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Synthesis, Screening and QSAR Studies of 3-Benzoyl-2-thioxo-1,2,3,4-tetrahydropyrimidine Analogues as Antibacterial Agents

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5-Acyl-6-methyl-4-substituted-2-thioxo-1,2,3,4-tetrahydropyrimidines (**1**) were synthesized by cycloconden-sation reaction between appropriate aldehyde, acetoacetate and thiourea in presence of aluminium chloride and hydrochloric acid which upon treatment with benzoyl chloride in presence of pyridine in benzene furnish the 3-benzoyl-2-thioxo-1,2,3,4-tetrahydropyrimidine analogues (**2a-l**). The structures of all these compounds have been confirmed on the basis of their analytical, IR and NMR spectral data. These compounds have also 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 (AM1_LUMO) and lipophilic descriptor (BCUT_SLOGP_1) both contributes negatively which suggest that minimizing both the Lowest Unoccupied Molecular Orbital energy and atomic contribution to partition coefficient (log P) may lead to better antibacterial compound from this series.

Key Words: 2-Thioxo-1,2,3,4-tetrahydropyrimidines, Antibacterial, QSAR.

INTRODUCTION

In recent years, substituted 2-oxo/thioxo-1,2,3,4-tetrahydropyrimidines received significant attention owing to their diverse range of biological properties such as calcium channel modulator[1], 1-adrenoreceptor selective antagonist[2], HIV gpl20-CD_4 inhibition[3], antiviral[4], anticancer with mitotic kinesin inhibition[5], inhibitor of Walker carcinosarcoma[6], oral antihypertensive[7], blood platelet aggregation inhibition[8], useful for the treatment of benign prostatic hyperplasia[9], antiinflammatory, antifungal and antibacterial[10]. The presence of several interacting functional groups in these compounds also determines their great synthetic potential[11].

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The resistance of common pathogens to standard antibiotic therapy is rapidly becoming a major health 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 problematic[12]. 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. QSAR models are highly effective in describing the structural basis of biological activity. It is now widely used for the prediction of physicochemical properties and biological activities in chemical, environmental and pharmaceutical areas. The success of QSAR approach can be explained by the insight offered into the structural determination of chemical properties and the possibility to estimate the properties of new chemical compounds without the need to synthesis and test them.

In the present paper, we describe the synthesis, screening and QSAR studies to investigate the relationship between the various physicochemical parameters and antibacterial activity of synthesized 3-benzoyl derivatives of 5-acyl-6-methyl-4-substituted-2-thioxo-1,2,3,4-tetrahydropyrimidines.

EXPERIMENTAL

Melting points of the synthesized compounds were determined in open capillary tubes 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. ^{1}H NMR spectra were recorded on Varian NMR 400 MHz spectrometer using $CDCl_3$/DMSO-d_6 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-thioxo-1,2,3,4-tetrahydropyrimidines (1): These compounds were synthesized by the reported cyclocondensation reaction[13,14] between aldehyde, acetoacetate and thiourea. The mixture of appropriate aldehyde (0.02 mol), acetoacetate (0.02 mol), thiourea (0.03 mol), aluminium chloride (0.01 mol), 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-benzoyl derivatives of 5-acyl-6-methyl-4-substituted-2-thioxo-1,2,3,4-tetrahydropyrimidines (2a-l): To a suspension of respective 5-acyl-6-methyl-4-substituted-2-thioxo-1,2,3,4-tetrahydropyrimidines (0.02 mol) and 4 mL of pyridine in 20 mL of dry benzene, benzoyl chloride (0.03 mol) was added dropwise at

room temperature. The resulting solution was heated to reflux for 2 h. After cooling 80 mL of water was added and allowed benzene layer to separate. Benzene layer was washed with 5 % sodium carbonate followed by water and treated with anhydrous magnesium sulphate. Supernatant benzene layer after decantation was concentrated to obtain oily residue which upon recrystallization with methanol yield solid product.

Ethyl-3-benzoyl-6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2a): Yield 66.17 %; m.p. 160 ºC. IR (KBr, ν_{max}, cm^{-1}): 3240, 3140 (N-H), 2970 (C-H), 1720 (C=O), 1700 (C=O), 1520 (C=S). ^{1}H NMR (δ ppm): 1.09 (t, 3H, ethyl CH_3), 2.08 (s, 3H, C_6-CH_3), 3.99 (q, 2H, OCH_2), 6.69 (s, 1H, methine CH), 7.42-7.44 (m, 5H, Ph), 7.76-7.77 (m, 5H, COPh), 9.39 (s, 1H, NH).

Ethyl-3-benzoyl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2b): Yield 42.80 %; m.p. 132 ºC. IR (KBr, ν_{max}, cm^{-1}): 3260, 3130 (N-H), 2960 (C-H), 1715 (C=O), 1690 (C=O), 1525 (C=S). ^{1}H NMR (δ ppm): 1.22 (t, 3H, ethyl CH_3), 2.31 (s, 3H, C_6-CH_3), 4.10 (q, 2H, OCH_2), 6.20 (s, 2H, methylene CH_2), 7.67-7.88 (m, 5H, COPh), 9.41 (s, 1H, NH).

Ethyl-3-benzoyl-4-(4-dimethylaminophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2c): Yield 66.66 %; m.p. 172 ºC. IR (KBr, ν_{max}, cm^{-1}) : 3245, 3140 (N-H), 2980 (C-H), 1710 (C=O), 1695 (C=O), 1515(C=S). ^{1}H NMR (δ ppm): 1.11 (t, 3H, ethyl CH_3), 2.08 (s, 3H, C_6-CH_3), 4.01 (q, 2H, OCH_2), 6.69 (s, 1H, methine CH), 7.24-7.26 (m, 4H, Ph), 7.71-7.77 (m, 5H, COPh), 2.83 (s, 6H, $N(CH_3)_2$, 9.40 (s, 1H, NH).

Ethyl-3-benzoyl-4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2d): Yield 42.10 %; m.p. 121 ºC. IR (KBr, ν_{max}, cm^{-1}) : 3250,3145 (N-H), 2975 (C-H), 1715 (C=O), 1695 (C=O), 1510 (C=S). ^{1}H NMR (δ ppm): 1.11 (t, 3H, ethyl CH_3), 2.08 (s, 3H, C_6-CH_3), 3.97 (q, 2H, OCH_2), 6.69 (s, 1H, methine CH), 6.69-7.36 (m, 4H, Ph), 7.71-7.77 (m, 5H, COPh), 3.60 (s, 3H, OCH_3), 9.38 (s, 1H, NH).

Ethyl-3-benzoyl-4-(2-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2e): Yield 45.54 %; m.p. 120 ºC. IR (KBr, ν_{max}, cm^{-1}): 3250, 3100 (N-H), 2980 (C-H), 1715 (C=O), 1680 (C=O), 1520 (C=S). ^{1}H NMR (δ ppm): 1.11 (t, 3H, ethyl CH_3), 2.08 (s, 3H, C_6-CH_3), 3.97 (q, 2H, OCH_2), 6.85 (s, 1H, methine CH), 6.78-6.95 (m, 4H, Ph), 7.71-7.77 (m, 5H, COPh), 9.03 (s, 1H, Ar-OH), 9.40 (s, 1H, NH).

Ethyl-3-benzoyl-4-(4-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2f): Yield 39.00 %; m.p. 140 ºC. IR (KBr, ν_{max}, cm^{-1}) : 3245,3100 (N-H), 2980 (C-H), 1715 (C=O), 1680 (C=O), 1520 (C=S). ^{1}H NMR (δ ppm): 1.11 (t, 3H, ethyl CH_3), 2.08 (s, 3H, C_6-CH_3), 3.99 (q, 2H, OCH_2), 6.69 (s, 1H, methine CH), 6.77-7.34 (m, 4H, Ph), 7.71-7.77 (m, 5H, COPh), 9.04 (s, 1H, Ar-OH), 9.41 (s, 1H, NH).

Methyl-3-benzoyl-6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2g): Yield 48.00 %; m.p. 190 ºC. IR (KBr, ν_{max}, cm^{-1}) : 3240, 3140 (N-H), 2970 (C-H), 1720 (C=O), 1690 (C=O), 1510 (C=S). ^{1}H NMR (δ ppm): 3.71 (s, 3H, $COOCH_3$), 2.08 (s, 3H, C_6-CH_3), 6.69 (s, 1H, methine CH), 7.20-7.44 (m, 5H, Ph), 7.76-7.77 (m, 5H, COPh), 9.38 (s, 1H, NH).

Methyl-3-benzoyl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2h): Yield 40.50 %; m.p. 150 ºC. IR (KBr, ν_{max}, cm^{-1}): 3260, 3125 (N-H), 2965 (C-H), 1710 (C=O), 1690 (C=O), 1515 (C=S). ^{1}H NMR (δ ppm): 3.70 (s, 3H, $COOCH_3$), 2.31 (s, 3H, C_6-CH_3), 6.20 (s, 2H, methylene CH_2), 7.67-7.75 (m, 5H, COPh), 9.40 (s, 1H, NH).

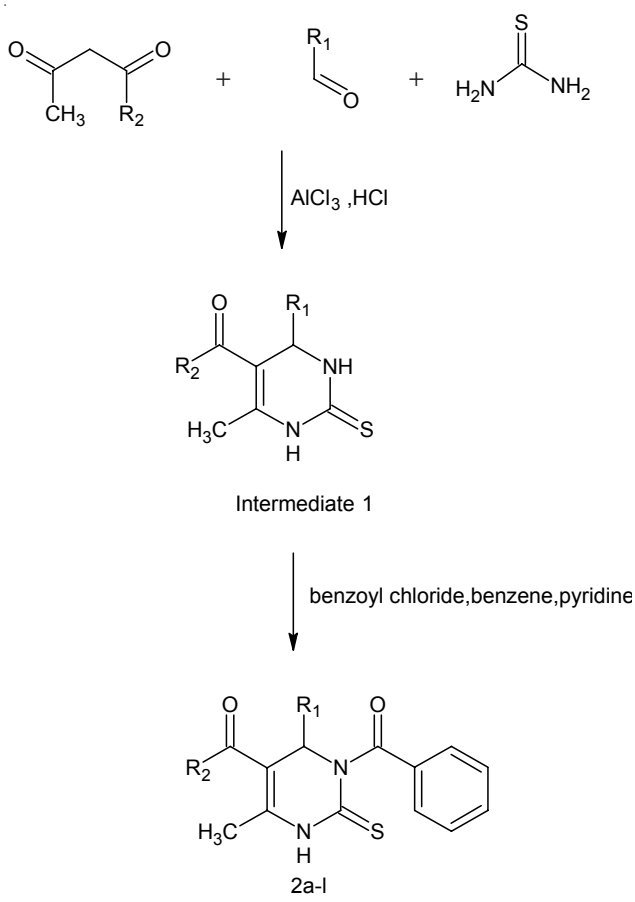
Methyl-3-benzoyl-4-(4-dimethylaminophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2i): Yield 41.34 %; m.p. 182 ºC. IR (KBr, ν_{max}, cm^{-1}) : 3245, 3135 (N-H), 2985 (C-H), 1715 (C=O), 1690 (C=O), 1510 (C=S). ^{1}H NMR (δ ppm): 3.71 (s, 3H, $COOCH_3$), 2.08 (s, 3H, C_6-CH_3), 6.69 (s, 1H, methine CH), 6.44-7.26 (m, 4H, Ph), 7.71-7.77 (m, 5H, COPh), 2.83 (s, 6H, $N(CH_3)_2$, 9.39 (s, 1H, NH).

Methyl-3-benzoyl-4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2j): Yield 50.50 %; m.p. 164 ºC. IR (KBr, ν_{max}, cm^{-1}): 3220, 3100 (N-H), 2980 (C-H), 1705 (C=O), 1690 (C=O), 1510 (C=S). ^{1}H NMR (δ ppm): 3.71 (s, 3H, $COOCH_3$), 2.08 (s, 3H, C_6-CH_3), 6.69 (s, 1H, methine CH), 6.95-7.36 (m, 4H, Ph), 7.71-7.77 (m, 5H, COPh), 3.60 (s, 3H, OCH_3), 9.38 (s, 1H, NH).

Methyl-3-benzoyl-4-(2-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2k): Yield 40.00 %; m.p. 200 ºC. IR (KBr, ν_{max}, cm^{-1}): 3250, 3100 (N-H), 2980 (C-H), 1715 (C=O), 1680 (C=O), 1520 (C=S). ^{1}H NMR (δ ppm): 3.71 (s, 3H, $COOCH_3$), 2.08 (s, 3H, C_6-CH_3), 6.85 (s, 1H, methine CH), 6.78-7.28 (m, 4H, Ph), 7.71-7.77 (m, 5H, COPh), 9.03 (s, 1H, Ar-OH), 9.41 (s, 1H, NH).

Methyl-3-benzoyl-4-(4-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2l): Yield 51.47 %; m.p. 165 ºC. IR (KBr, ν_{max}, cm^{-1}): 3240, 3100 (N-H), 2980 (C-H), 1715 (C=O), 1680 (C=O), 1520 (C=S). ^{1}H NMR (δ ppm): 3.71 (s, 3H, $COOCH_3$), 2.08 (s, 3H, C_6-CH_3), 6.69 (s, 1H, methine CH), 6.77-7.34 (m, 4H, Ph), 7.71-7.77 (m, 5H, COPh), 9.05 (s, 1H, Ar-OH), 9.42 (s, 1H, NH).

Antibacterial activity: Antibacterial activity of these 12 compounds was tested *in vitro* against gram-positive bacteria *Staphylococcus aureus* (NCIM-2079) by the cup-plate agar diffusion method, using DMSO as solvent and trimethoprim as standard drug. Further minimum inhibitory concentration (MIC) of all these compounds was determined by double dilution method[15]. The biological data minimum inhibitory concentration (MIC) in mg/mL were converted to negative logarithmic dose in moles (pMIC) for QSAR analysis.



Synthetic Scheme

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. 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 (r^2), standard error of estimation (SE), sequential Fischer test (F). Quality and predictability of model was estimated from the cross validated squared correlation coefficient (q^2)[16].

RESULTS AND DISCUSSION

The purity and homogeneity of all these 12 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 67 % to minimum 39 %. 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 ^{1}H 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).

TABLE-1
CHARACTERIZATION DATA OF THE TITLE COMPOUNDS (2a-l)

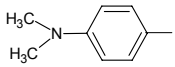
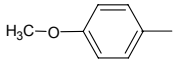
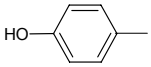
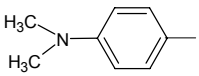
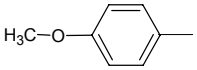
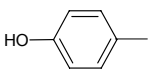
Compd./ m.f.	R_1	R_2	Yield (%) / m.p. (ºC)	Elemental analysis %: Found (Calcd.)		
				C	H	N
2a $C_{21}H_{20}N_2O_3S$		OC_2H_5	66.17 160	66.21 (66.29)	5.20 (5.30)	7.27 (7.36)
2b $C_{15}H_{16}N_2O_3S$	H	OC_2H_5	42.80 132	59.15 (59.19)	5.22 (5.30)	9.24 (9.20)
2c $C_{23}H_{25}N_3O_3S$		OC_2H_5	66.66 172	65.18 (65.23)	5.92 (5.95)	9.89 (9.92)
2d $C_{22}H_{22}N_2O_4S$		OC_2H_5	42.10 121	64.33 (64.37)	5.35 (5.40)	6.78 (6.82)
2e $C_{21}H_{20}N_2O_4S$		OC_2H_5	45.54 120	63.56 (63.62)	4.01 (5.08)	7.02 (7.07)
2f $C_{21}H_{20}N_2O_4S$		OC_2H_5	39.00 140	63.57 (63.62)	4.98 (5.08)	7.01 (7.07)
2g $C_{20}H_{18}N_2O_3S$		OCH_3	48.00 190	65.51 (65.55)	4.87 (4.95)	7.57 (7.64)
2h $C_{14}H_{14}N_2O_3S$	H	OCH_3	40.50 150	57.87 (57.92)	4.82 (4.86)	9.61 (9.65)
2i $C_{22}H_{23}N_3O_3S$		OCH_3	41.34 180	64.48 (64.53)	5.62 (5.66)	10.21 (10.26)
2j $C_{21}H_{20}N_2O_4S$		OCH_3	50.50 164	63.58 (63.62)	5.03 (5.08)	7.01 (7.07)
2k $C_{20}H_{18}N_2O_4S$		OCH_3	40.00 200	62.79 (62.81)	4.71 (4.74)	7.29 (7.33)
2l $C_{20}H_{18}N_2O_4S$		OCH_3	51.47 165	62.78 (62.81)	4.69 (4.74)	7.28 (7.33)

TABLE-2
ANTIBACTERIAL ACTIVITY OF THE TITLE COMPOUNDS (**2a-l**) ON *S. aureus*

Comp.	Minimum inhibitory concentration (MIC) in µg/mL	pMIC
2a	500	2.8813
2b	62	3.6910
2c	1000	2.6269
2d	125	3.5164
2e	500	2.8992
2f	62	3.8058
2g	32	4.0589
2h	250	3.0650
2i	1000	2.6123
2j	62	3.8058
2k	500	2.8836
2l	62	3.7902

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.

TABLE-3
CALCULATED MOLECULAR DESCRIPTORS OF THE TITLE COMPOUNDS (**2a-l**)

Compd.	[A]AM1_ HOMO	[B]AM1_ LUMO	[C]BCUT_ PEOE_1	[D]BCUT_ SLOGP_1	[E]GCUT_ SMR_1
2a	-8.7820	-0.7676	-0.6044	-0.4982	-0.2040
2b	-8.9427	-1.0326	-0.5083	-0.4083	-0.1805
2c	-8.4160	-0.6605	-0.5083	-0.4529	-0.1805
2d	-8.7706	-0.7371	-0.5870	-0.5181	-0.2018
2e	-8.7094	-0.6340	-0.5659	-0.4645	-0.1940
2f	-8.8150	-0.7713	-0.6443	-0.5381	-0.2154
2g	-8.8068	-0.8215	-0.6045	-0.4983	-0.2042
2h	-8.9476	-1.0628	-0.5083	-0.4083	-0.1805
2i	-8.4271	-0.7155	-0.5083	-0.4531	-0.1805
2j	-8.8127	-0.8617	-0.5873	-0.5182	-0.2020
2k	-8.7121	-0.6855	-0.5660	-0.4645	-0.1942
2l	-8.8215	-0.8635	-0.6443	-0.5381	-0.2157

A = Highest Occupied Molecular Orbital energy (eV), B = Lowest Unoccupied Molecular Orbital energy (eV), C = PEOE charge BCUT (1/3), D = log P BCUT (1/3), E = Molar refractivity GCUT (1/3)

pMIC = -16.68163-1.98654 (±0.6074)* AM1_HOMO-5.43404 (±2.2627)* BCUT_SLOGP_1, n = 12, r^2 = 0.65627, q^2 = 0.454244, SE = 0.3394, F = 8.60 (Model-1).
pMIC = -2.47491-2.21734 (±0.7429)* AM1_LUMO-7.02341 (± 1.9642)* BCUT_PEOE_1, n = 12, r^2 = 0.67344, q^2 = 0.437427, SE = 0.3309, F = 9.28 (Model-2).
pMIC = -3.01472-2.73795 (±0.7516)* AM1_LUMO-8.59160 (± 2.2639)* BCUT_SLOGP_1, n = 12, r^2 = 0.69591, q^2 = 0.450788, SE = 0.3192, F = 10.31 (Model-3).
pMIC = -3.87359-2.17494 (±0.7239)* AM1_LUMO-27.71014 (± 7.4456)* GCUT_SMR_1, n = 12, r^2 = 0.68856, q^2 = 0.457455, SE = 0.3235, F = 9.92 (Model-4).
pMIC = -14.08855-1.59552 (±0.6849)* AM1_HOMO-17.51894 (±8.7138)* GCUT_SMR_1, n = 12, r^2 = 0.61078, q^2 = 0.400033, SE = 0.3614, F = 7.05 (Model-5).

Out of the five models, model-3 was selected on the basis of statistical criteria; r^2 = 0.69591, SE = 0.3192 and F = 10.31. The internal predictivity of the model was assessed by cross-validated squared correlation coefficient (q^2 = 0.450788), which shows good correlation between predicted activity and observed activity (Table-4). Correlation matrix shows poor correlation between descriptors (Table-5).

TABLE-4
OBSERVED (OBS.), PREDICTED (PRED.) PMIC AND RESIDUAL VALUES FOR MODEL-3

Comp.	pMIC observed	pMIC predicted	Residuals
2a	2.8813	3.3673	-0.4859
2b	3.6910	3.3199	0.3711
2c	2.6269	2.6850	-0.0581
2d	3.5164	3.4544	0.0620
2e	2.8992	2.7117	0.1875
2f	3.8058	3.7201	0.0857
2g	4.0589	3.5154	0.5435
2h	3.0650	3.4028	-0.3378
2i	2.6123	2.8368	-0.2245
2j	3.8058	3.7972	0.0086
2k	2.8836	2.8531	0.0305
2l	3.7902	3.9726	-0.1824

It is evident from the QSAR studies that in model-3, electronic descriptor (AM1_LUMO) and lipophilic descriptor (BCUT_SLOGP_1) are responsible for the activity and both contributes negatively to biological activity, which indicates that minimizing both the Lowest Unoccupied Molecular Orbital

energy and atomic contribution to partition coefficient (log P) may lead to better antibacterial compound from this series.

TABLE-5
CORRELATION MATRIX

	pMIC	AM1_ HOMO	AM1_ LUMO	BCUT_ PEOE_1	BCUT_ SLOGP_1	GCUT_ SMR_1
pMIC	1.0000					
AM1_HOMO	-0.6603	1.0000				
AM1_LUMO	-0.4575	0.7398	1.0000			
BCUT_PEOE_1	-0.5918	0.3279	-0.1730	1.0000		
BCUT_SLOGP_1	-0.4979	0.0440	-0.3436	0.9151	1.0000	
GCUT_SMR_1	-0.6130	0.3308	-0.1550	0.9980	0.9298	1.0000

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REFERENCES

1. C.O. Kappe, *Molecules*, **3**, 1 (1998).
2. J.C. Barrow, K.L. Glass, H.G. Selnick, R.M. Freidinger, R.S.L. Chang, S.S. O'Malley and C. Woyden, *Bioorg. Med. Chem. Lett.*, **10**, 1917 (2000).
3. A.D. Patil, N.V. Kumar, W.C. Kokke, M.F. Bean, A.J. Freyer, C. Debrose, S. Mai, A. Trunch, D.J. Falkner, B. Carte, A.L. Breen, R.P. Hertzberg, R.K. Johnston, J.W. Westely and B.C.M. Ports, *J. Org. Chem.*, **6**, 1182 (1995).
4. E.W. Hurst and R. Hull, *J. Med. Pharm. Chem.*, **3**, 215 (1961).
5. T.V. Meyer, T.M. Kapoor, S.J. Haggarty, R.W. King, S.L. Schreiber and T.J. Mitchison, *Science*, **286**, 71 (1991).
6. K. Kumasars, A. Valena, G. Dubers, J. Uldrikis and A. Ziderman, *Biokhimiya*, **36**, 1201 (1971).
7. C.O. Kappe, *Acc. Chem. Res.*, **33**, 879 (2000).
8. B. Tozkoparan, H. Akgun, M. Ertan, Y. Sara and N. Ertekin, *Arch. Pharm.*, **328**, 169 (1995).
9. D. Nagarathnam, J.M. Wetzel, S.W. Miao, M.R. Marzabad, G. Chiu, W.C. Wang, X. Hong, J. Fang, C. Forry, T.A. Branchek, W.E. Heydora, R.S.L. Chang, T. Broten, T. Schora and C. Gluchowski, *J. Med. Chem.*, **41**, 5320 (1998).
10. C.O. Kappe, *Eur. J. Med. Chem.*, **35**, 1043 (2000).
11. C.O. Kappe, *Tetrahedron*, **49**, 6937 (1993).
12. H.C. Neu, *Science*, **257**, 1064 (1992).
13. D. Russowsky, F.A. Lopes, V.S.S. da Silva, K.F.S. Canto, M.G. Montes D'Oca and M.N. Godoi, *J. Braz. Chem. Soc.*, **15**, 165 (2004).
14. S. Kumar, A. Saini and J.S. Sandhu, *Indian J. Chem.*, **43B**, 1485 (2004).
15. L.A. Kirven and C. Thornsberry, *Antimicrob. Agents Chemother.*, **10**, 340 (1978).
16. H. Kubinyi, QSAR: Hansch Analysis and Related Approaches, Weinheim, New York, p. 91 (1993).

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