



SYNTHESIS, SCREENING AND QSAR STUDIES OF 3-FORMYL-2-OXO-1, 2, 3, 4-TETRAHYDROPYRIMIDINE ANALOGUES AS ANTIBACTERIAL AGENTS

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ABSTRACT

5-Acyl-6-methyl-4-substituted-2-oxo-1,2,3,4-tetrahydropyrimidines (**1**) were prepared by cyclocondensation reaction between appropriate aldehyde, acetoacetate and urea using aluminium chloride and concentrate hydrochloric acid as catalyst. These compounds (**1**) upon treatment with dimethylformamide and phosphorous oxychloride furnish the title compounds (**2a-1**). The structures of all title compounds have been confirmed on the basis of their analytical, IR and NMR spectral data. The title compounds have been tested for antibacterial activity against *Staphylococcus aureus*. A quantitative structure activity relationship study was made using various descriptors. Several statistical expressions were developed using stepwise multiple linear regression analysis. The best quantitative structure activity relationship model was further cross validated. The study revealed that electronic property (heat of formation) contributes negatively and spatial descriptor (standard dimension-3) contributes positively. The study suggested that minimizing the heat of formation and increasing the surface area may lead to better antibacterial compound from this series.

Key words: 2-Oxo-1,2,3,4-tetrahydropyrimidines, Antibacterial, QSAR.

INTRODUCTION

The resistance of common pathogens to standard antibiotic therapy is rapidly becoming a major problem throughout the world. The resistance of multidrug-resistant gram-positive bacteria is increasing and infections caused by *Staphylococcus aureus*, *enterococci* and *pneumococci* are particularly problematic¹. There is a real perceived need for the discovery of new compounds endowed with antibacterial property.

QSAR studies of antimicrobial activity represent an emerging and exceptionally important topic in the area of computer-aided drug design. Although the demand for

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'insilico' discovery is clear in all areas of human therapeutics, the field of anti-infective drugs has a particular need for computational solutions enabling rapid identification of novel therapeutic leads. As a result, there is an urge for new antimicrobial driven by critical situation, such as increased prevalence of multidrug-resistant bacteria and the emergence of deadly infectious diseases.

In recent years, substituted 2-oxo-1,2,3,4-tetrahydropyrimidines received significant attention owing to their diverse range of biological properties such as calcium channel modulator², 1-adrenoreceptor selective antagonist³, HIV gp120-CD₄ inhibition⁴, antiviral⁵, anticancer with mitotic kinesin inhibition⁶, inhibitor of Walker carcinosarcoma⁷, oral antihypertensive⁸, blood platelet aggregation inhibition, useful for the treatment of benign prostatic hyperplasia¹⁰, anti-inflammatory, antifungal and antibacterial¹¹. The presence of several interacting functional groups in these compounds also determines their great synthetic potential¹².

In the present paper, the synthesis, screening and QSAR studies to investigate the relationship between the various physicochemical parameters and antibacterial activity of synthesized 3-formyl derivatives of 5-acyl-6-methyl-4-substituted-2-oxo-1,2,3,4-tetrahydropyrimidines have been described.

EXPERIMENTAL

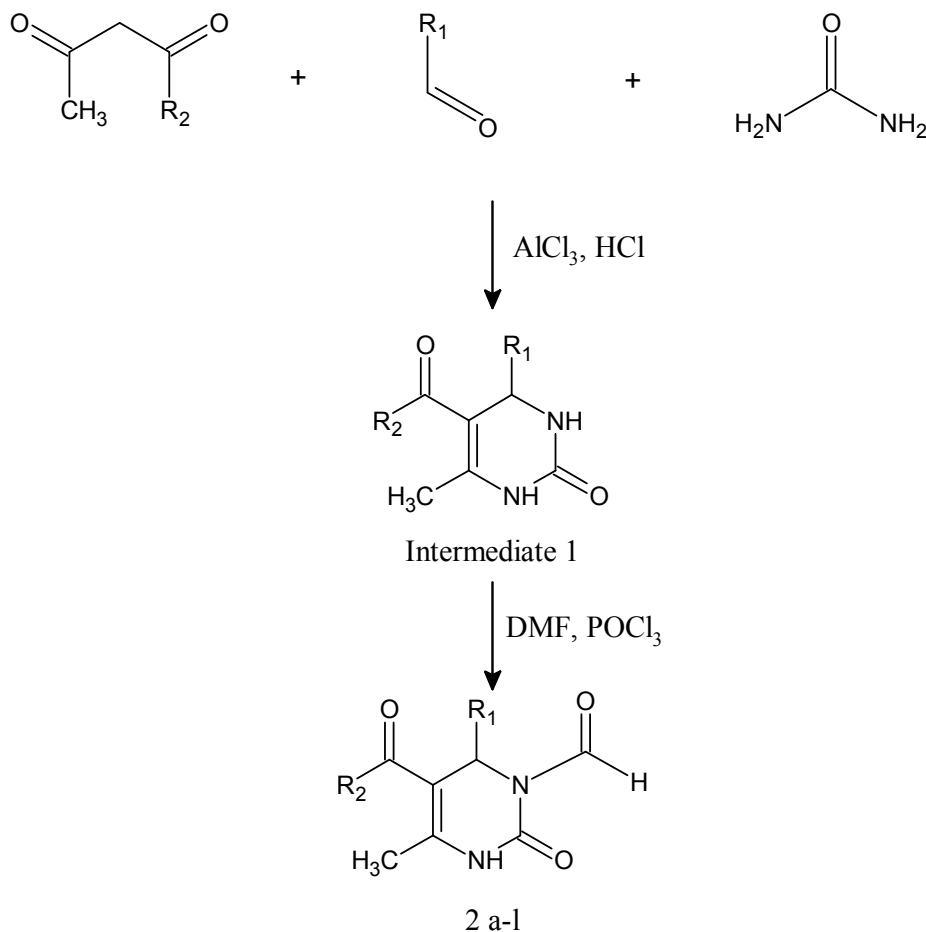
Melting points of the synthesized compounds were determined in open capillary tubes and are therefore uncorrected. The structures of the title compounds were established on the basis of elemental analysis and spectral data. The IR spectra were recorded on JASCO FTIR 4100 spectrophotometer. ¹H NMR spectra were recorded on Varian NMR 400 MHz spectrometer using CDCl₃/DMSO-d₆ as solvent with TMS as an internal standard. Purity of the synthesized compounds was checked by silica gel - G plate using benzene and ethyl acetate as developer.

General procedure for the synthesis of 5 – acyl – 6 – methyl – 4 – substituted – 2 – oxo – 1,2,3,4 – tetrahydropyrimidines (1)

These compounds were synthesized by the reported cyclocondensation reaction¹ between aldehyde, acetoacetate and urea. The mixture of appropriate aldehyde (0.02 mole), acetoacetate (0.02 mole), urea (0.03 mole), aluminium chloride (0.01 mole), conc. hydrochloric acid (2 drops) in methanol were refluxed for 4 h. The solid thus separated on cooling was filtered, washed with cold methanol, dried and recrystallized from methanol.

General procedure for the synthesis of 3 – formyl derivatives of 5-acyl – 6 – methyl – 4 – substituted – 2 – oxo – 1,2,3,4 – tetrahydropyrimidines (2a – l)

To a suspension of respective 5-acyl-6-methyl-4-substituted-2-oxo-1,2,3,4-tetrahydropyrimidines (0.02 mole) in 20 mL of dry dimethylformamide, phosphorous oxychloride (0.02 mole) was added in ice-bath. The resulting solution was heated at 70°C and kept there for 40 minutes and then was poured into 150 mL of ice-water to yield the solid product. The solid product thus separated was filtered, washed with cold water, dried and recrystallized from ethanol.

**Scheme 1**

Ethyl 3-formyl-6-methyl-2-oxo-4-phenyl-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (2a)

Yield: 83.76%, M.P:180°C, IR (KBr) (cm⁻¹): 3240, 3140 (N-H), 2970 (C-H), 1730 (C=O), 1720 (C-O), 1700 (C=O), 1650, 1490 (aromatic), ¹H NMR δ: 1.11 (t, 3H, ethyl CH₃), 2.30 (s, 3H, C₆-CH₃), 3.99 (q, 2H, OCH₂), 6.55 (s, 1H, methine CH), 7.09-7.74 (m, 5H, Ph), 9.19 (s, 1H, formyl CH), 8.56 (s, 1H, NH).

Ethyl 3-formyl-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (2b)

Yield: 42.14%, M.P: 138°C, IR (KBr) (cm⁻¹): 3260, 3130 (N-H), 2960 (C-H), 1725 (C=O), 1715 (C-O), 1690 (C=O), ¹H NMR δ: 1.22 (t, 3H, ethyl CH₃), 2.46 (s, 3H, C₆-CH₃), 4.10 (q, 2H, OCH₂), 4.71 (s, 2H, methylene CH₂), 9.09 (s, 1H, formyl CH), 8.86 (s, 1H, NH).

Ethyl 4-[4-(dimethylamino)phenyl]-3-formyl-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (2c)

Yield: 56.36%, M.P: 212°C, IR (KBr) (cm⁻¹): 3245, 3140 (N-H), 2980 (C-H), 1730 (C=O), 1710 (C=O), 1695 (C=O), 1655, 1500 (aromatic), ¹H NMR δ: 1.11 (t, 3H, ethyl 4 CH₃), 2.30 (s, 3H, C₆-CH₃), 4.01 (q, 2H, OCH₂), 6.55 (s, 1H, methine CH), 6.47-7.56 (m, 4H, Ph), 2.83 (s, 6H, N((CH₃)₂)), 9.19 (s, 1 H, formyl CH), 8.56 (s, 1H, NH).

Ethyl 3-formyl-4-(4-methoxyphenyl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (2d)

Yield: 44.00%, M.P: 136°C, IR (KBr) (cm⁻¹): 3250, 3145 (N-H), 2975 (C-H), 1730 (C=O), 1715 (C=O), 1695 (C=O), 1660, 1495 (aromatic), ¹H NMR δ: 1.12 (t, 3H, ethyl CH₃), 2.31 (s, 3H, C₆-CH₃), 3.99 (q, 2H, OCH₂), 6.54 (s, 1H, methine CH), 7.00-7.63 (m, 4H, Ph), 3.60 (s, 3H, OCH₃), 9.20 (s, 1H, formyl CH), 8.58 (s, 1H, NH).

Ethyl 3-formyl-4-(2-furyl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (2e)

Yield: 41.81%, M.P: 270°C, IR (KBr) (cm⁻¹): 3240, 3120 (N-H), 2980 (C-H), 1720 (C=O), 1710 (C=O), 1680 (CO), ¹H NMR δ: 1.13 (t, 3H, ethyl CH₃), 2.32 (s, 3H, C₆-CH₃), 3.97 (q, 2H, OCH₂), 6.30 (s, 1H, methine CH), 5.99-6.84 (m, 3H, furan), 9.19 (s, 1H, formyl CH), 8.57 (s, 1H, NH).

Ethyl 3 – formyl – 4 – (2 – hydroxyphenyl) – 6 – methyl – 2 – oxo – 1, 2, 3, 4 – tetrahydropyrimidine – 5 – carboxylate (2f)

Yield: 48.00%, M.P: 182°C, IR (KBr) (cm⁻¹): 3250, 3100 (N-H), 2980 (C-H), 1730 (C=O), 1715 (C=O), 1680 (C=O), 1640, 1490 (aromatic), ¹H NMR δ: 1.13 (t, 3H, ethyl CH₃), 2.30 (s, 3H, C₆-CH₃), 3.99 (q, 2H, OCH₂), 6.43 (s, 1H, methine CH), 6.84-7.55 (m, 4H, Ph), 6.39 (s, 1H, Ar-OH), 9.19 (s, 1H, formyl CH), 8.56 (s, 1H, NH).

Methyl 3 – formyl – 6 – methyl – 2 – oxo – 4 – phenyl – 1, 2, 3, 4 – tetrahydropyrimidine – 5 – carboxylate (2g)

Yield: 74.07%, M.P: 220°C, IR (KBr) (cm⁻¹): 3240, 3140 (N-H), 2970 (C-H), 1730 (C=O), 1720 (C=O), 1690 (C=O), 1640, 1495 (aromatic), ¹H NMR δ: 3.71 (s, 3H, COOCH₃), 2.29 (s, 3H, C₆-CH₃), 6.55 (s, 1H, methine CH), 7.10-7.74 (m, 5H, Ph), 9.16 (s, 1H, formyl CH), 8.54 (s, 1H, NH).

Methyl 3 – formyl – 6 – methyl – 2 – oxo – 1, 2, 3, 4 – tetrahydropyrimidine – 5 – carboxylate (2h)

Yield: 40.00%, M.P: 262°C, IR (KBr) (cm⁻¹): 3260, 3125 (N-H), 2965 (C-H), 1720 (C=O), 1710 (C=O), 1690 (C=O), ¹H NMR δ: 3.72 (s, 3H, COOCH₃), 2.46 (s, 3H, C₆-CH₃), 4.71 (s, 2H, methylene CH₂), 9.09 (s, 1H, formyl CH), 8.86 (s, 1H, NH).

Methyl 4 – [4 – (dimethylamino)phenyl] – 3 – formyl – 6 – methyl – 2 – oxo – 1, 2, 3, 4 – tetrahydropyrimidine – 5 – carboxylate (2i)

Yield: 64.51%, M.P: 226°C, IR (KBr) (cm⁻¹): 3245, 3135 (N-H), 2985 (C-H), 1730 (C=O), 1715 (C=O), 1690 (C=O), 1645, 1490 (aromatic), ¹H NMR δ: 3.71 (s, 3H, COOCH₃), 2.30 (s, 3H, C₆-CH₃), 6.55 (s, 1H, methine CH), 6.47-7.56 (m, 4H, Ph), 2.83 (s, 6H, N(CH₃)₂), 9.19 (s, 1H, formyl CH), 8.57 (s, 1H, NH).

Methyl 3 – formyl – 4 – (4 – methoxyphenyl) – 6 – methyl – 2 – oxo – 1, 2, 3, 4 – tetrahydropyrimidine – 5 – carboxylate (2j)

Yield: 56.36%, M.P: 176°C, IR (KBr) (cm⁻¹): 3220, 3100 (N-H), 2980 (C-H), 1720 (C=O), 1705 (C=O), 1690 (C=O), 1655, 1490 (aromatic), ¹H NMR δ: 3.71 (s, 3H, COOCH₃), 2.30 (s, 3H, C₆-CH₃), 6.55 (s, 1H, methine CH), 6.92-7.63 (m, 4H, Ph), 3.61 (s, 3H, OCH₃), 9.18 (s, 1H, formyl CH), 8.56 (s, 1H, NH).

Methyl 3 – formyl – 6 – methyl – 2 – oxo – 4 – [(E) – 2 – phenylvinyl] – 1, 2, 3, 4 – tetrahydropyrimidine – 5 – carboxylate (2k)

Yield: 43.88%, M.P: 135°C, IR (KBr) (cm⁻¹): 3225, 3105 (N-H), 2990 (C-H), 1730 (O=O), 1715 (C=O), 1695 (C=O), 1640, 1480 (aromatic), ¹H NMR δ : 3.71 (s, 3H, COOCH₃), 2.31 (s, 3H, C₆-CH₃), 5.48 (s, 1H, methine CH), 6.60 (s, 1H, Ph-CH), 6.64 (s, 1H, CH-C₆), 7.27-7.32 (m, 5H, Ph), 9.36 (s, 1H, formyl CH), 8.84 (s, 1H, NH).

Methyl 3 – formyl – 4 – (2 – furyl) – 6 – methyl – 2 – oxo – 1, 2, 3, 4 – tetrahydropyrimidine – 5 – carboxylate (21)

Yield: 44.61%, M.P: 276°C, IR (KBr) (cm⁻¹): 3240, 3110 (N-H), 2985 (C-H), 1720 (C=O), 1705 (C=O), 1690 (C=O), ¹H NMR δ : 3.70 (s, 3H, COOCH₃), 2.30 (s, 3H, C₆-CH₃), 6.30 (s, 1H, methine CH), 5.99-6.84 (m, 3H, furan), 9.19 (s, 1H, formyl CH), 8.56 (s, 1H, NH).

Antibacterial activity

Antibacterial activity of these twelve compounds was tested *in vitro* against gram-positive bacteria *Staphylococcus aureus* (NCIM-2079) by the cup-plate agar diffusion method, using dimethyl sulfoxide as solvent and trimethoprim as standard drug. Further minimum inhibitory concentration (MIC) of all these compounds was determined by double dilution method¹⁵. The biological data minimum inhibitory concentration (MIC) in (mg/mL) were converted to negative logarithmic dose in moles (pMIC) for QSAR analysis.

The series was subjected to QSAR analysis using MOE 2006.08 running on P-IV processor. Structures of all the compounds were sketched using builder module of the programme. These structures were then subjected to energy minimization using Hamiltonian force field molecular mechanics-MMFF 94X by fixing root mean square (RMS) gradient as 0.01 kcal/mol Å^o. The descriptor values for all the molecules were calculated using "compute descriptor" module of the programme. All the calculated descriptors were considered as independent variable and biological activity (pMIC) as dependent variable. Stepwise multiple linear regression analysis method was used to perform QSAR analysis to generate several models. The best model was selected on the basis of various statistical parameters such as squared correlation coefficient (r²), standard error of estimation (SE) and sequential Fischer test (F). Quality and predictability of model was estimated from the cross validated squared correlation coefficient (q²)¹⁶.

RESULTS AND DISCUSSION

The purity and homogeneity of all the title compounds were confirmed by their sharp melting points and TLC. In all cases, these compounds were obtained in solid state and the yields varied from maximum 84% to minimum 40%. The synthesized compounds were subjected to physico-chemical characterization and elemental analysis (Table 1). The structures of these compounds were confirmed by C, H and N analytical data, IR and ^1H NMR spectral data. Antimicrobial activity data against *Staphylococcus aureus*, minimum inhibitory concentration (MIC) in mg/mL was converted to negative logarithmic dose in moles (pMIC) for QSAR analysis (Table 2). Values of descriptors (Table 3), which are significant in model, are showing high correlation with biological activity. Performing stepwise multiple linear regression analysis results in several equations, out of that five are found to be statistically significant QSAR models.

$$\text{pMIC} = -6.65726 + 2.91592 (\pm 0.6572) * \text{GCUT}^{\wedge}\text{SLOGP}_3 - 0.01920 (\pm 0.0042) * \text{MNDO_HF}, n=12, r^2=0.75998, q^2=0.484092, \text{SE}=0.3037, F=14.25 \text{ (Model-1)}$$

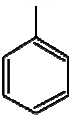
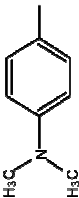
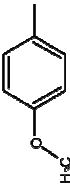
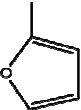
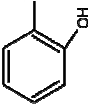
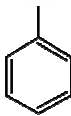
$$\text{pMIC} = -7.83838 + 1.55969 (\pm 0.3908) * \text{VAdjMa} - 0.01907 (\pm 0.0044) * \text{PM3_HF}, n=12, r^2=0.73514, q^2=0.460294, \text{SE}=0.3191, F=12.49 \text{ (Model-2)}$$

$$\text{pMIC} = -1.92407 + 0.02605 (\pm 0.0061) * \text{zagreb} - 0.01955 (\pm 0.0044) * \text{MNDO_HF}, n=12, r^2=0.74517, q^2=0.459367, \text{SE}=0.3130, F=13.16 \text{ (Model-3)}$$

$$\text{pMIC} = -3.15816 + 1.99980 (\pm 0.4663) * \text{PEOE_PC} + -0.01528 (\pm 0.0040) * \text{PM3_HF}, n=12, r^2=0.75896, q^2=0.499449, \text{SE}=0.3044, F=14.17, \text{ (Model-4)}$$

$$\text{pMIC} = -0.74566 - 0.01642 (\pm 0.0038) * \text{MNDO_HF} + 1.42990 (\pm 0.2930) * \text{std_dim3}, n=12, r^2=0.79023, q^2=0.548233, \text{SE}=0.2840, F=16.95, \text{ (Model-5)}$$

Table 1. Characterization data of the title compounds (2a-l)

Comp.	R ₁	R ₂	Mol. formula	Yield (%)	MP (°C)	Analysis found (Cal.) %		
						C	H	N
2a		OC ₂ H ₅	C ₁₅ H ₁₆ N ₂ O ₄	83.76	180	62.41 (62.49)	5.52 (5.59)	9.63 (9.72)
2b	H	OC ₂ H ₅	C ₉ H ₁₂ N ₂ O ₄	42.14	138	50.85 (50.94)	5.62 (5.70)	13.02 (13.20)
2c		OC ₂ H ₅	C ₁₇ H ₂₁ N ₃ O ₄	56.36	212	61.54 (61.62)	6.31 (6.39)	12.59 (12.68)
2d		OC ₂ H ₅	C ₁₆ H ₁₈ N ₂ O ₅	44.00	136	60.32 (60.37)	5.60 (5.70)	8.70 (8.80)
2e		OC ₂ H ₅	C ₁₃ H ₁₄ N ₂ O ₅	41.81	270	56.09 (56.11)	5.01 (5.07)	10.02 (10.07)
2f		OC ₂ H ₅	C ₁₅ H ₁₆ N ₂ O ₅	48.00	182	59.10 (59.21)	5.21 (5.30)	9.13 (9.21)
2g		OCH ₃	C ₁₄ H ₁₄ N ₂ O ₄	74.07	220	61.22 (61.312)	5.06 (5.14)	10.12 (10.21)

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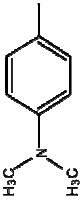

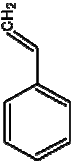
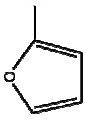
Comp.	R ₁	R ₂	Mol. formula	Yield (%)	MP (°C)	Analysis found (Cal.) %		
						C	H	N
2h	H	OCH ₃	C ₈ H ₁₀ N ₂ O ₄	40.00	262	48.39 (48.48)	5.01 (5.09)	14.06 (14.14)
2i		OCH ₃	C ₁₆ H ₁₉ N ₃ O ₄	64.51	226	60.46 (60.56)	5.95 (6.03)	13.22 (13.24)
2j		OCH ₃	C ₁₅ H ₁₆ N ₂ O ₅	56.36	176	59.12 (59.21)	5.22 (5.30)	9.13 (9.21)
2k		OCH ₃	C ₁₆ H ₁₆ N ₂ O ₄	43.88	135	63.91 (63.99)	5.31 (5.37)	9.22 (9.33)
2l		OCH ₃	C ₁₂ H ₁₂ N ₂ O ₅	44.61	276	54.47 (54.55)	4.51 (4.58)	10.52 (10.60)

Table 2. Antibacterial activity of the title compounds (2a -l) on *S. aureus*

Comp.	Minimum inhibitory concentration (MIC) in $\mu\text{g/mL}$	pMIC
2a	500	2.7609
2b	1000	2.3268
2c	500	2.8213
2d	250	3.1049
2e	500	2.7455
2f	250	3.0854
2g	500	2.7392
2h	1000	2.2971
2i	500	2.8026
2j	16	4.2792
2k	1000	2.4777
2l	62	3.6296

Table 3. Calculated molecular descriptors of the title compounds (2a-l)

Comp.	^A GCUT_SLOGP_3	^B V AdjMa	^C Zagreb	^D PEOE_PC+	^E MNDO_HF	^F PM3_HF	^G std_dim3
2a	2.6026	5.4594	104	2.0422	-112.8434	-125.5291	1.2300
2b	2.2665	4.9069	70	1.7181	-112.9104	-119.6412	0.7310
2c	2.695	5.6439	120	2.2236	-65.1793	-86.3890	1.4778
2d	2.6466	5.585	114	2.2488	-118.6648	-122.7770	1.4817
2e	2.5316	5.3923	100	2.2149	-111.5959	-112.4507	1.3175
2f	2.6358	5.5236	110	2.2762	-121.4409	-131.4696	1.4361
2g	2.5726	5.3923	100	2.0043	-92.3657	-120.8682	1.2418

Cont...

Comp.	^A G _{CUT} _SLOGP_3	^B V AdjMa	^C Zagreb	^D PEOE_PC+	^E MNDO_HF	^F PM3_HF	^G std_dim3
2h	2.2128	4.8074	66	1.6947	-140.3118	-152.0492	0.5784
2i	2.6701	5.585	116	2.2002	-96.3653	-124.7239	1.5033
2j	2.6191	5.5236	110	2.2253	-146.9882	-158.0519	1.5095
2k	2.5356	5.5236	108	2.1188	-96.2787	-81.0662	1.3602
2l	2.4978	5.3219	96	2.1915	-142.5653	-147.9133	1.3291

A: LogP GCUT (3/3), B: Vertex adjacency information (mag), C: Zagreb index, D: Total positive partial charge, E: MNDO heat of formation (kcal), F: PM3 heat of formation (kcal), G: Standard dimension 3.

Out of the five models, model-5 was selected on the basis of statistical criteria; $r = 0.79023$, $SE = 0.2840$ and $F = 16.95$. The internal predictivity of the model was assessed by cross-validated squared correlation coefficient ($q^2 = 0.548233$), which shows good correlation between predicted activity and observed activity (Table 4 and Fig. 1). Correlation matrix shows poor correlation between descriptors (Table 5).

Table 4. Observed (obs.), Predicted (pred.) pMIC and residual values for model - 5

Comp.	pMIC		Residuals
	observed	predicted	
2a	2.7609	2.8658	-0.1049
2b	2.3268	2.1535	0.1733
2c	2.8213	2.4375	0.3838
2d	3.1049	3.3213	-0.2164
2e	2.7455	2.9705	-0.2250
2f	3.0854	3.3017	-0.2163
2g	2.7392	2.5466	0.1926
2h	2.2971	2.3852	-0.0881
2i	2.8026	2.9861	-0.1835

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Comp.	pMIC		Residuals
	observed	predicted	
2j	4.2792	3.8261	0.4530
2k	2.4776	2.7800	-0.3025
2l	3.6296	3.4956	0.1340

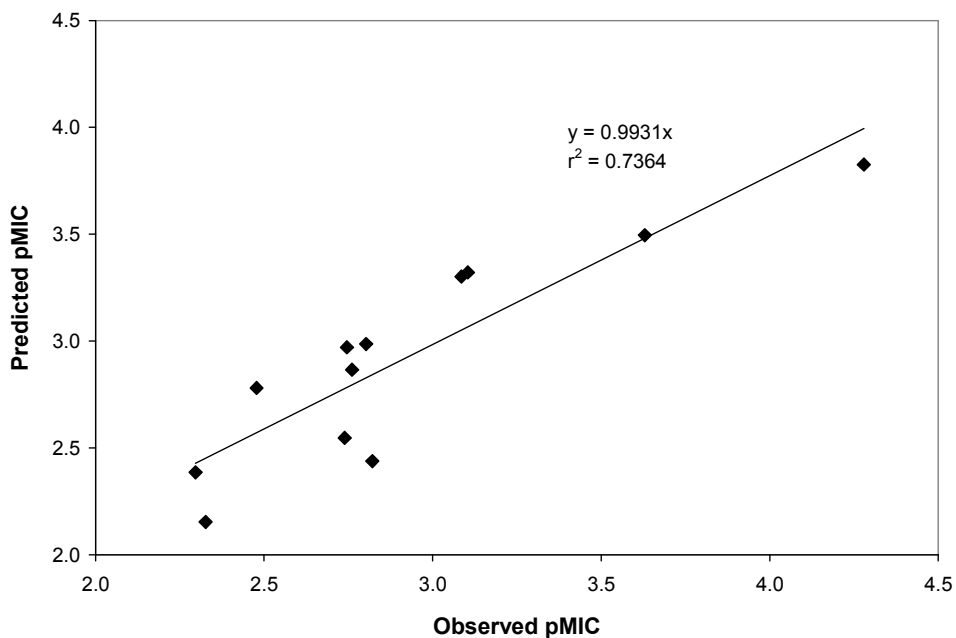


Fig. 1: Plot between observed V/s predicted pMIC values for model - 5

Table 5. Correlation matrix

	pMIC	GCUT_ SLOGP_3	VAdjMa	zagreb	PEOE PC+	MNDO HF	PM3 HF	std dim3
pMIC	1.0000							
GCUT_ SLOGP_3	0.4487	1.0000						
VAdjMa	0.4403	0.9677	1.0000					

Cont...

	pMIC	GCUT_ SLOGP_3	VAdjMa	zagreb	PEOE PC+	MNDO HF	PM3 HF	std dim3
zagreb	0.4360	0.9737	0.9956	1.0000				
PEOE PC+	0.5713	0.8942	0.8951	0.8957	1.0000			
MNDO HF	0.3985	0.3092	0.3397	0.3483	0.0349	1.0000		
PM3 HF	0.3095	0.1876	0.3582	0.3341	0.0667	0.8939	1.0000	
std dim3	0.5763	0.9556	0.9649	0.9633	0.9601	0.1908	0.1789	1.0000

It is evident from the QSAR studies that in model- 5, electronic descriptor (heat of formation) and spatial descriptor (standard dimension- 3) are responsible for the activity. Heat of formation contributes negatively and standard dimension- 3 contributes positively to biological activity, which indicates that minimizing the heat of formation and increasing the surface area probably leads to better antibacterial compound from this series.

ACKNOWLEDGEMENT

The authors are grateful to Dr. H. N. More, Principal, Bharti Vidyapeeth College of Pharmacy, Kolhapur for providing necessary facilities for this work.

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Accepted : 04.12.2007