QSAR ANALYSIS OF 2-OXO-1,2,3,4-TETRAHYDROPYRIMIDINE ANALOGUES OF ANTIBACTERIALS

Ramesh L. SAWANT[a,*] and Manish S. BHATIA[b]

[a] *Department of Pharmaceutical Chemistry, Pd. Dr. Vithalrao Vikhe Patil Foundation's College of Pharmacy, Vilad Ghat, Post-MIDC, Ahmednagar-414111, Maharashtra, India; e-mail: sawantrl@yahoo.com*

[b] *Department of Pharmaceutical Chemistry, Bharati Vidyapeeth College of Pharmacy, Near Chitranagari, Kolhapur-416013, Maharashtra, India; e-mail: drmsb13@yahoo.com*

Received April 18, 2009
Accepted June 22, 2009
Published online September 16, 2009

QSAR analysis of two sets of analogues of 2-oxo-1,2,3,4-tetrahydropyrimidine was performed to investigate the relationship between their physicochemical parameters and antibacterial activity. Predictive and statistically significant models were generated. On the basis of these models new compounds were synthesized, structurally characterized and evaluated for their antibacterial potential. The potential of newly synthesized compounds was higher than the training set of compounds, in close agreement with QSAR prediction.

Keywords: QSAR; 2-Oxo-1,2,3,4-tetrahydropyrimidine; Antibacterial activity; Electronic features; Steric features.

Microbial infections are the most common cause of the diseased state. Most widely used antibacterials are antibiotics but recently fluoroquinolones and other synthetics are used to combat newer and resistant microbial infections[1]. Many research programme efforts are directed to the design of new and available drugs because of the unsatisfactory status of side effects of present drugs and the acquisition of resistance of the infecting organisms to the present drugs. The emergence and spread of bacterial resistance are a severe global problem. Pathogenic microorganisms develop physiological mechanisms to block the actions of repeatedly used antimicrobial agents and, after a period of time, the newly introduced compounds become less effective in producing microbicidal or static response. The escalating resistance has led to the appearance of multiresistant *Staphylococci*, *Enterococci* and *Pneumococci* in nosocomial and community acquired infections[2]. There is a real perceived need for the discovery of new compounds endowed with antibacterial properties, possibly acting through mechanisms that are dis-

doi:10.1135/cccc2009054

tinct from those of the well-known classes of antibacterial agents to which many clinically relevant pathogens are now resistant.

QSAR studies of antimicrobial activity are an exceptionally important topic in the area of computer-aided drug design[3,4]. Although the demand for *in-silico* discovery is clear in all areas of human therapeutics, the field of anti-infective drugs shows a particular need for computational solutions enabling rapid identification of novel therapeutic leads. As a result, there is an urge for new antimicrobials driven by critical situation, such as increased prevalence of multidrug-resistant bacteria and emergence of deadly infectious diseases.

Pyrimidine derivatives play a vital role in many biological processes, the ring system being present in nucleic acids, several vitamins and coenzymes, uric acid and other purines. Many synthetics of the group are also important as drugs and chemotherapeutic agents. 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 modulator[5], selective 1-adrenoreceptor antagonist[6], HIV gpl20-CD_4 inhibitior[7], antiviral[8], anticancer drug with mitotic kinesin inhibition[9], oral antihypertensive[10], blood platelet aggregation inhibitor[11], drug for the treatment of benign prostatic hyperplasia[12], anti-inflammatory[13], muscarinic[14], antifungal and antibacterial drugs[15]. The presence of several interacting functional groups in the pyrimidine compounds also determines their great synthetic potential.

RESULTS AND DISCUSSION

In both sets the minimum inhibitory concentration (MIC) data (in mg/ml) against *Staphylococcus aureus* was converted to negative logarithmic dose in moles (pMIC) for QSAR analysis (Table I). The values of descriptors (Table II) that are significant in the model show high correlation with biological activity. The correlation among the descriptors and their correlation with antibacterial activity is demonstrated by construction of correlation matrix (Table III).

Performing stepwise multiple linear regression analysis in set 1 results in several equations. The following four of which are statistically significant QSAR models.

pMIC = 4.97312 + 0.04823 (±0.0231)* PEOE_VSA_PNEG – 0.02076 (±0.0061)* PEOE_VSA_PPOS – 1.85275 (±0.3356)* FCASA-

n = 18, r^2 = 0.73706, q^2 = 0.564376, SE = 0.2372, F = 13.08, p = 0.0002 (*1a*)

pMIC = 4.95113 – 0.31731 (±0.1341)* PC+ – 0.02626 (±0.0130)* Q_VSA_PNEG + 0.01250 (±0.0029)* SMR_VSA7
n = 18, r^2 = 0.76165, q^2 = 0.584635, SE = 0.2258, F = 14.91, p = 0.0001 (*1b*)

pMIC = 4.96716 – 0.32007 (±0.1361)* PC+ + 0.01163 (±0.0032)* SMR_VSA7 – 0.70285 (±0.3643)* FCASA-
n = 18, r^2 = 0.75649, q^2 = 0.588355, SE = 0.2243, F = 14.50, p = 0.0001 (*1c*)

pMIC = 4.35070 + 0.01201 (±0.0077)* PEOE_VSA_PPOS – 0.63991 (±0.1704)* PC+ + 0.01820 (±0.0033)* SMR_VSA7
n = 18, r^2 = 0.73685, q^2 = 0.553238, SE = 0.2373, F = 13.07, p = 0.0002 (*1d*)

For set 2, following statistically significant QSAR models are obtained.

pMIC = –6.65726 + 2.91592 (±0.6572)* GCUT_SLOGP_3 – 0.01920 (±0.0042)* MNDO_HF
n = 12, r^2 = 0.75998, q^2 = 0.484092, SE = 0.3037, F = 14.25, p = 0.0016 (*2a*)

pMIC = –7.83838 + 1.55969 (±0.3908)* VadjMa – 0.01907 (±0.0044)* PM3_HF
n = 12, r^2 = 0.73514, q^2 = 0.460294, SE = 0.3191, F = 12.49, p = 0.0025 (*2b*)

pMIC = –1.92407 + 0.02605 (±0.0061)* zagreb – 0.01955 (±0.0044)* MNDO_HF
n = 12, r^2 = 0.74517, q^2 = 0.459367, SE = 0.3130, F = 13.16, p = 0.0021 (*2c*)

pMIC = –3.15816 + 1.99980 (±0.4663)* PEOE_PC+ – 0.01528 (±0.0040)* PM3_HF
n = 12, r^2 = 0.75896, q^2 = 0.499449, SE = 0.3044, F = 14.17, p = 0.0017 (*2d*)

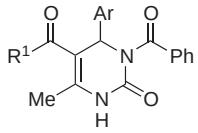
pMIC = –0.74566 – 0.01642 (±0.0038)* MNDO_HF + 1.42990 (±0.2930)* std_dim3
n = 12, r^2 = 0.79023, q^2 = 0.548233, SE = 0.2840, F = 16.95, p = 0.0009 (*2e*)

Out of these models model (*1b*) of set 1 and model (*2e*) of set 2 were selected on the basis of statistical criteria. The internal predictivity of the model was assessed by cross-validated squared correlation coefficient (q^2). The high q^2 in both the models are indicative of its reliability in prediction of antibacterial activity in the series. Predicting the antibacterial activity validated the predictive ability. The low residual activity observed (Table IV) indicates the reliability of the selected QSAR model.

In the case of set 1, it is evident from the selected best QSAR model that the total positive partial charge (PC+) and the total polar negative van der Waals surface area (Q_VSA_PNEG) contribute negatively whereas the contribution of the van der Waals surface area to molar refractivity

(SMR_VSA7) to antibacterial activity is positive. The new compounds having less positive partial charge and polar negative van der Waals surface area with higher contribution of van der Waals surface area to molar refractivity may lead to improved antibacterial activity from this series.

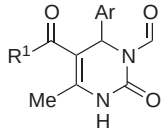
TABLE Ia
Antibacterial (*S. Aureus*) activity of set 1 compounds



Compound	Ar	R^1	MIC, μg/ml	pMIC
6b	Ph	C_2H_5O	250	3.1636
6c	4-$MeOC_6H_4$	C_2H_5O	125	3.4991
6d	4-$Me_2NC_6H_4$	C_2H_5O	62	3.8177
6e	4-CH_2=CHC_6H_4	C_2H_5O	1000	2.5916
6f	2-OHC_6H_4	C_2H_5O	500	2.8813
6h	2-furyl	C_2H_5O	500	2.8517
7a	H	CH_3O	125	3.3413
7b	Ph	CH_3O	250	3.1466
7e	4-CH_2=CHC_6H_4	CH_3O	500	2.8767
7f	2-OHC_6H_4	CH_3O	500	2.8650
7h	2-furyl	CH_3O	500	2.8342
8a	H	CH_3	62	3.6197
8b	Ph	CH_3	250	3.1263
8c	4-$MeOC_6H_4$	CH_3	32	4.0564
8d	4-$Me_2NC_6H_4$	CH_3	125	3.4799
8e	4-CH_2=CHC_6H_4	CH_3	1000	2.5568
8f	2-OHC_6H_4	CH_3	500	2.8456
8h	2-furyl	CH_3	125	3.4154

In the case of set 2, it is evident from the selected best QSAR model that heat of formation (MNDO_HF) and standard dimension 3 (std_dim3) 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 lead to better antibacterial compounds of this series.

TABLE Ib
Antibacterial (*S. Aureus*) activity of set 2 compounds



Compound	Ar	R^1	MIC, μg/ml	pMIC
4a	H	C_2H_5O	1000	2.3268
4b	Ph	C_2H_5O	500	2.7609
4c	4-$MeOC_6H_4$	C_2H_5O	250	3.1049
4d	4-$Me_2NC_6H_4$	C_2H_5O	500	2.8213
4f	2-OHC_6H_4	C_2H_5O	250	3.0854
4h	2-furyl	C_2H_5O	500	2.7455
5a	H	CH_3O	1000	2.2971
5b	Ph	CH_3O	500	2.7392
5c	4-$MeOC_6H_4$	CH_3O	16	4.2792
5d	4-$Me_2NC_6H_4$	CH_3O	500	2.8026
5e	4-CH_2=CHC_6H_4	CH_3O	1000	2.4776
5h	2-furyl	CH_3O	62	3.6296

Based on the QSAR studies data, the new compounds were designed taking into account the extent to which particular descriptors governed antibacterial activity. It is evident from the QSAR studies that electronic descriptors contribute negatively whereas spatial descriptors contribute positively to antibacterial activity. Considering the above fact new compounds

TABLE IIa
Calculated molecular descriptors of set 1 compounds

Compd.	PEOE_VSA_PNEG[a]	PEOE_VSA_PPOS[b]	PC+[c]	Q_VSA_PNEG[d]	SMR_VSA7[e]	FCASA-[f]
6b	43.3414	45.0986	4.8960	43.3414	66.6520	1.6270
6c	45.8452	45.0986	5.1080	45.8452	102.0359	1.4768
6d	43.3414	45.0986	5.5840	43.3414	132.4464	1.4232
6e	43.3414	45.0986	5.2180	55.5963	66.6520	1.8380
6f	51.1090	55.4227	5.2780	51.1090	66.6520	1.7826
6h	43.3414	63.8813	5.3040	43.3414	66.6520	1.4479
7a	43.3414	45.0986	4.0020	43.3414	68.7099	1.4326
7b	43.3414	45.0986	4.8960	43.3414	68.7099	1.7299
7e	43.3414	45.0986	5.2180	55.5963	68.7090	1.9344
7f	51.1090	55.4227	5.2780	51.1090	68.7099	1.9028
7h	43.3414	63.8813	5.3040	43.3414	68.7090	1.5176
8a	40.8377	30.3901	3.5720	40.8377	66.6520	1.3479
8b	40.8377	30.3901	4.4660	40.8377	66.6520	1.6847
8c	43.3414	30.3901	4.6780	43.3414	102.0359	1.5140
8d	40.8377	30.3901	5.1540	40.8377	132.4464	1.4465
8e	40.8377	30.3901	4.7880	53.0926	66.6520	1.8762
8f	48.6052	40.7142	4.8480	48.6052	66.6520	1.8224
8h	40.8377	49.1728	4.8740	40.8377	66.6520	1.4325

[a] Total polar negative vdw surface area. [b] Total polar positive vdw surface area. [c] Total positive partial charge. [d] Total polar negative vdw surface area. [e] vdw surface area in molar refractivity (SMR). [f] Fractional charge-weighed negative surface area.

were designed containing trimethoxyphenyl substituent at Ar position in the general structure of both the series. The antibacterial activity of these new compounds was predicted by evaluating selected most significant QSAR models of the series. The activity prediction for the new compounds was done by compute-model evaluate module of the MOE 2006.08 software[16]. The predicted activity of the new compounds was higher than the most active compound of the series. Subsequently, these new compounds were synthesized, characterized and screened for their antibacterial activity. The observed activity was higher than that of training set compounds, in close agreement with QSAR prediction and comparable to the currently clinically used pyrimidine antimicrobial trimethoprim (Table V).

TABLE IIb
Calculated molecular descriptors of set 2 compounds

Compd.	GCUT_ SLOGP_3[a]	VAdjMa[b]	zagreb[c]	PEOE_ PC+[d]	MNDO_HF[e]	PM3_HF[f]	std_dim3[g]
4a	2.2665	4.9069	70.0000	1.7181	–112.9104	–119.6412	0.7310
4b	2.6026	5.4594	104.0000	2.0422	–112.8434	–125.5291	1.2300
4c	2.6466	5.5850	114.0000	2.2488	–118.6648	–122.7770	1.4817
4d	2.6950	5.6439	120.0000	2.2236	–65.1793	–86.3890	1.4778
4f	2.6358	5.5236	110.0000	2.2762	–121.4409	–131.4696	1.4361
4h	2.5316	5.3923	100.0000	2.2149	–111.5959	–112.4507	1.3175
5a	2.2128	4.8074	66.0000	1.6947	–140.3118	–152.0492	0.5784
5b	2.5726	5.3923	100.0000	2.0043	–92.3657	–120.8682	1.2418
5c	2.6191	5.5236	110.0000	2.2253	–146.9882	–158.0519	1.5095
5d	2.6701	5.5850	116.0000	2.2002	–96.3653	–124.7239	1.5033
5e	2.5356	5.5236	108.0000	2.1188	–96.2787	–81.0662	1.3602
5h	2.4978	5.3219	96.0000	2.1915	–142.5653	–147.9133	1.3291

[a] Log P 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.

TABLE IIIa
Correlation matrix set 1

	pMIC	PEOE_VSA_PNEG	PEOE_VSA_PPOS	PC+	Q_VSA_PNEG	SMR_VSA7	FCASA-
pMIC	1.0000						
PEOE_VSA_PNEG	–0.2753	1.0000					
PEOE_VSA_PPOS	–0.3750	0.4660	1.0000				
PC+	–0.2163	0.3324	0.4763	1.0000			
Q_VSA_PNEG	–0.5668	0.4457	0.1359	0.3277	1.0000		
SMR_VSA7	0.4055	–0.1111	–0.2380	0.4278	–0.2923	1.0000	
FCASA-	–0.5315	0.4305	0.0233	0.3333	0.8257	–0.3773	1.0000

TABLE IIIb
Correlation matrix set 2

	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					
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

EXPERIMENTAL

Selection of Compounds

Data set for 18 analogues of 3-benzoyl-2-oxo-1,2,3,4-tetrahydropyrimidine (set 1) and 12 analogues of 3-formyl-2-oxo-1,2,3,4-tetrahydropyrimidine (set 2) from our previously published work were used[17,18]. Antibacterial activity 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. Minimum inhibitory concentrations (MIC) of all these compounds were determined by the double dilution method[19]. The biological data MIC in mg/ml were converted to negative logarithmic doses in moles (pMIC) for QSAR analysis.

TABLE IVa
Observed, predicted pMIC and residuals for set 1 compounds

Compound	pMIC observed	pMIC predicted	Residuals
6b	3.1636	3.0926	0.0710
6c	3.4991	3.4018	0.0972
6d	3.8177	3.6966	0.1211
6e	2.5916	2.6687	–0.0771
6f	2.8813	2.7674	0.1138
6h	2.8517	2.9631	–0.1114
7a	3.3413	3.4020	–0.0607
7b	3.1466	3.1183	0.0283
7e	2.8767	2.6944	0.1823
7f	2.8650	2.7932	0.0718
7h	2.8342	2.9889	–0.1546
8a	3.6197	3.5785	0.0412
8b	3.1263	3.2948	–0.1685
8c	4.0564	3.6040	0.4524
8d	3.4799	3.8988	–0.4188
8e	2.5568	2.8780	–0.3140
8f	2.8456	2.9696	–0.1241
8h	3.4154	3.1653	0.2501

TABLE IVb
Observed, predicted pMIC and residuals for set 2 compounds

Compound	pMIC observed	pMIC predicted	Residuals
4a	2.3268	2.1535	0.1733
4b	2.7609	2.8658	–0.1049
4c	3.1049	3.3213	–0.2164
4d	2.8213	2.4375	0.3838
4f	3.0854	3.3017	–0.2163
4h	2.7455	2.9705	–0.2250
5a	2.2971	2.3852	–0.0881
5b	2.7392	2.5466	0.1926
5c	4.2792	3.8261	0.4530
5d	2.8026	2.9861	–0.1835
5e	2.4776	2.7800	–0.3025
5h	3.6296	3.4956	0.1340

TABLE V
Antibacterial (*S. Aureus*) activity of lead compounds and standard drug

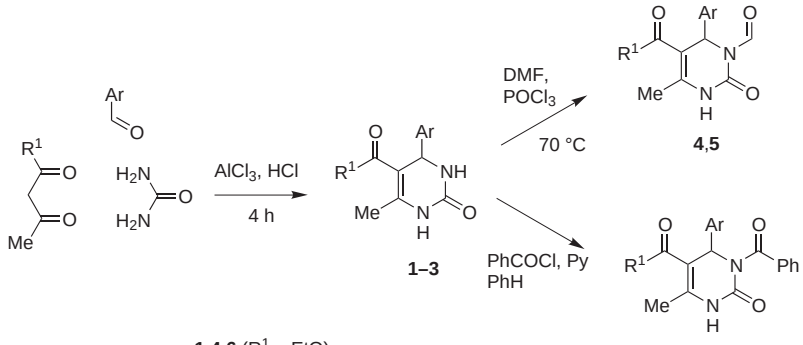
Compound	MIC, μg/ml	pMIC observed	pMIC predicted	Residuals
4g	8	4.6748	5.0171	–0.3423
5g	8	4.6584	4.9665	–0.3081
6g	16	4.4534	4.2134	0.2400
7g	16	4.4398	4.2224	0.2174
Trimethoprim	8	–	–	–

QSAR Analysis

The series were subjected to QSAR analysis using MOE 2006.08 running on P-IV processor. Structures of all the compounds were sketched using the 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 compounds were calculated using the "compute descriptor" module of the programme. All the calculated descriptors were considered as independent variables and biological activity (pMIC) as the dependent variable. Stepwise multiple linear regression analysis 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 the model was estimated[20] from the cross-validated squared correlation coefficient (q^2).

Methods

Melting points of the synthesized compounds were determined in an open capillary tube and hence are uncorrected. The structures of the title compounds were established on the basis of spectral data. The IR spectra (KBr; ν, cm^{-1}) were recorded on a Jasco FTIR 4100 spectrophotometer. ^1H NMR spectra (δ, ppm; J, Hz) were recorded on a Varian NMR 400 MHz spectrometer using $CDCl_3$ as solvent with TMS as an internal standard. Mass spectra were recorded to know the M + 1 peak on an LC-MS Thermofinigen spectrometer. Purity of the synthesized compounds was checked by silica gel G plate using benzene and ethyl acetate as mobile phases.



1,**4**,**6** (R^1 = EtO) **2**,**5**,**7** (R^1 = MeO) **3**,**8** (R^1 = Me)	Ar
a	H
b	Ph
c	4-$MeOC_6H_4$
d	4-$Me_2NC_6H_4$
e	4-CH_2=CHC_6H_4
f	2-OHC_6H_4
g	3,4,5-$(MeO)_3C_6H_2$
h	furyl

SCHEME 1

Synthesis of New Compounds

Ethyl 6-methyl-2-oxo-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1g**)[21,22]. A mixture of 3,4,5-trimethoxybenzaldehyde (0.02 mol), ethyl acetoacetate (0.02 mol), urea (0.03 mol), aluminium chloride (0.01 mol), and few drops of concentrated hydrochloric acid in methanol was refluxed for 4 h. The solid separated on cooling was filtered, washed with cold methanol, dried and recrystallized from methanol.

Methyl 6-methyl-2-oxo-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**2g**)[21,22]. The same procedure was followed as for **1g**. Instead of ethyl acetoacetate methyl acetoacetate was used.

Ethyl 3-formyl-6-methyl-2-oxo-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4g**). To a suspension of **1g** (0.02 mol) in 20 ml of dry dimethylformamide, phosphorus oxychloride (0.02 mol) was added in ice bath. The resulting solution was heated at 70 °C and kept there for 40 min. Then it was poured into 150 ml of ice-water to yield the solid product. The product thus separated was filtered, washed with cold water, air dried and recrystallized from ethanol. Yield 66.7%; m.p. 176 °C. IR: 3240, 3140 (N–H), 2943 (C–H), 1703 (C=O), 1687 (C=O), 1674 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): 1.20 (t, J = 7, 3 H, ethyl CH_3), 2.38 (s, 3 H, C_6-CH_3), 3.80 (s, 9 H, OCH_3), 4.10 (q, J = 7, 2 H, OCH_2), 6.43 (s, 1 H, CH), 6.96 (s, 2 H, Ph), 7.22 (s, 1 H, NH), 8.20 (s, 1 H, formyl CH). LC-MS (M + 1): 379.590.

Methyl 3-formyl-6-methyl-2-oxo-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**5g**). The same procedure was followed as for 4g. Instead of **1g**, **2g** were used. Yield 69.1%; m.p. 194 °C. IR: 3210, 3097 (N–H), 2943 (C–H), 1701 (C=O), 1643 (C=O), 1593 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): 2.38 (s, 3 H, C_6-CH_3), 3.70 (s, 3 H, $COOCH_3$), 3.83 (s, 9 H, OCH_3), 6.43 (s, 1 H, CH), 6.96 (s, 2 H, Ph), 7.23 (s, 1 H, NH), 8.40 (s, 1 H, formyl CH). LC-MS (M + 1): 365.077.

Ethyl 3-benzoyl-6-methyl-2-oxo-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**6g**). To a suspension of **1g** (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 the benzene layer was allowed to separate. The benzene layer was washed with 5% sodium carbonate followed by water and dried with anhydrous magnesium sulfate. The benzene solution was concentrated to obtain oily residue which on crystallization from methanol yielded a solid product. Yield 62.9%; m.p. 96 °C. IR: 3230, 3097 (N–H), 2948 (C–H), 1724 (C=O), 1708 (C=O), 1653 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): 1.21 (t, J = 7, 3 H, ethyl CH_3), 2.40 (s, 3 H, C_6-CH_3), 3.83 (s, 9 H, OCH_3), 4.18 (q, J = 7, 2 H, OCH_2), 6.57 (s, 1 H, CH), 6.62 (s, 2 H, Ph), 7.77–7.88 (m, 5 H, COPh), 7.18 (s, 1 H, NH). LC-MS (M + 1): 455.019.

Methyl 3-benzoyl-6-methyl-2-oxo-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**7g**). The same procedure was followed as for **6g**. Instead of **1g**, **2g** were used. Yield 64.3%; m.p. 110 °C. IR: 3220, 3180 (N–H), 2945 (C–H), 1733 (C=O), 1703 (C=O), 1685 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): 2.27 (s, 3 H, C_6-CH_3), 3.62 (s, 3 H, $COOCH_3$), 3.83 (s, 9 H, OCH_3), 6.50 (s, 1 H, CH), 7.10 (s, 2 H, Ph), 7.76–7.88 (m, 5 H, COPh), 7.08 (s, 1 H, NH). LC-MS (M + 1): 441.007.

CONCLUSION

QSAR analysis reveals that electronic and steric features govern the antibacterial potential of 2-oxo-1,2,3,4-tetrahydropyrimidines. The designed and

synthesized compounds based on these observations are good antibacterials. QSAR models generated are highly significant. This study could help in design and development of promising antibacterials.

The authors thank Dr. H. N. More, Bharti Vidyapeeth College of Pharmacy, Kolhapur, for providing facilities.

REFERENCES

1. Rao G. K., Sen S., Rajendra B.: *Indian Drugs* **2004**, *41*, 524.
2. Cohen M. L.: *Science* **1992**, *257*, 1050.
3. Gonzalez D. H., Prado P. F., Ubeira F. M.: *Curr. Top. Med. Chem.* **2008**, *8*, 1676.
4. Gonzalez D. H., Vilar S., Santana L., Uriarte E.: *Curr. Top. Med. Chem.* **2007**, *7*, 1015.
5. Kappe C. O.: *Molecules* **1998**, *3*, 1.
6. Barrow J. C., Glass K. L., Selnick H. G., Freidinger R. M., Chang R. S. L., O'Malley S. S., Woyden C.: *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1917.
7. Patil A. D., Kumar N. V., Kokke W. C., Bean M. F., Freyer A. J., Debrose C., Mai S., Trunch A., Falkner D. J., Carte B., Breen A. L., Hertzberg R. P., Johnston R. K., Westely J. W., Ports B. C. M.: *J. Org. Chem.* **1995**, *60*, 1182.
8. Hurst E. W., Hull R.: *J. Med. Pharm. Chem.* **1961**, *3*, 215.
9. Kappe C. O., Shishkin O. V., Uray G., Verdino P.: *Tetrahedron* **2000**, *56*, 1859.
10. Kappe C. O.: *Acc. Chem. Res.* **2000**, *33*, 879.
11. Tozkoparan B., Akgun H., Ertan M., Sara Y., Ertekin N.: *Arch. Pharm.* **1995**, *328*, 169.
12. Nagarathnam D., Wetzel J. M., Miao S. W., Marzabad M. R., Chiu G., Wang W. C., Hong X., Fang J., Forry C., Branchek T. A., Heydora W. E., Chang R. S. L., Broten T., Schora T., Gluchowski C.: *J. Med. Chem.* **1998**, *41*, 5320.
13. Tozkoparan B., Yarim M., Sarac S., Ertan M., Kelicen P., Altinok G., Demirdamar R.: *Arch. Pharm.* **2000**, *333*, 415.
14. Jung M. H., Park J. G., Lee M. J.: *Arch. Pharm.* **2001**, *334*, 79.
15. Kappe C. O.: *Eur. J. Med. Chem.* **2000**, *35*, 1043.
16. Vilar S., Cozz G., Moro S.: *Curr. Top. Med. Chem.* **2008**, *8*, 1555.
17. Sawant R. L., Bhatia M. S.: *Bull. Chem. Soc. Ethiopia* **2008**, *22*, 391.
18. Sawant R. L., Bhatia M. S.: *Int. J. Chem. Sci.* **2008**, *6*, 45.
19. Kirven L. A., Thornsberry C.: *Antimicrob. Agents Chemother.* **1978**, *10*, 335.
20. Narasimhan B., Kumari M., Dhake A., Sundaravelan C.: *Arkivoc* **2006**, *13*, 73.
21. Russowsky D., Lopes F. A., Da Silva V. S. S., Canto K. F. S., Montes M. G., D'Oca, Godoi M. N.: *J. Braz. Chem. Soc.* **2004**, *15*, 165.
22. Kumar S., Saini A., Sandhu J. S.: *Indian J. Chem., B* **2004**, *43*, 1485.