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An efficient synthesis and quantitative structure-activity relationship studies on some substituted 1,2-diazaphenanthrenes as potential antimicrobial agents

Manisha Sharma

Department of Chemistry, Mangalayatan University, Aligarh, India

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ABSTRACT

*A new series of 1,2-diazaphenanthrene derivatives **3a-p** has been synthesized and subjected to evaluate their antibacterial properties. All the synthesized compounds of the series elicit remarkable activity in comparison to standard drug (ampicillin). A number of descriptors were tested to adjudge a quantitative correlation between activity and structural features. However, significant correlation has emerged between activity and physicochemical parameters viz. hydrophobic parameter (log P). Moreover, results are interpreted on the basis of multiple regression analysis and cross-validation methodology.*

Key words: Physicochemical parameters, Hydrophobic parameter, Quantitative structure-activity relationship (QSAR), and 1,2-Diazaphenanthrene.

INTRODUCTION

A number of polycyclic aromatic hydrocarbons (PAH), including some nitrogen-heterocyclic analogues and aza derivatives, have been shown to be carcinogenic to some extent in animals[1]. However, to a greater extent polycyclic aromatic hydrocarbons together with corresponding polycyclic aza-aromatic compounds are of immense importance in astrophysics and life sciences[2-4]. Isolation of polycyclic aza-aromatic compounds from natural /environmental sources is very difficult, and hence, under these conditions biochemical studies has to rely on synthetic materials. A great deal of interest in the chemistry of these substances and their interaction with bio molecules is a subject of intense research now a day. The development of efficient and mild methods of synthesis of heterocyclic compounds represents a thrust area of intense research and development of these compounds[5-10]. In this context, nitrogen-containing heterocycles are among the most useful and widely demonstrated categories[11-16].

In spite of the great biological potential residing in these compounds, little progress has been made in deducing antimicrobial behavior of poly aromatic hydrocarbons, which need to be investigated very thoroughly. Further it has been observed that potency of several bacteria against commercially available drugs increases tremendously. As a result there is an urgent need for new antibiotic agents, which would fight against bacterial infections. These threats have rekindled our interest in search of new compounds as potential antimicrobial agents. Thus in continuation of our

previous work on heterocyclic systems[17-21], we herein report a short novel strategy to synthesize a number of 1,2-diazaphenanthrene derivatives and evaluation of their antimicrobial behavior against a representative panel of bacterial pathogens.

Quantitative structure-activity relationship (QSAR) studies have also been performed on the basis of the fact that the biological activity of a compound is a function of its physicochemical properties[22-24]. For the sake of present study QSAR analysis of 1,2-diazaphenanthrene derivatives **3a-p** was performed based on the assumption of linear additive contributions of the different physicochemical properties viz., vander waals volume (VDW), connolly accessible area (CAA), connolly molecular area (CMA), connolly solvent excluded area (CSEV), dipole-dipole energy (DDENE), partition coefficient (log P). Multiple regression analysis was applied to generate QSAR models and to obtain statistical parameters, i.e., correlation coefficient (*r*), standard deviation (*s*), F-test, cross validated correlation coefficient (r^2_{CV}), sum of square standard error (S_{PRESS}), predicted residual sum of squares (*PRESS*) and sum of the squares of response value (*SSY*). These statistical data were utilized in order to have a judicious interpretation for effective QSAR models. The best-derived QSAR model was used to predict activity of the tested compounds and to suggest structural features, which should be incorporated to improve the pharmacological activity of the synthesized compounds.

MATERIALS AND METHODS

All the chemicals used were of analytical grade purity. Melting points were taken in open capillary tubes using an electric melting point apparatus. All the melting points reported are uncorrected. ^{1}H NMR spectra were recorded at 300MHz with a Bruker advance DRX 300 instrument using TMS as an internal stranded. IR spectra were run on a Perkin Elmer model 377-spectrophotometer using KBr pellets. Analytical thin layer chromatography was performed using E. Merck Silica gel-G 0.50 mm plates (Merck No. 5700).

2.1 Synthesis of (*E*)-diphenyldiazene[1a-p]

An appropriate quantity of diazoaminobenzene (0.012M, 2.5 mL) and a pertinent aniline derivative (0.01M) was taken in a 100 mL flask. To this, 1.3 g freshly prepared aniline hydrochloride was added and allowed to undergo heating at 40-45^0 C for 1h on water bath with constant stirring. The reaction mixture was then permitted to stand for 15 min at room temp. Now 15.0 mL (1:1) glacial acetic acid was added to contents and shaken thoroughly to remove excess aniline as aniline acetate. After allowing the mixture to stand as such for15 min yellow crystals of (*E*)-diphenyldiazene were obtained, filtered on Buchner funnel and dried in vacuum.

2.2 Synthesis of 1,2-diazaphenanthrene [3a-p]

(*E*)-diphenyldiazene (1.0mmol) in benzene (1000ml) was irradiated in a Pyrex vessel with 350nm U.V light in a photochemical reactor for 8h with stirring. Benzene was evaporated using a rotatory evapororator followed by the addition of acetone (30mL) to dissolve unreacted compound. Shiny crystals of final compound **[3a-p]** were obtained upon vacuum filtration. An overview of synthetic illustration is depicted in scheme-1. Physical characteristics and structural assignment are giving in Table-1.

The synthesis of 1,2-diazaphenanthrene derivatives was carried out as per Scheme1. The substrate (*E*)-diphenyldiazene **1a-p** was prepared by condensation of pertinent aniline and diaminoazobenzene[25]. Upon treatment of **1a-p** with benzene in a photochemical reactor **2** was yielded as an *insitu* intermediate, which in turn finally gave 1,2-diazaphenanthrene derivatives

3a-p as the desired products. An overview of a representative compound **3a** is depicted in Fig.1, delineating the PM3 optimized geometry.

RESULT AND DISCUSSION

3.1 Biological activities

The *in-vitro* antibacterial activity of the substituted 1,2-diazaphenanthrene derivatives has been investigated against several representative pathogenic bacteria. Nutrient agar media was employed for bacterial growth. Inocula containing approximately 10^7CFUs/mLof bacteria were prepared from broth culture in log phase. Bacterial plate was incubated at 37^0C for 24 h. Four microbial strains i.e., *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas diminuta* were used in antimicrobial assay. Ampicillin trihydrate was also screened under similar conditions as reference antibacterial drug. All the synthesized compounds have been found to delineate profound antimicrobial potency as compared to reference drug within a MIC range of 4-48 µg/mL. The screening results depicted in Table-2, reveal that reported compounds showed a remarkable effect on the bacteriocidal/ bacterostatic potency, as per the pattern shown below:

B. subtilis > S.aureus >E. coli> P.dimunata

3.2 QSAR analysis

3.2.1. Calculation of physicochemical properties

In order to deduce the correlation of observed activity, in terms of MIC (µg/mL) of reported compounds with different structural parameters, systematic QSAR investigations have been carried out using the model proposed by Hansch and coworkers[26].

The activity data (MIC) represents the concentration of compounds that inhibited visible growth. The same are further expressed as –log MIC on molar basis and used as dependent variables to get linear relationship in QSAR model. The calculated parameters used in present studies include vander waals volume (VDW), connolly accessible area (CAA), connolly molecular area (CMA), connolly solvent excluded area (CSEV), dipole-dipole energy (DDENE), partition coefficient (log P). The above-mentioned parameters were calculated by using Chem 3D 6.0 software[27]. Further, HOMO and LUMO energies were calculated by semiempirical PM3[28] studies using MOPAC 6.0 package[29].

3.2.2. Multiple linear regression analysis

Multiple linear regression (MLR) analysis was used to investigate the correlation between biological activity and physicochemical properties. The MLR was performed by using the VALSTAT[30] by the stepwise method. The highest correlation of independent variables with dependent variable was chosen for deriving the QSAR model. The statistical values, multiple correlation coefficient (r), standard errors (s), cross validation r^2 (q^2) and standard error of prediction (SPRESS) were used to evaluate the obtained QSAR models. Several combinations of independent variables were firstly attempted using three variables (one representative from each property) for individual models, and then, more variables were added in order to optimize the statistical values but not more than five independent variables were used. The best model derived from the MLR analysis was used to predict the inhibitory activity of the synthesized compounds. Calculated parameters and correlation matrix needed are shown in Tables 3 and 4.

The resulting mono parametric models are depicted in Eqs. 1-4, along with statistical parameters of the regression. No outliers have been determined the equations were derived using the entire data set (n=16).

QSAR model for *B. subtilis*

-log MIC = [2.946(± 0.236)] +log P [0.571(± 0.101)] (1)
n=16, r=0.950 std=0.0905, F=147.51

The comparison of above correlation coefficient (Table-2) shows that the partition coefficient (log P) plays a dominating role in the theoretical modeling of the activity and also shows the direct relationship with the activity. Comparison also demonstrates the significance of other parameters in deciding the activity quantitatively.

Further improvement in statistically significant models was achieved by incorporating another parameter i.e. CSEV in above eq. (1). and testing the validity of bi-parametric correlation.

Bi parametric QSAR model for *B. subtilis*

-log MIC = [2.264(± 0.683)]+logP[0.501(±0.112)] +CSEV [0.00506(± 0.00483)]
n=16, r=0.968, std=0.079, F=98.634

Results from the bi-parametric combination are not encouraging and model obtained is statistically not allowed. This also conforms the results of Eq. (1)

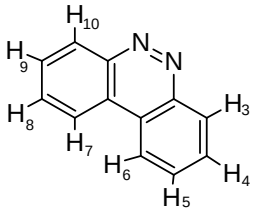
QSAR model for *S.aureus*
-log MIC = [2.945(± 0.389)] +log P [0.501(± 0.167)] (2)
n=16, r=0.865, std=0.148, F=41.915
QSAR model for *E.coli*
-log MIC = [2.921(± 0.326)] +log P [0.466(± 0.140)] (3)
n=16, r=0.887, std=0.124, F=51.85
QSAR model for *P.diminuta*
-log MIC = [2.952(± 0.315)] +log P [0.440(± 0.135)] (4)
n=16, r=0.883, std=0.120, F=49.60

The *F*-values obtained in Eqs. 1-4 are found statistically significant at 99% level. Similarly, cross validation of obtained equations were checked by employing the leave one out (LOO) method (r^2_{cv} > 0.83). The calculated and predicted activities of the synthesized compounds were in accordance with the observed activities as shown in Figs. 2 and 3.

PRESS (predicted residual sum of squares) is an important cross-validation parameter, which is a good approximation of the real predictive error of the models. Its value being less than SSY (sum of the squares of response value) points out that the model predicts better than chance and can be considered statistically important. In the present case all the proposed models have PRESS << SSY demonstrating them to be better than chance and statistically significant.

To have a dependable QSAR model, PRESS/SSY should be smaller than 0.4. Thus, the data presented in Table-5 show ratio of PRESS/SSY ranging between 0.15-0.45 indicating that all the proposed models are reliable QSAR models.

Table-1 – Physical characteristics and spectral assignment for synthesized 1,2-diazaphenanthrene derivatives



Compd.	M.P. (^{0}C)	Yield (%)	IR (υcm^{-1})	^{1}H NMR (δ ppm)	^{13}C NMR (δ ppm)
3a	135-36	81	3051 (C-H, sp^2), 2944(C-H, sp^3), 1628(C=C/C=N), 1610,1533, 1446(C⋯⋯C,ringstr),954,868,751 (sub. phenyl) 722(CH_2)	7.10(t,4H, H_4,H_5,H_8,H_9) 7.51 (d,2H,H_3,H_{10} J=8.0Hz), ,8.29(d, 2H,H_6,H_7)	16.1(CH_3),29.0(CH_2),125.0($C_{8,9}$)129.5($C_{4,13}$), 132.1(C5,12),132.2(C $_{6,11}$),148.5($C_{3,14}$).
3b	136-37	79	3055 (C-H, sp^2), 2943(C-H, sp^3), 1630(C=C/C=N), 1624,1531, 1438(C⋯⋯C,ringstr),956,862,743 (sub. phenyl)	7.12(t, 4H, H_4,H_5,H_8,H_9), 7.55(d,2H,H_3,H_{10} J=8.0Hz), 8.33 (d, 2H,H_6,H_7)	16.0(CH_3),29.2(CH_2),124.0($C_{8,9}$)128.5($C_{4,13}$), 132.5(C5,12), 132.1(C $_{6,11}$),151.5($C_{3,14}$).
3c	132-33	76	3047 (C-H, sp^2), 2947(C-H, sp^3), 1636(C=C/C=N), 1622,1534, 1441(C⋯⋯C,ringstr),953,854,741 (sub. phenyl)	7.11(t, 4H,H_4,H_5,H_8,H_9), 7.54(d,2H,H_3,H_{10} J=8.0Hz), 8.28(d, 2H,H_6,H_7)	14.3(CH_3),65.1(O-CH_2),120.0($C_{8,9}$)131.5($C_{4,13}$), 134.1(C5,12),135.2(C $_{6,11}$) 149.5($C_{3,14}$).
3d	131-32	78	3055 (C-H, sp^2), 2942(C-H, sp^3), 1628(C=C/C=N), 1630,1534, 1439(C⋯⋯C,ringstr),952,851,741 (sub. phenyl)	7.15(t,4H, H_4,H_5,H_8,H_9), 7.52(d, 2H,H_3,H_{10} J=8.0Hz), 8.31 (d, 2H,H_6,H_7)	14.3(CH_3),65.1(O-CH_2),125.6($C_{8,9}$)130.($C_{4,13}$), 133.1(C5,12),134.4(C $_{6,11}$) 150.5($C_{3,14}$).
3e	126-27	82	3058 (C-H, sp^2), 2945(C-H, sp^3), 1629(C=C/C=N), 1631,1534, 1442(C⋯⋯C,ringstr),953,851,747 (sub. phenyl)	7.13(t,4H, H_4,H_5,H_8,H_9), 7.56(d,2H,H_3,H_{10} J=8.0Hz), 8.32 (d, 2H,H_6,H_7)	125.0($C_{8,9}$)129.5(C-Cl), 132.1(C5,12), 132.2(C $_{6,11}$)148.5($C_{3,14}$).
3f	128-29	77	3049 (C-H, sp^2), 2945(C-H, sp^3), 1618 (C=C/C=N), 1633,1531, 1440 (C⋯⋯C,ringstr),950,858,740 (sub. phenyl)	7.11 (t,4H, H_4,H_5,H_8,H_9), 7.57 (d,2H,H_3,H_{10} J=8.0Hz), 8.30 (d, 2H,H_6,H_7)	56.0(O-CH_3),125.0($C_{8,9}$)129.5(C-Cl),132.1(C5,12),132.2(C $_{6,11}$)148.5($C_{3,14}$).
3g	132-33	81	3051 (C-H, sp^2),2954(C-H, sp^3), 1620(C=C/C=N),1623,1534,1442 (C⋯⋯C,ringstr),951,855,745(sub.phenyl)	7.10 (t,4H, H_4,H_5,H_8,H_9), 7.54 (d,2H,H_3,H_{10} J=8.0Hz), 8.32 (d, 2H,H_6,H_7)	56.2(O-CH_3),121.0($C_{8,9}$),126.5($C_{4,13}$), 130.1(C5,12),132.2(C $_{6,11}$), 151.5($C_{3,14}$).
3h	135-	80	3056 (C-H, sp^2), 2942(C-H, sp^3),	7.09 (t,4H, H_4,H_5,H_8,H_9), 7.59	56.0(O-CH_3),129.0($C_{8,9}$),135.5($C_{4,13}$),

	36		1628(C=C/C=N), 1610,1529, 1444(C⋯⋯C,ringstr),950,853,742 (sub. phenyl),	(d,2H,H_3,H_{10} J=8.0Hz), 8.28 (d, 2H,H_6,H_7)	136.1(C5,12),132.2(C $_{6,11}$),151.8($C_{3,14}$).
3i	132-33	77	3048 (C-H, sp^2), 2951(C-H, sp^3), 1630 (C=C/C=N),1632,1531,1438 (C⋯⋯C,ringstr),951,859,741(sub. phenyl)	7.10 (t,4H, H_4,H_5,H_8,H_9), 7.57 (d,2H,H_3,H_{10} J=8.0Hz), 8.30 (d, 2H,H_6,H_7)	21.2(C-CH_3), 125.0($C_{8,9}$)129.5($C_{4,13}$), 132.1(C5,12),132.2(C $_{6,11}$), 148.5 ($C_{3,14}$).
3j	134-35	78	3041 (C-H, sp^2), 2943 (C-H, sp^3), 1619(C=C/C=N), 1630,1535, 1442(C⋯⋯C,ringstr),955,856,742 (sub. phenyl)	7.16 (t,4H, H_4,H_5,H_8,H_9), 7.57 (d,2H,H_3,H_{10} J=8.0Hz), 8.34 (d, 2H,H_6,H_7)	21.8(C-CH_3), 125.0($C_{8,9}$), 129.5($C_{4,13}$), 132.1(C5,12),132.2(C $_{6,11}$), 148.5($C_{3,14}$).
3k	132-33	76	3052 (C-H, sp^2), 2951(C-H, sp^3), 1625(C=C/C=N), 1630,1531, 1438(C⋯⋯C,ringstr),950,861,743 (sub. phenyl)	7.13 (t,4H, H_4,H_5,H_8,H_9), 7.53 (d,2H,H_3,H_{10} J=8.0Hz), 8.34 (d, 2H,H_6,H_7)	56.0(C-O),105(C_8),125.0(C_{12}),126.9(C_9), 128.0(C_7),129.5($C_{4,}$),131.0(C_{13}),132.1 (C_5),132.2(C_6),148.5(C_{14}),151.0(C_3), 164(C_{11}).
3l	131-32	83	3058 (C-H, sp^2), 2949(C-H, sp^3), 1628(C=C/C=N), 1622,1533, 1440(C⋯⋯C,ringstr),952,860,740 (sub. phenyl)	7.11 (t,4H, H_4,H_5,H_8,H_9), 7.51 (d,2H,H_3,H_{10} J=8.0Hz), 8.30 (d, 2H,H_6,H_7)	105.1(C_{10}),125.5(C_{12}),126.5(C_8),128.2(C_7), 129.4($C_{4,}$),131.5(C_{13}),132.6(C_5),132.7(C_6), 148.1(C_{14}),151.2(C_3),159.9(C-OH), 164.2(C_{11}).
3m	129-30	80	3049 (C-H, sp^2), 2952(C-H, sp^3), 1629(C=C/C=N), 1625,1534, 1441(C⋯⋯C,ringstr),952,854,749 (sub. phenyl)	7.12 (t,4H, H_4,H_5,H_8,H_9), 7.50 (d,2H,H_3,H_{10} J=8.0Hz), 8.29 (d, 2H,H_6,H_7)	109.4(C_{10}),125.5(C_{12}),126.9(C_8),128.2(C_7), 129.5($C_{4,}$),131.3(C_{13}),132.6(C_5),132.7(C_6), 148.1(C_{14}),151.2(C_3), 159.5(C-OH) 164.2(C_{11}).
3n	132-33	79	3047(C-H, sp^2), 2942(C-H, sp^3), 1632(C=C/C=N), 1630,1535, 1446(C⋯⋯C,ringstr),956,855,748 (sub. phenyl)	7.15 (t,4H, H_4,H_5,H_8,H_9), 7.52 (d,2H,H_3,H_{10} J=8.0Hz), 8.34 (d, 2H,H_6,H_7))	124.6(C_{10}),124.7(C_9),125.4(C_{12}),126.9(C_8), 128.0(C_7),129.5($C_{4,}$),131.3(C_{13}),132.1(C_5), 132.2(C_6),144.1(C-NO_2),146.1(C_{14}),151.0 (C_3), 152.2(C_{11}).
3o	135-36	79	3045 (C-H, sp^2), 2941(C-H, sp^3), 1626(C=C/C=N), 1620,1529, 1442(C⋯⋯C,ringstr),956,852,741 (sub. phenyl)	7.11 (t,4H, H_4,H_5,H_8,H_9), 7.57 (d,2H,H_3,H_{10} J=8.0Hz), 8.30 (d, 2H,H_6,H_7)	124.5(C_{10}),124.9(C_9),125.1(C_{12}),126.7(C_8), 128.2(C_7),129.1($C_{4,}$),131.6(C_{13}),132.2(C_5), 132.5(C_6),144.2(C-NO_2),146.3(C_{14}), 151.2 (C_3), 152.1 (C_{11}).
3p	138-39	78	3045(C-H,sp^2),2940(C-H, sp^3), 1625(C=C/C=N),1601,1506,1440 (C⋯⋯C,ring.str), 950,854, 745(sub. phenyl)	7.16 (t,4H, H_4,H_5,H_8,H_9), 7.55 (d,2H,H_3,H_{10} J=8.0Hz), 8.31 (d, 2H,H_6,H_7)	125.0($C_{8,9}$)129.5($C_{4,13}$),132.1(C5,12), 132.2(C $_{6,11}$) 148.5($C_{3,14}$).

Table- 2. The *in vitro* antimicrobial activity of 1,2-diazaphenanthrenes [3a-p]

Compd.	R	-logMIC in µg/mL			
		B.S	S.A	E.C	P.D
3a	3-C_2H_5	4.74	4.64	4.5	4.445
3b	4-C_2H_5	4.64	4.57	4.39	4.34
3c	3-OC_2H_5	4.60	4.47	4.29	4.26
3d	4-OC_2H_5	4.53	4.33	4.20	4.17
3e	3-Cl	4.40	4.21	4.15	4.12
3f	4-Cl	4.40	4.15	4.10	4.03
3g	3-OCH_3	4.31	4.09	4.03	3.99
3h	4-OCH_3	4.27	4.05	3.95	3.93
3i	3-CH_3	4.20	3.94	3.87	3.87
3j	4-CH_3	4.15	3.91	3.84	3.82
3k	3-COOH	4.15	3.93	3.83	3.83
3l	3-OH	4.07	3.86	3.77	3.74
3m	4-OH	4.02	3.83	3.73	3.71
3n	3-NO_2	3.92	3.85	3.76	3.75
2o	4-NO_2	3.83	3.82	3.74	3.73
3p	H	3.72	3.72	3.62	3.60
A	-	3.90	4.60	4.43	4.60

A = *ampicillin*, BS = *B. subtilis;* SA = *S. aureus;* EC=*E.coli; P.D = P. diminuta*.

Table-3. Values of selected descriptors calculated for 1,2-diazaphenanthrenes [3a-p]

R	HOMO	LUMO	DDENE	VDW	NVDW	Log P	CSEV	CAA	CMA
3-C_2H_5	-5.306	-0.858	0.823	9.686	0.517	2.851	175.577	175.577	214.678
4-C_2H_5	-8.616	-0.663	0.815	9.896	3.107	2.849	179.391	409.081	212.356
3-OC_2H_5	-8.749	-0.660	0.906	11.583	1.248	2.843	185.519	185.519	226.678
4-OC_2H_5	-8.696	-0.6793	0.739	11.426	16.547	2.843	186.216	186.216	224.425
3-Cl	-9.014	-0.936	1.302	8.787	0.607	2.646	165.713	396.206	203.133
4-Cl	-8.915	-0.891	1.432	8.984	5.645	2.646	159.326	382.523	194.503
3-OCH_3	-8.778	-0.682	0.906	10.922	1.341	2.314	168.689	403.945	206.428
4-OCH_3	-8.713	-0.692	0.736	10.719	12.089	2.314	168.579	398.019	204.833
3-CH_3	-8.878	-0.721	0.824	8.968	0.652	2.321	161.898	389.889	198.594
4-CH_3	-8.842	-0.712	0.801	9.061	7.606	2.320	160.999	379.482	194.232
3-COOH	-9.139	-1.242	2.563	7.826	0.926	2.047	165.713	396.206	203.133
3-OH	-8.829	-0.724	0.893	7.045	0.443	2.227	149.536	367.044	184.884
4-OH	-8.748	-0.750	0.904	8.409	-1.316	1.821	145.238	359.245	179.996
3-NO_2	-11.360	-5.565	1.646	9.060	1.490	1.470	164.745	394.089	201.94
4-NO_2	-11.243	-5.431	1.978	8.235	-1.84952	1.470	167.695	392.422	201.305
H	-8.879	-0.72	0.824	8.969	0.649	1.525	154.957	372.622	188.529
A	-8.956	-0.228	7.445	0.675	-1.204	280.439	304.619	555.251	9.114

A = ampicillin

Table-4. Correlation matrix of used molecular descriptors

	HOMO	LUMO	DDENE	VDW	NVDW	LogP	CSEV	CAA	CMA
HOMO	1.000								
LUMO	0.720	1.000							
DDENE	0.503	0.574	1.000						
VDW	0.242	0.255	0.480	1.000					
NVDW	0.106	0.275	0.336	0.548	1.000				
Log P	0.650	0.643	0.423	0.521	0.407	1.000			
CSEV	0.182	0.015	0.086	0.766	0.412	0.595	1.000		
CAA	0.539	0.219	0.320	0.515	0.258	0.509	0.579	1.000	
CMA	0.217	0.035	0.077	0.774	0.379	0.609	0.988	0.634	1.000

Table-5. Cross-validation parameters

Eq.	Compd. used	PRESS	SSY	PRESS/SSY	S_{PRESS}	SDEP	r^2_{CV}	r^2_{bsp}
1	16	0.156	1.009	0.155	0.105	0.098	0.913	0.892
2	16	0.414	0.926	0.447	0.172	0.160	0.749	0.718
3	16	0.294	0.807	0.364	0.144	0.135	0.787	0.757
4	16	0.273	0.719	0.380	0.140	0.131	0.779	0.759

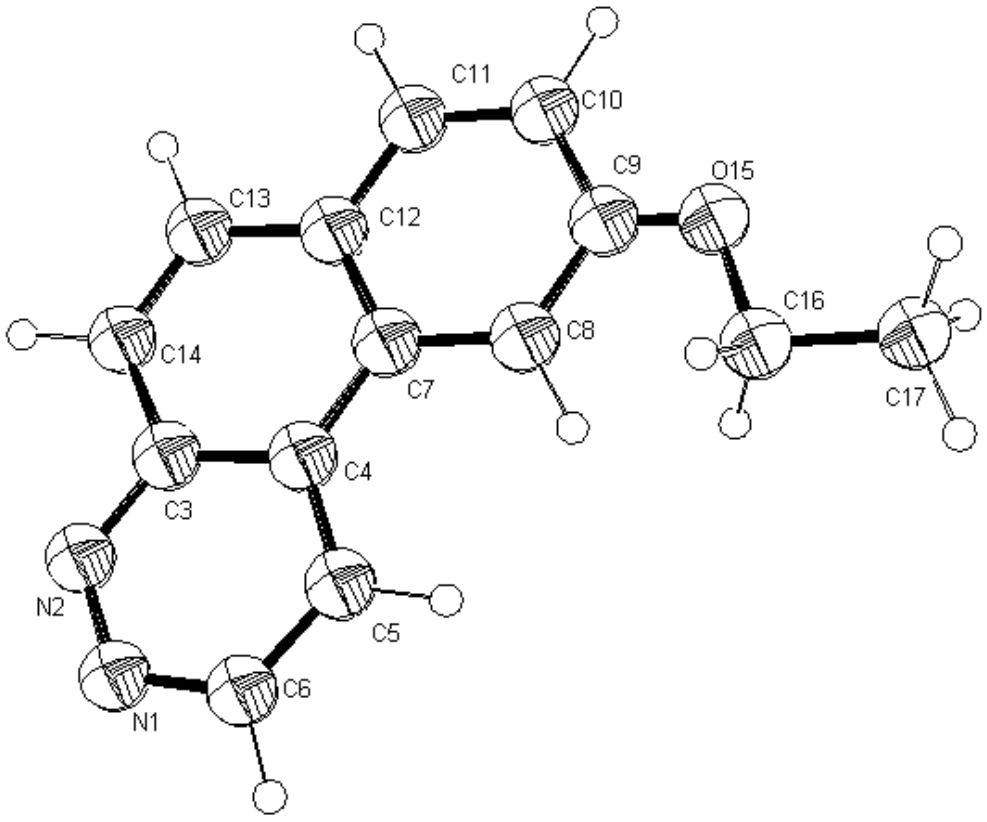


Figure. 1. ORTEP diagram of 3a (PM3 optimized geometry) with atom numbering. Thermal ellipsoids are scaled to the 50% probability. The atom numbering is arbitrary and has nothing to do with the IUPAC nomenclature.

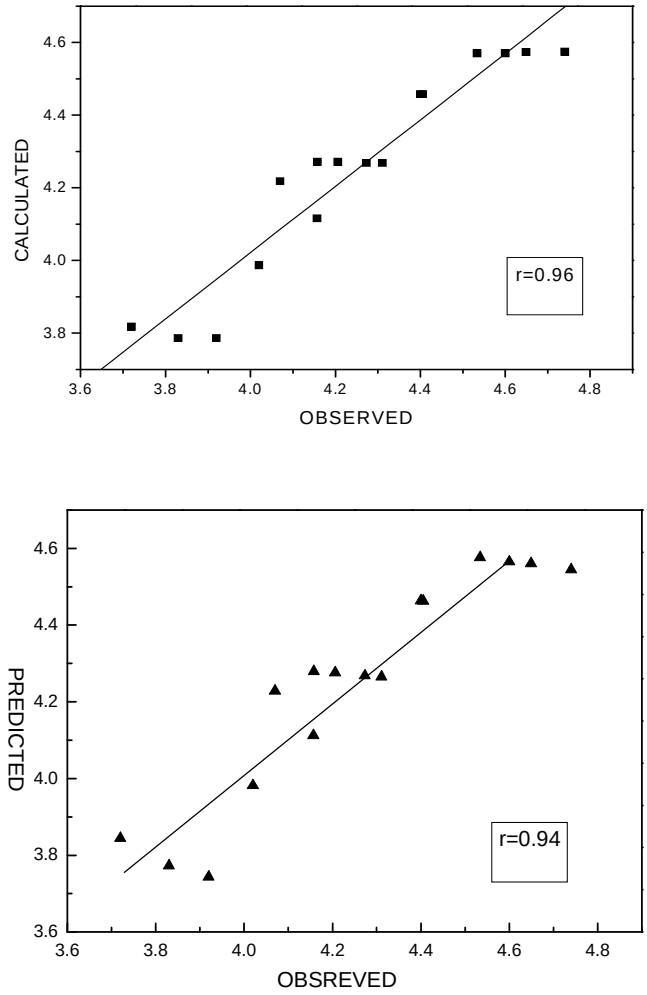
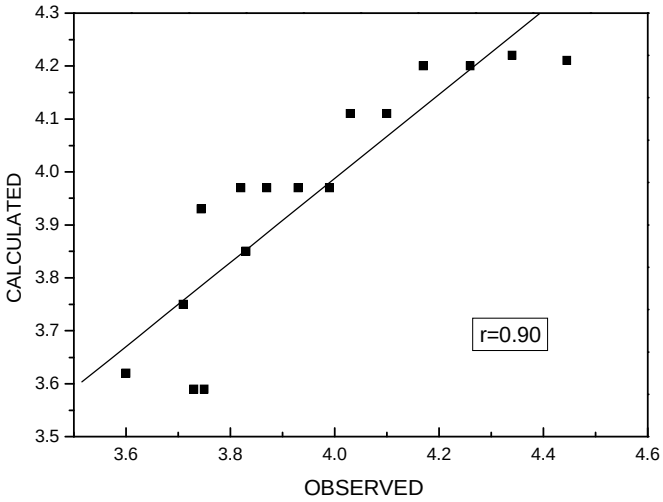


Figure 2. Plots of observed *vs* calculated and observed *vs* predicted activity of 1,2- diazaphenanthrene *[3a-p]* against *B. Subtilius*.



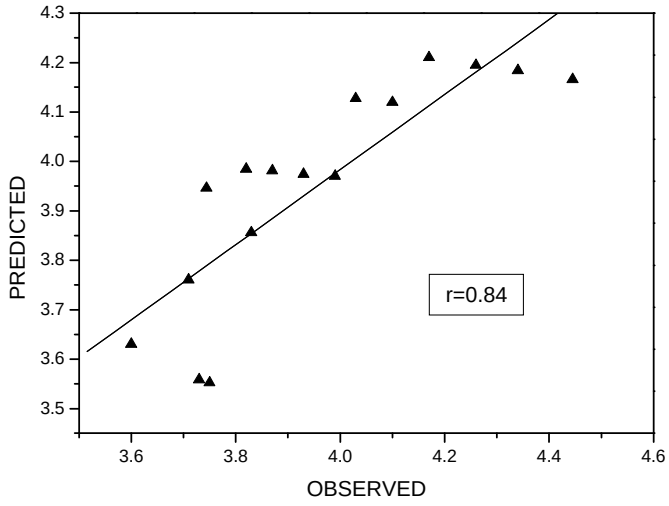
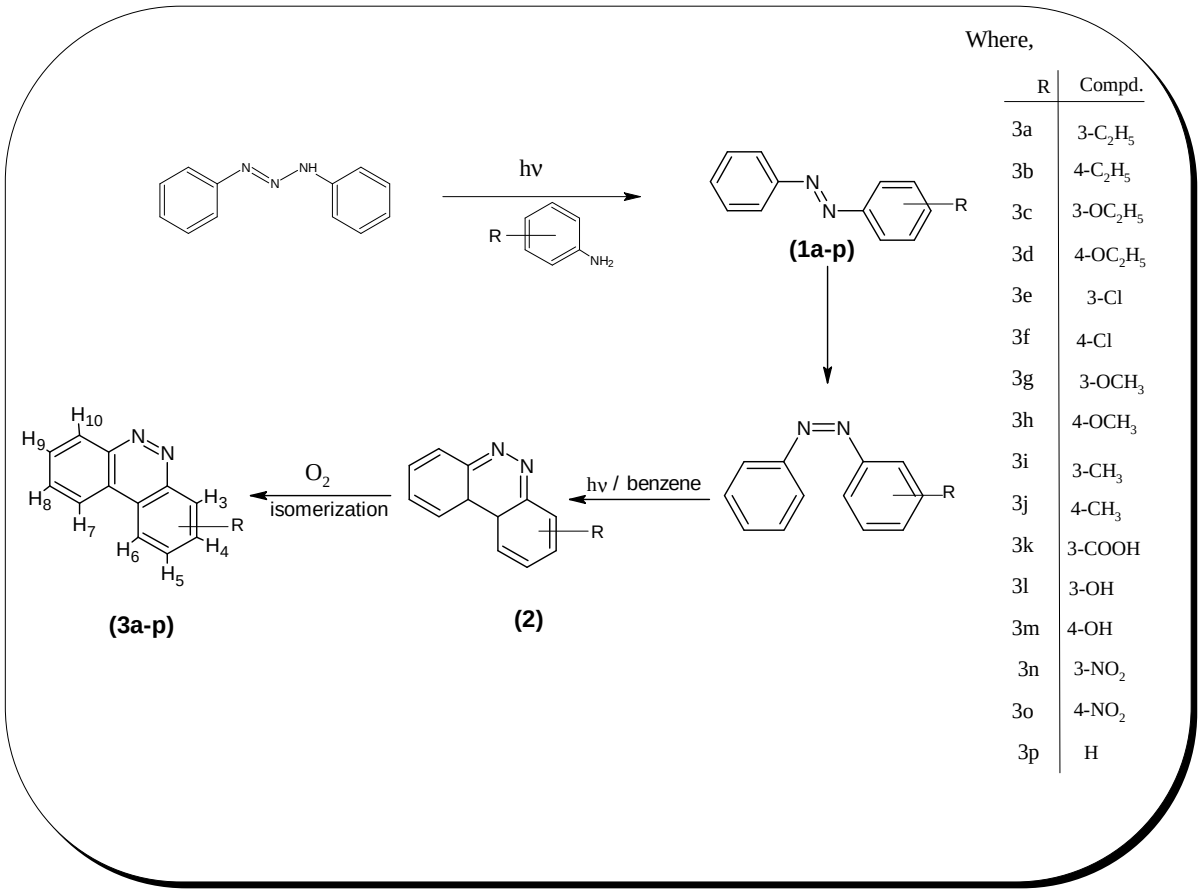


Figure 3. Plots of observed *vs* calculated and observed *vs* predicted activity of 1,2-diazaphenanthrene *[3a-p]* against *P.diminuta*



Scheme-1

CONCLUSION

Conclusively, a series of 1,2-diazaphenanthrene derivatives has been synthesized as potent antimicrobial agents. Furthermore, QSAR studies performed on these compounds have revealed that the positive coefficient of the log P descriptor, which relates to the hydrophobicity of the molecule, suggested that an increase in the lipophilicity might increase the activity. This corresponds to the presence of hydrophobic binding site in the 1,2-diazaphenanthrenes.

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[30] Valstat software developed at department of pharmacy SGSITS, 23, park road, indore, India (available on request).