found C 59.29 %,H 4.23 %,N 19.76 % ; IR: 2958, 1483, (-CH_3)1550, 1406(-C=N Str.), 3056,1597,997 (Aromatic ring), 3370 (-NH str.) 1530 (NH bend.), 752 (C-Cl); ^{1}HNMR: 2.55 (s, 3H, -CH_3), 7.14-7.68 (m, 12 H, Ar-H), 8.24 (s, 1H, -NH-) 8.42 (s,2H,-NH); Mass (FAB) :425 (M^+).

4', 6'- bis-(chloro aniline)-2-(3-toluidine)-s-triazine (b): Yield 86% , m. p. 220^{0}C. Anal. Cald for $C_{21}H_{18}N_6Cl_2$: C 58.19 %,H 4.15 %,N 19.55 % found C 59.29 %,H 4.23 %,N 19.76 % ; IR: 2960, 1485, (-CH_3), 1560, 1420 (-C=N Str.), 3060,1600,993 (Aromatic ring), 3375 (-NH str.) 1540 (NH bend.), 758 (C-Cl); ^{1}HNMR: 2.60 (s, 3H, -CH_3), 7.20-7.76 (m, 12 H, Ar-H), 8.03 (s, 1H, -NH-) 8.06 (s,2H,-NH); Mass (FAB) :425 (M^+).

4', 6'- bis-(chloro aniline)-2-(4-toluidine)-s-triazine (c): Yield 79% , m. p. 235^{0}C. Anal. Cald for $C_{21}H_{18}N_6Cl_2$: C 58.15 %,H 4.16 %,N 19.71 % found C 59.29 %,H 4.23 %,N 19.76 % ; IR: 2959, 1490, (-CH_3), 1558, 1425 (-C=N Str.), 3065, 1598, 923 (Aromatic ring), 3380 (-NH str.) 1535 (NH bend.), 760 (C-Cl); ^{1}HNMR: 2.58 (s, 3H, -CH_3), 7.17-7.79 (m, 12 H, Ar-H), 8.19 (s, 1H, -NH-), 8.32 (s,2H,-NH); Mass (FAB) :425 (M^+).

4', 6'- bis-(chloro aniline)-2-(2-chloro anilin)-s-triazine (d): Yield 90% , m. p. 220^{0}C. Anal. Cald for $C_{21}H_{15}N_6Cl_3$: C 54.95 %,H 3.18 %,N 18.16 % found C 55.08 %,H 3.27 %,N 18.36 % ; IR: 1570, 1400 (-C=N Str.), 3072, 1598, 927 (Aromatic ring), 3372 (-NH str.) 1550 (NH bend.), 765 (C-Cl); ^{1}HNMR: 7.40-7.87 (m, 12 H, Ar-H), 8.19 (s, 3H, -NH-), mass (FAB) :457(M^+).

4', 6'- bis-(chloro aniline)-2-(3-chloro anilin)-s-triazine (e): 4', 6'- bis-(chloro aniline)-2-(2-chloro anilin)-s-triazine (d): Yield 92% , m. p. 224^{0}C. Anal. Cald for $C_{21}H_{15}N_6Cl_3$: C 54.76 %,H 3.09 %,N 18.25 % found C 55.08 %,H 3.27 %,N 18.36 % ; IR: 1560, 1430 (-C=N Str.), 3075, 1595, 927 (Aromatic ring), 3378 (-NH str.) 1550 (NH bend.), 765 (C-Cl); ^{1}HNMR: 7.22-7.83, (m, 12 H, Ar-H), 8.05 (s, 3H, -NH-), mass (FAB) :457 (M^+).

4', 6'- bis-(chloro aniline)-2-(4-chloro anilin)-s-triazine (f): 4', 6'- bis-(chloro aniline)-2-(2-chloro anilin)-s-triazine (d): Yield 88 % , m. p. 220^{0}C. Anal. Cald for $C_{21}H_{15}N_6Cl_3$: C 54.90 %,H 3.19 %,N 18.20 % found C 55.08 %,H 3.27 %,N 18.36 % ; IR: 1560, 1430 (-C=N Str.), 3075, 1595, 973 (Aromatic ring), 3378 (-NH str.) 1556 (NH bend.), 767 (C-Cl); ^{1}HNMR: 7.26-7.84 (m, 12 H, Ar-H), 8.07 (s, 3H, -NH-), mass (FAB) :457 (M^+).

Considerable attention has been paid to the analysis of chemical in the s-triazine group, due to their widespread use in agricultural chemistry and their subsequent degradation in biological syistems. For initial chemical screening of the activity of newly synthesized compounds it is recommended first to determine their lipopholicity, an important physico-chemical property in relation to biological activity. Lipophilicity is difficult to quantitate, but the most widely accepted measure of lipopholicity is the octanol-water partition coefficient, defined as the ratio of the concentrations of the solute in the two phases of a saturated 1-octanol-water system. Measurement of the octanol-water partition coefficient is achieved by an alternative method, reversed-phase liquid chromatography. Reversed-phase thin-layer chromatography (RP TLC) has been found to offer a rapid method for the analysis of a large number of s-triazine type compounds.

Certain relationships between the structure of s-triazine compounds and their mobility on silica gel impregnated with paraffin oil have recently been demonstrated. The retention behavior of compounds in various chromatographic systems is believed to be different by nature, i.e. the different physico-chemical properties of an analyte can influence its retention. Most recently, much effort has been done with the major aim of finding a mathematical model relating the retention of a given analyte to physico-chemical and structural parameters (descriptors) of test molecules. These correlations are known as quantitative structure-retention relationships (QSRR). Besides practical application in optimization strategies, QSRR studies can significantly contribute to getting some insight into the molecular mechanism of separation. The QSRR equations describing RM0 determined for different mobile phase organic component in terms of logarithms of n-octanol-water partition coefficients were derived. The partition coefficients (AlogP, IAlogP, ClogP, logPKowin, XlogP, ACDlogP) were calculated by using different software packages. The purpose of the work described in this paper was, therefore, to select the logP data and TLC system that best characterize octanol/water partitioning, and thus the Lipophilicity of the investigated molecules.

Six derivative of s-triazines were investigated. Standard solutions (1 mg cm^{-3}) were prepared in methanol, acetone, or chloroform. Samples were spotted on the plates by means of a micro-pipette. TLC was performed on 20 × 20 cm glass plates precoated with impregnate silica gel. The thin-layer of impregnate silica gel was prepared by suspending 25 g silica gel 60 GF254 (Merck) in 100 ml diethyl ether containing 2.5 % paraffin oil. To ease the visualization, fluorescent indicator F254 (Merck) was incorporated into the layers. Impregnate silica gel layer was developed using the following mobile phases: Aprotic solvents: Acetonitrile-water (φ=0.2-0.6; v/v), Acetone-water (φ= 0.5-0.8; v/v), Tetrahydrofuran-water (φ=0.45-0.7; v/v), Dioxane-water (φ =0.5-0.8; v/v). Protic solvents: Methanol-water (φ=0.5-0.8; v/v), Ethanol-water (φ =0.5-0.8; v/v).The plates were developed to a distance of 15 cm by the ascending technique at room temperature without previous saturation of the chamber with mobile phase. Dark spots were observed under UV light (λ =254 nm). R_M values were calculated from RM = log[(1/Rf) – 1. All calculations were performed using the computer software Origin, Version 6.1. The partition coefficients AlogP, IAlogP, ClogP, logP_{Kowin} and

XlogP, were calculated for the compounds by applying different theoretical procedures. ACDlogP was calculated using commercial software and the other partition coefficients were obtained from the internet .

Determination of Retention Constants, RM_0 , TLC Equations

When the R_M values calculated from R_f values (retention factor defined as the distance migrated by the sample from the origin compared with the distance migrated by the solvent front from the origin) were plotted against mobile phase composition for each compound there was a range in which a linear relationship was observed between the RM values and organic modifier concentration in the mobile phase, which can be expressed by the equation $R_M = R_{M0} S\varphi$, indicative of the reversed-phase chromatography, were φ is the amount (%) of organic compounds in the mobile phase . The obtained slopes, S, and intercept values, RM0, of TLC equation for each solute are presented in Table The correlation coefficients of the TLC equations were satisfactory.

Correlation Between Retention Constants, RM0, and Slope, S

A linear relationship was observed between the intercept, RM0, and slope, S, for protic and aprotic solvents, as shown by the equations given in Table 3.3.3. The best correlation was obtained for aceton as mobile-phase modifier (r = 0.994). There is a good correlation between RM0 and S, which might reflect the suitability of the systems examined for estimating the lipophilicity of the compounds. The RM_0 values, which are chromatographic data describing the partitioning between a non-polar stationary and a polar mobile phase, may therefore be appropriate for the assessment of lipophlicity.

Table:3.3.3: Equation for the relationships between the retention constant R_{MO} and Slope, S

Mobile Phase	Equation	r	SD	n
Acetone-Water	R_{MO} = - 0.572-1.121S	0.994	0.101	18
Acetonitrile-Water	R_{MO} = -1.717 -1.356S	0.954	0.590	18
Dioxane-Water	R_{MO} = - 1.895-0.965S	0.920	0.392	18
Tetrahydrofuran-Water	R_{MO} = - 1.895 – 0.965S	0.985	0.140	18
Methanol-Water	R_{MO} = - 0.231-1.231S	0.987	0.110	18
Ethanol-Water	R_{MO} = - 0.786 – 1.152S	0.962	0.283	18

Based on the results obtained on silica gel impregnated paraffin oil, RM0 is directly dependent on the nature of mobile phase modifiers. In other words, the selectivity of separation of the tested substances are the result of specific interactions with the mobile phase.

Correlation of Retention Constants, RM_0 and logP

Lipophilic character often seems to be the most important physico-chemical parameter in determining the biological activity of chemical agents. Lipophilicity can be expressed in terms of many different descriptors (logP, logkw, RM, RM0), obtained experimentally or calculated. The experimental parameters most frequently used are the retention constants RM_0 (RPTLC) and logkw (RPHPLC), whereas the calculated quantity is logP. The partiton coefficient, logP, of a given compound between a non-aqueous and an aqueous phase can be used as an expression of its lipophilic character [15]. Because the retention of a compound in reversed-phase chromatography is governed by hydrophobic interactions, linear relationships between the retention constant, RM0,

and logP could be expected [16].The partition coefficients (AlogP, IAlogP, ClogP, logPKowin, XlogP, ACDlogP) of striazine derivatives are listed in Table: 1

Table:1:.Partition coefficients calculated by different theoretical methods

Compd	AlogP	IAlogP	ClogP	$logP_{Kowin}$	XlogP	ACDlogP
a	5.25	5.06	4.85	5.07	4.83	3.87
b	5.29	5.11	4.96	5.11	4.89	3.89
c	5.28	5.12	4.99	5.14	4.91	3.91
d	5.94	7.08	6.28	6.36	6.07	5.06
e	5.98	7.12	6.23	6.41	6.11	5.08
f	5.99	7.16	6.21	6.39	6.01	5.09

Table: 2:. Correlation coefficients (r) for the correlation between R_{M0} and different logP values

Compd	$Alog_P$	$IAlog_P$	$Clog_P$	$logP_{Kowin}$	$Xlog_P$	$ACDlog_P$
Acetone	0.835	0.705	0.858	0.877	0.795	0.804
Acetonitrile	0.763	0.708	0.828	0.875	0.671	0.757
Dioxane	0.747	0.624	0.815	0.900	0.681	0.770
Tetrahydrofuran	0.570	0.533	0.648	0.756	0.532	0.707
Methanol	0.702	0.604	0.794	0.895	0.665	0.750
Ethanol	0.855	0.795	0.822	0.838	0.900	0.825

By comparing the calculated values to define the lipophilicity of the investigated molecules, it is evident that ethanol as a modifier gives the highest correlation (calculated average correlation coefficient is 0.839).

Retention Constants, RM_0 for QSRR

The QSRRs are statistical models which quantify the relationship between the structure of a molecule and its chromatographic retention parameters in different kinds of chromatography. The application of QSRR allows the prediction of the retention of a new solute, identification of the most informative structural descriptors, elucidation of the molecular mechanisms of separation in a given chromatographic system, evaluation of complex physico-chemical properties of solutes and estimation of biological activities.

The relationship between the retention and the structural characteristics of a molecule explains the effect of chemical structure on the retention behavior in a more accurate way.The use of multiple linear regression (MLR) analysis for fourteen s-triazine derivatives led to statistically significant equations relating lipophilicity (estimated by R_{M0} values (dependent variable) to different theoretically calculated six types of log P namely AlogP, ClogP, ACDlogP, logPKowin, X logP and IAlogP values for each compound (independent variable). The specifications for the best-selected MLR models are shown in Table 3 and Table 4.

These relationships were analyzed and the best model was selected on the basis of various statistical parameters like correlation coefficient (r), and standard deviation (SD). In the first phase of work, the multilinear relationships between the retention constant and two variable lipophilicity descriptors was examined.

Table: 3 :. Statistical parameters for multilinear dependence between RM0 and two variables descriptors Lipophilicity

Modifier	Descriptors		$R_{Mo} = a\log p_1 + b\log p_2 + c$				
R_{Mo}	$\log p_1$	$\log p_2$	a	b	c	r	SD
Acetone	$\log P_{Kowin}$	XlogP	0.0993	0.648	-0.313	0.916	0.329
Dioxane	AlogP	$\log P_{Kowin}$	0.312	0.813	-0.410	0.949	0.306
Methanol	$\log P_{Kowin}$	XlogP	0.571	0.672	-0.357	0.953	0.234

The analysis of these results indicates that the proposed models can correctly represent the relationship between the retention parameters of the investigated compounds on silica gel and different log P values calculated for various compound solely from the molecular structure. These models are suitable for prediction of the retention of structurally similar compounds under the same chromatographic conditions.

Table: 4: Statistical parameters for multilinear dependence between R_{M0} and three variables descriptors Lipophilicity

Modifier	Descriptors			$R_{Mo} = a\log p_1 + b\log p_2 + c\log p_3 + d$					
R_{Mo}	$\log p_1$	$\log p_2$	$\log p_3$	a	b	c	d	r	SD
Acetone	$Alog_P$	$\log P_{Kowin}$	$Xlog_P$	-1.969	0.811	0.524	-0.632	0.948	0.274
Acetonitrile	$Alog_P$	$\log P_{Kowin}$	$Xlog_P$	0.731	0.853	-0.292	-0.231	0.957	0.294
Dioxane	$\log P_{Kowin}$	$Xlog_P$	$IAlog_P$	-2.713	1.401	0.756	-1.203	0.901	0.659
Tetrahydrofuran	$\log P_{Kowin}$	$Xlog_P$	$ACDlog_P$	0.664	0.271	-0.609	0.791	0.904	0.280
Methanol	$\log P_{Kowin}$	$Xlog_P$	$IAlog_P$	0.948	0.708	-0.251	-0.208	0.964	0.216
Ethanol	$\log P_{Kowin}$	$Xlog_P$	$Clog_P$	0.625	0.408	0.537	-0.503	0.907	0.398

Experimentally obtained Rf RM_0 values depend on the nature of organic modifier in the mobile phase. A linear relationship between RM0 and slope, S, values was found for all mobile phases. Satisfactory linear correlation was obtained between the retention constants and AlogP, ClogP, ACDlogP, logPKowin, X logP and IAlogP. According to the correlationcoefficients, RM0 is a useful property for evaluation of the relative lipophilicity of the examined compounds. The correlations between the retention constants, RM0, and selected lipofilicity parameter (different logP values) of the solutes were expressed by multiparametric equations of high statistical significance, indicate that these models can be used to predict the retention constants of these molecules.

Table- 5: Antibacterial activity of the newly synthesized derivatives

Compound code	*Escherichia coli*		*Bucillus Subsniss*		*Staphyloi aures*		*Sligelly*	
	2%	4%	2%	4%	2%	4%	2%	4%
a	++	+++	++	+++	++	+++	+	++
b	++	+++	++	+++	++	+++	+	++
c	+	+	+	+	-	+	-	+
d	+	++	+	++	+	++	-	+
e	++	++	-	+	+	++	-	+
f	+	++	-	+	-	+	-	+

Std- = stremtomycin inhibition diameter in mm
Highly active = +++ (inhibition zoes>15)
moderatively active= ++ (inhibition zone 10-15)
slightly active = + (inhibition 10)

inactive inhibition zone -6) For bacteria

Table 6 : Antifungal activity of the synthesized compound derivatives

Compound code	Aspergillus niger		Aspergillus Purasities		Tricroderm uridue		Chrysoporium Sps	
	2%	4%	2%	4%	2%	4%	2%	4%
a	++	+++	++	++	++	+++	+	++
b	++	+++	+	+++	++	++	++	+++
c	-	+	-	++	-	+	+	++
d	++	+++	+	+++	++	+++	++	+++
e	++	+++	++	+++	++	+++	++	+++
f	++	+++	++	+++	++	-	++	+

Std- Exriseofulvin inhibition diameter in mm
Highly active = +++ (inhibition zones>15)
moderatively active= ++ (inhibition zone 10-15)
slightly active = + {inhibition 10]
Inactive = - (inhibition zone) Zone<-6) for bacteria

RESULTS AND DISCUSSION

Given rise to the the final product a to f most of the compound of the series where white crystalline which where systematically crystallize and purified before sent for elemental analysis and there structural characterization. The Synthesised compounds where simulated on the computer using PC Model Software [Sarena Version 3.01] visualize steric arrangement and the spatial elongation of the substitutes groups and they relative position. As expected form the molecular structure and their substitution.

Table-8: Variation of IR, ^{1}HNMR and PC Model data values for different substituted derivatives (a to f)

Compd	Dipole Moment	VdW Force	Molar Volume	IR cm^{-1}		^{1}HNMR ppm		
				C-N str	N-H str	-NH	-NH	Ar-H (C-H)
a	1.020	16.089	285	1406.7	3370.2	8.12	8.69	7.21-7.78
b	2.073	16.533	286	1420.7	3375.5	8.08	8.68	7.20-7.76
e	1.163	16.851	286	1425.3	3380.8	8.19	8.17	7.19-7.79
d	1.273	16.516	283	1400.2	3376.7		8.01	7.53-7.83
e	2.186	16.339	283	1428.9	3377.3		8.06	7.40-7.78
f	2.229	16.330	283	1430.3	3378.5		8.08	7.42-7.86

Thus an overall comparison of the compounds in this series viz. there overall steric performance relative variation in the simulation data and the values obtained and result of characterization justifies the selection of these compounds for synthesis in the present work.

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