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Original article

QSAR studies on benzoylaminobenzoic acid derivatives as inhibitors of β-ketoacyl-acyl carrier protein synthase III

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Abstract

Fatty acid biosynthesis is essential for most of the bacterial survival. Components of this biosynthetic pathway have been identified as attractive targets for the development of new antibacterial agents. FabH, β-ketoacyl-ACP synthase III, is a attractive target since it is central to the initiation of fatty acid biosynthesis. Quantitative structure–activity relationship (QSAR) studies have been carried out on a series of benzoylaminobenzoic acid derivatives as potent inhibitors of FabH and antibacterial activity against *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Enterococcus faecalis*, *Neisseria meningitidis* and *Escherichia coli*, which demonstrate FabH inhibitory activity in cell free and whole cell system. The QSAR studies revealed that inhibitory activity increases with increase in hydrophobicity, molar refractivity, aromaticity, and presence of OH group (on *x* position of the nucleus). On the other side presence of hetero-atoms like N, O, or S at R_1 position of the nucleus decreases the inhibitory activity. The comparison of QSAR between the FabH inhibitory activity and antibacterial activity against *S. aureus*, *S. pneumoniae*, *S. pyogenes*, *E. faecalis*, *N. meningitidis* also demonstrates that the hydrophobocity, aromaticity and presence of OH group (on *x* position of the nucleus) are conducive for the inhibitory activity.

Keywords: QSAR; Benzoylaminobenzoic acid derivatives; β-Ketoacyl-acyl carrier protein synthase III inhibitors; Hansch–Free-Wilson mixed approach

1. Introduction

The emergence of resistance in most of the pathogenic bacteria to the currently available antibacterial agents is the major problem in the treatment of serious bacterial infections caused by these organisms. These resistant strains curtail the life span of the drug. Therefore, in recent years, the research has been focused toward development of new antibacterial agents, which may act through novel target, surpassing the problem of acquired resistance. Fatty acid biosynthesis (FabH) is an essential pathway for survival of prokaryotes [1]. The β-ketoacyl-acyl carrier protein (ACP) synthase III is a bacterial condensing enzyme in Gram-positive and Gram-negative bacteria that initiates the fatty acid biosynthesis (FAB) cycle by catalyzing the first condensation step between acetyl Co-A and malonyl-ACP [2] (Fig. 1). Large multifunctional proteins termed type I fatty acid synthases catalyze these essential reactions in eukaryotes [3]. In contrast, bacteria use multiple enzymes to accomplish the same goal and are referred to as type II, or dissociated, fatty acid synthases [4]. Some benzoylaminobenzoic acid derivatives are reported as inhibitors of β-ketoacyl-ACP synthase III. Previously this enzyme is targeted by some synthetic derivatives like triclosan, isoniazid and diazoborines, and some natural products like cerulenin and thiolactomycin. These agents have various shortcomings and limited to use [5] in comparison to the benzoylaminobenzoic acid analogues.

Various sets of compounds were screened in enzymatic assays to generate leads that were co-crystallized with various

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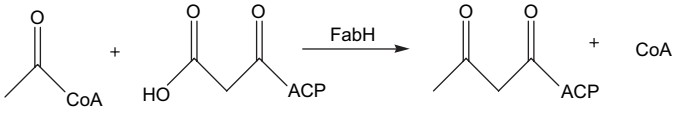


Fig. 1. FabH-catalyzed initiation reaction of fatty acid biosynthesis.

pathogenic FabH proteins and subsequently optimized using structure guided drug design methods [6–8]. Compound selection proceeded via searches of substructure; the pharmacophore models describe specific areas for desired protein–ligand interaction and limit the molecular volume to be appropriate for the FabH active site [9]. This benzoylaminobenzoic acid as a lead was obtained using structure-based drug design approach [10]. Forty-six compounds were screened with this lead and quantitative structure–activity relationship (QSAR) studies have been performed toward this end. The quantitative structure activity data are guiding further modifications of the current series [10] with the hopes of improving both enzymatic inhibition and physical properties.

2. Experimental

The QSAR study on benzoylaminobenzoic acid derivatives as β-ketoacyl-ACP synthase III inhibitors has been carried out employing Hansch and Free-Wilson approach. The fatty acid biosynthetic (FabH) inhibitory activities of the compounds were taken as dependent parameter and different physicochemical properties as independent parameter. The biological activity data (IC_{50} in μm) for these β-ketoacyl-ACP synthase III inhibitor derivatives, taken from literature [10], were converted to negative logarithmic dose ($-\log IC_{50}$) in mole (Fig. 2 and Table 1) to reduce skewness of data set for QSAR studies. The values for physicochemical properties viz. steric (molar refractivity or MR), hydrogen acceptor (H_A), hydrogen donor (H_D), hydrophobic (π) and electronic (field effect or $\mathcal{F}$, resonance effect or $\mathcal{R}$, sigma or σ), were calculated and/or computed from literature values [11–14]. The list of various indicator variables employed for QSAR studies is defined in Table 2. The calculated values of physicochemical parameters and different indicator variables are given in Table 3. Some of the compounds reported in the original series were excluded in the present study because of their nonspecific quantitative activity data or presence of uncommon structural feature.

The structure database of the compounds under study (Fig. 2 and Table 1) has been generated in ChemDraw [15]

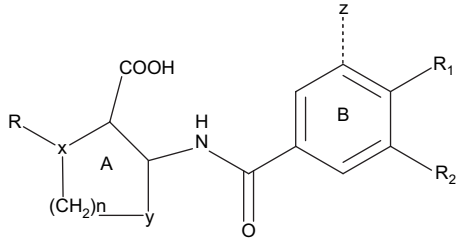


Fig. 2. Benzoylaminobenzoic acid derivatives as inhibitors of FabH and antibacterial agents.

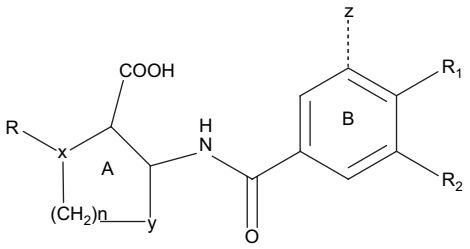
using the standard procedure. Dragon software [16] has been used for the computation of different topological parameters of this structure database. It offered 224 topological descriptors for these molecules. As the number of topological descriptors in the study is large, the model development involving these variables is carried out in combinatorial protocol-multiple linear regression (CP-MLR). The CP-MLR is a 'filter' based variable selection procedure for model development in QSAR studies [17–25]. The procedure involves a combinatorial strategy with appropriately placed 'filters' interfaced with MLR and extracts diverse models having unique combination of descriptors from the data set. The filters set the thresholds for the descriptors in terms of inter-parameter correlation cut-off limits in subset regressions (filter-1), *t*-values of the regression coefficients (filter-2), internal explanatory power (filter-3; square-root of adjusted multiple correlation coefficient of regression equation, *r*-bar) and the external consistency (filter-4; q^2 i.e. cross-validated r^2 from the leave-one-out procedure). Throughout this study, for the filter-1, -2, and -4 the thresholds were assigned as 0.30, 2.0, and $0.3 \leq q^2 \leq 1.0$, respectively, and for the filter-3 it was assigned as an initial value of 0.71. In order to collect the descriptors with higher information content, the threshold of filter-3 was successively incremented with increasing number of descriptors (per equation) by considering the *r*-bar value of the preceding optimum model as the new threshold for next generation. Further, any chance correlations emerging from the study have been ruled out in randomization test [19,25] by exploring correlations with repeated randomization of the biological response.

The correlation and regression analyses were performed using SYSTAT version 7.0.1. [26] and in-house program VALSTAT [27]. The data were transferred to the statistical program in order to establish a correlation between physicochemical parameters and $-\log IC_{50}$. The equations were selected on the basis of statistically significance i.e. the observed squared correlation coefficient (r^2), the standard error of estimate (s), the sequential Fischer test (F), the inter-correlation among the parameter (ICAP), the cross-validated squared correlation coefficient using leave-one-out procedure (q^2), predicted squared correlation coefficient (r^2_{pred}) and the chance statistics (evaluated as the ratio of the equivalent regression equations to the total number of randomized sets; a chance value of 0.001 corresponds to 0.1% chance of fortuitous correlation).

3. Results and discussion

Initially the QSAR studies were performed on different subsets of series, which were divided on the basis of substituents. Subsequently, the different subsets were combined in a single set of series, to establish the correlation between the biological activity of series and different physicochemical properties. The Pearson inter-correlation matrix among the physicochemical parameters for all the compounds has been shown in Table 4. Several significant equations obtained for different subsets and set of series have been given in Table 5 and the statistics of the significant QSAR equation has been shown in Table 6.

Table 1
Structure and activity of benzoylaminobenzoic acid derivatives as inhibitors of FabH and antibacterial agents



Compd no.	*n*	x	y	z	R_1	R_2	$-\log IC_{50}$
1[a]	2	CH	CH	CH_3	Br	$SO_2N(C_2H_5)_2$	3.796
2	2	CH	CH	H	Br	$SO_2N(C_2H_5)_2$	5.796
3	2	CH	CH	H	Ph	$SO_2N(C_2H_5)_2$	5.796
4	2	CH	CH	H	OMe	$SO_2N(C_2H_5)_2$	4.943
5	2	CH	CH	H	F	$SO_2N(C_2H_5)_2$	5.076
6	2	CH	CH	H	Piperidinyl	$SO_2N(C_2H_5)_2$	5.658
7	2	CH	CH	H	Phenoxy	$SO_2N(C_2H_5)_2$	5.215
8	2	CH	CH	H	OCH_2-cyclopentane	$SO_2N(C_2H_5)_2$	5.678
9	2	CH	CH	H	H	Phenoxy	5.569
10	2	CH	CH	H	F	Phenoxy	5.420
11	2	CH	CH	H	Br	Phenoxy	5.959
12	2	CH	CH	H	Piperizinyl-1	Phenoxy	3.733
13	2	CH	CH	H	4-Methyl piperazinyl-1	Phenoxy	4.602
14	2	CH	CH	H	3,5-Dimethyl-piperazinyl-1	Phenoxy	4.420
15	2	CH	CH	H	*N*-Morpholine	Phenoxy	5.495
16	2	CH	CH	H	*N*-Thiomorpholine	Phenoxy	5.921
17	2	CH	CH	H	Piperidinyl-1	Phenoxy	6.538
18	2	CH	CH	H	3,5-Dimethylpiperidinyl-1	Phenoxy	6.569
19	2	CH	CH	H	4-Pyrazolyle	Phenoxy	4.658
20	2	CH	CH	H	3-Pyridyle	Phenoxy	6.959
21	2	CH	CH	H	Phenyl	Phenoxy	7.252
22	2	CH	CH	H	4-CF_3-phenyl	Phenoxy	7.018
23	2	CH	CH	H	4-Methylphenyl	Phenoxy	6.795
24	2	CH	CH	H	4-Carboxyphenyl	Phenoxy	5.678
25	2	CH	CH	H	4-Hydroxyphenyl	Phenoxy	6.387
26	2	CH	CH	H	4-Ethoxyphenyl	Phenoxy	6.657
27	2	CH	CH	H	4-SO_2Me-phenyl	Phenoxy	7.552
28	2	CH	CH	H	3-Isopropylphenyl	Phenoxy	6.102
29	2	CH	CH	H	3-OCF_3-phenyl	Phenoxy	6.328
30	2	CH	CH	H	4-F-3-CH_3-phenyl	Phenoxy	6.619
31	2	CH	CH	H	3-Cl-4-F-phenyl	Phenoxy	6.244
32	2	CH	CH	H	3,4-Difluorophenyl	Phenoxy	6.481
33	2	CH	CH	H	3-Me-4-Cl-phenyl	Phenoxy	6.602
34	2	CH	CH	H	2,4-Diflurophenyl	Phenoxy	6.795
35	1	S	CH	–	H	Phenoxy	4.996
36	1	CH	S	H	H	Phenoxy	4.367
37	2	N	CH	–	H	Phenoxy	3.538
38[b]	2	CH	N	–	H	Phenoxy	–
39	2	CH	CH	F	H	Phenoxy	5.222
40	2	CH	CH	OH	H	Phenoxy	6.387
41	2	CH	CH	H	H	Pyridoxy	5.000
42	2	CH	CH	H	H	*O*-*m*-Benzoic acid	5.432
43	2	CH	CH	H	H	*O*-*p*-Benzoic acid	5.357
44	2	CH	CH	H	H	*O*-*p*-Fluorophenyl	5.301
45	2	CH	CH	OH	Br	Phenoxy	7.207
46	2	CH	CH	OH	Ph	Phenoxy	8.398

R_1 denotes various substitution parts, z substitution does not take the part of group because the biological activity analysis not represent the good result so we have omitted one compound noted as first of this part, and R_2 substitution is done initially by the *N*,*N*-diethyl sulphonamide and then by the phenoxy group.

[a] Compound not included in study.

[b] Not included in study due to the fact that the compound does not have significant biological activity. A-Part represents the substitution with the five- or six-membered aromatic, or heteroaromatic ring system.

Table 2
Indicator variables used in the present study and their definitions

Indicator Variable	Definition
I_n	Indicator variable having value 1 if $n=2$ of the aryl nucleus, value 0 if $n=1$, present at the same position which means A ring is either pentacyclic aromatic carboxylic acid or hexa cyclic aromatic carboxylic acid
I_x	Indicator variable having value 1 if heteroatom is present at x position of the aryl nucleus, value 0 if carbon is attached at the same position in A ring
$I_{x\text{-R}}$	Indicator variable having value 1 if electronegative atom is present at R on substitution position (x) of the aryl nucleus A, value 0 if R is absent at the same position in A ring
$I_{x\text{-OH}}$	Indicator variable having value 1 if electronegative atom at R is specially the OH group at substitution position (x) of the aryl nucleus, value 0 if OH is absent at the same position in A ring
I_y	Indicator variable having value 1 if heteroatom is present at y position of the aryl nucleus, value 0 if carbon is attached at the same position in A ring
I_{arom}	Indicator variable having value 1 if phenyl is present at R_1 position of the benzene (B) nucleus, value 0 if hydrogen is attached at the same position
I_{HETERO}	Indicator variable having value 1 if any electronegative group is present at 4th position in phenyl ring of R_1 substitution present at the benzene B nucleus, value 0 if carbon is attached at the same position
I_{N_4}	Indicator variable having value 1 if nitrogen is present at 4th position in aryl ring of the R_1 substitution of the benzene B nucleus, value 0 if carbon is attached at the same position
I_{pC}	Indicator variable having value 1 if the carbon with any substitution is present at 4th position in Ring R_1, value 0 if carbon without any substitution is present at the same position

3.1. Study of compd nos. 2–21

First the correlation was sought between the first set of compound i.e. for the compd nos. **2–21**, when the A ring is aromatic and is constant for these compounds, QSAR study resulted in Eqs. (1) and (2):

$$\begin{aligned}-\log \text{IC}_{50} &= 5.679(\pm 0.307) - 1.326(\pm 0.633) I_{N_4} \\ &\quad + 0.988(\pm 0.709) I_{\text{arom}} \\ &\quad n=20, r=0.822, r^2=0.676, s=0.522, \\ &\quad F=17.76, q^2=0.508, S_{\text{press}}=0.644, \\ &\quad S_{\text{DEP}}=0.593, \text{ICAP}=0.210, \text{Chance} \le 0.001 \end{aligned} \quad (1)$$

$$\begin{aligned}-\log \text{IC}_{50} &= 5.492(\pm 0.463) - 1.217(\pm 0.662) I_{N_4} \\ &\quad + 0.956(\pm 0.709) I_{\text{arom}} + 0.164(\pm 0.305)\pi \\ &\quad n=20, r=0.837, r^2=0.701, s=0.518, F=12.50, \\ &\quad q^2=0.437, S_{\text{press}}=0.710, S_{\text{DEP}=}0.635, \\ &\quad \text{ICAP}=0.328, \text{Chance} \le 0.001 \end{aligned} \quad (2)$$

Eqs. (1) and (2) describe the good correlation coefficient value $r=0.822$ and 0.837, respectively, of high statistical significance (>99.99%). Eqs. (1) and (2) correlate the FabH enzyme inhibitory activity of benzoylaminobenzoic acid derivatives with indicator variable I_{N_4} which denotes the presence of nitrogen atom at 4th position in the ring (aromatic/aliphatic ring) at R_1 substituents (Fig. 2). The negative sign in I_{N_4} indicates that nitrogen atom in ring is not favorable for activity. Positive I_{arom} indicates the preference of aromatic ring for better enzyme inhibitory activity. Eq. (2) correlates FabH inhibitory activity with I_{N_4} and two additional parameters I_{HETERO} and π (hydrophobocity). I_{HETERO} stands for the presence of a heteroatom (O, S, N) at 4th position of a six membered ring at R_1. Its negative sign shows that heteroatom at this position is unfavorable for activity.

The positive sign of π shows that hydrophobicity is an important physicochemical property of these analogues for better enzyme inhibitory activity. Hydrophobic substituents at R_1 position may involve in hydrophobic interaction with the enzyme, which results in better enzyme–inhibitor association. The presence of heteroatom like nitrogen or oxygen in ring at R_1 position may decrease the hydrophobicity. As a whole Eqs. (1) and (2) indicate the preference of hydrophobic atom/group at R_1 position.

3.2. Study of compd nos. 9–34

The correlation for the second set of compound (compd nos. **9–34**) resulted in Eqs. (3) and (4). In these compounds diethylsulphonamide group has been replaced by phenoxy group at R_2 position.

$$\begin{aligned}-\log \text{IC}_{50} &= 5.924(\pm 0.175) - 1.571(\pm 0.291) I_{N_4} \\ &\quad + 0.707(\pm 0.213) I_{\text{arom}} \\ &\quad n=26, r=0.878, r^2=0.771, s=0.464, \\ &\quad F=38.636, q^2=0.707, S_{\text{press}}=0.524, \\ &\quad S_{\text{DEP}}=0.493, \text{ICAP}=0.497, \text{Chance} \le 0.001 \end{aligned} \quad (3)$$

$$\begin{aligned}-\log \text{IC}_{50} &= 5.725(\pm 0.264) - 1.687(\pm 0.312) I_{N_4} \\ &\quad + 0.011(\pm 0.011)\text{MR} + 0.560(\pm 0.56) I_{\text{arom}} \\ &\quad n=26, r=0.884, r^2=0.781, s=0.475, \\ &\quad F=26.129, q^2=0.698, S_{\text{press}}=0.544, \\ &\quad S_{\text{DEP}}=0.500, \text{ICAP}=0.497, \text{Chance} \le 0.001 \end{aligned} \quad (4)$$

Further data set was divided into a training set of 21 compounds and a test set of 5 compounds (compd nos. **10**, **11**, **14**, **23**, **24**) to ensure the robustness of the equation (Eq. (4a)) using the external cross-validation method.

$$\begin{aligned}-\log \text{IC}_{50} &= 5.848(\pm 0.869) - 2.110(\pm 0.674) I_{N_4} \\ &\quad + 0.020(\pm 0.029)\text{MR} + 0.290(\pm 0.496) I_{\text{arom}} \\ &\quad n=21,\ r=0.867,\ r^2=0.752,\ s=0.505, \\ &\quad F=17.163,\ q^2=0.576,\ S_{\text{press}}=0.660, \\ &\quad S_{\text{DEP}}=0.594,\ \text{ICAP}=0.493,\ \text{Chance} \le 0.001, \\ &\quad r^2_{\text{pred}}=0.505 \end{aligned} \quad (4a)$$

Table 3
Descriptors and their values used in the study

Compd no.	π[b]	MR[c]	I_{N_4}	I_{arom}	I_{HETERO}	$I_{pC\ sub}$	I_x	I_y	$I_{x\text{-}R}$	$I_{x\text{-}OH}$	−log IC_{50}[d]				
											Obsd.	Eq. (10)		Eq. (11)	
												Calc. Velstat	Loo pred	Calc. Velstat	Loo pred
1[a]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
2	0.86	8.88	0	0	0	0	0	0	0	0	5.796	5.212	5.188	5.371	5.351
3	2.13	25.36	0	1	0	0	0	0	0	0	5.796	6.588	6.639	6.595	6.646
4	0.39	7.87	0	0	0	0	0	0	0	0	4.943	5.212	5.223	5.371	5.392
5	0.60	0.92	0	0	0	0	0	0	0	0	5.076	5.212	5.218	5.371	5.386
6	1.92	24.26	0	0	0	0	0	0	0	0	5.658	5.212	5.194	5.371	5.357
7	2.08	27.68	0	0	0	0	0	0	0	0	5.215	5.212	5.212	5.371	5.379
8	2.29	28.46	0	0	0	0	0	0	0	0	5.678	5.212	5.193	5.371	5.357
9	0.00	1.03	0	0	0	0	0	0	0	0	5.569	5.212	5.198	5.371	5.362
10	0.14	0.92	0	0	0	0	0	0	0	0	5.42	5.212	5.204	5.371	5.369
11	0.86	8.88	0	0	0	0	0	0	0	0	5.959	5.212	5.182	5.371	5.343
12	−0.018	26.33	1	0	1	0	0	0	0	0	3.733	5.212	5.272	4.353	4.560
13	0.864	30.95	1	0	1	0	0	0	0	0	4.602	5.212	5.237	4.353	4.270
14	1.172	35.57	1	0	1	0	0	0	0	0	4.42	5.212	5.244	4.353	4.331
15	0.31	23.76	0	0	1	0	0	0	0	0	5.495	5.212	5.201	5.371	5.365
16	0.928	30.13	0	0	1	0	0	0	0	0	5.921	5.212	5.183	5.371	5.345
17	1.69	24.26	0	0	0	0	0	0	0	0	6.538	5.212	5.158	5.371	5.315
18	2.75	33.5	0	0	0	0	0	0	0	0	6.569	5.212	5.157	5.371	5.313
19	−0.12	17.49	1	0	1	0	0	0	0	0	4.657	5.212	5.235	4.353	4.252
20	0.20	20.28	0	1	0	0	0	0	0	0	6.959	6.588	6.565	6.595	6.572
21	1.67	25.36	0	1	0	0	0	0	0	0	7.25	6.588	6.546	6.595	6.553
22	2.55	29.35	0	1	0	1	0	0	0	0	7.018	6.588	6.561	6.595	6.568
23	2.33	29.98	0	1	0	1	0	0	0	0	6.8	6.588	6.575	6.595	6.582
24	1.41	31.26	0	1	0	1	0	0	0	0	5.68	6.588	6.646	6.595	6.654
25	1.00	27.18	0	1	0	1	0	0	0	0	6.39	6.588	6.601	6.595	6.608
26	2.14	36.8	0	1	0	1	0	0	0	0	6.66	6.588	6.584	6.595	6.591
27	0.04	37.82	0	1	0	1	0	0	0	0	7.55	6.588	6.527	6.595	6.534
28	2.44	39.29	0	1	0	0	0	0	0	0	6.1	6.588	6.619	6.595	6.627
29	2.35	32.19	0	1	0	0	0	0	0	0	6.32	6.588	6.605	6.595	6.613
30	2.47	29.87	0	1	0	1	0	0	0	0	6.62	6.588	6.586	6.595	6.593
31	2.52	30.25	0	1	0	1	0	0	0	0	6.244	6.588	6.610	6.595	6.618
32	1.95	25.14	0	1	0	1	0	0	0	0	6.481	6.588	6.595	6.595	6.602
33	3.04	34.98	0	1	0	1	0	0	0	0	6.602	6.588	6.587	6.595	6.595
34	1.95	25.14	0	1	0	1	0	0	0	0	6.8	6.588	6.575	6.595	6.582
35	2.08	27.68	0	0	0	0	1	0	0	0	4.996	5.212	5.221	5.371	5.390
36	2.08	27.68	0	0	0	0	0	1	0	0	4.367	5.212	5.246	5.371	5.420
37	2.08	27.68	0	0	0	0	1	0	0	0	3.538	5.212	5.280	5.371	5.460
38[e]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
39	2.08	27.68	0	0	0	0	0	0	1	0	5.222	5.212	5.212	5.371	5.379
40	2.08	27.68	0	0	0	0	0	0	1	1	6.387	6.872	7.126	6.923	7.205
41	0.38	26.95	0	0	0	0	0	0	0	0	5.000	5.212	5.221	5.371	5.389
42	2.05	34.61	0	0	0	0	0	0	0	0	5.432	5.212	5.203	5.371	5.368
43	2.05	34.61	0	0	0	0	0	0	0	0	5.357	5.212	5.206	5.371	5.372
44	2.22	28.6	0	0	0	0	0	0	0	0	5.301	5.212	5.208	5.371	5.375
45	2.08	27.68	0	0	0	0	0	0	1	1	7.208	6.872	6.696	6.923	6.773
46	2.08	27.68	0	1	0	0	0	0	1	1	8.398	8.248	8.158	8.147	7.994

[a] Compound not included in the study.
[b] Hydrophobicity.
[c] Molar refractivity.
[d] Observed and calculated enzyme inhibitory activity.
[e] Not included in the study as the compound does not have significant biological activity.

Eqs. (3)–(4a) share the I_{N_4} and I_{arom} descriptors with Eqs. (1) and (2) with similar sign. These descriptors indicate that activity decreases with the presence of heteroatom and aliphatic groups at R_1 (Fig. 2). The positive coefficient of MR shows that the molar refractivity/bulkiness is an important physicochemical property for R_1 substitution. Here hydrophobicity and MR are intercorrelated with 0.607. It indicates that hydrophobic bulky groups may be important substituents for better activity.

3.3. Study of compd nos. **9–46**

In next step the study has been carried out with 37 compounds together from compd nos. **9–46**.

Table 4
Pearson inter-correlation matrix among the physicochemical parameters of benzoylaminobenzoic acid derivatives for compounds **2–46**

	π	MR	I_{N_4}	I_{arom}	I_{HETERO}	I_n	I_x	$I_{x\text{-R}}$	I_y	$I_{x\text{-OH}}$
π	1.00									
MR	0.580	1.00								
I_{N_4}	−0.383	0.064	1.00							
I_{arom}	0.313	0.353	−0.251	1.00						
I_{HETERO}	−0.460	0.071	0.796	−0.315	1.000					
I_n	−0.131	−0.046	0.069	−0.173	0.087	1.00				
I_x	0.131	0.046	−0.069	−0.173	−0.087	−0.476	1.00			
$I_{x\text{-R}}$	0.162	0.057	−0.086	−0.215	−0.107	−0.374	0.374	1.00		
I_y	0.189	0.067	−0.100	−0.089	−0.126	0.069	−0.069	0.228	1.00	
$I_{x\text{-OH}}$	0.162	0.057	−0.086	−0.029	−0.107	0.059	−0.059	0.855	−0.073	1.00

$$-\log IC_{50} = 5.158(\pm 0.309) + 1.478(\pm 0.456) I_{arom} + 1.679(\pm 0.827) I_{x\text{-OH}}$$
$$n = 37, r = 0.792, r^2 = 0.628, s = 0.674,$$
$$F = 26.769, q^2 = 0.0.575, S_{press} = 0.721,$$
$$S_{DEP} = 0.691, \text{ICAP} = 0.059, \text{Chance} \leq 0.001 \quad (5)$$

$$-\log IC_{50} = 5.364(\pm 0.313) - 1.011(\pm 0.693) I_{N_4} + 1.281(\pm 0.433) I_{arom} + 1.539(\pm 0.753) I_{x\text{-OH}}$$
$$n = 37, r = 0.840, r^2 = 0.706, s = 0.607,$$
$$F = 26.536, q^2 = 0.645, S_{press} = 0.668,$$
$$S_{DEP} = 0.631, \text{ICAP} = 0.303, \text{Chance} \leq 0.001 \quad (6)$$

Eqs. (5) and (6) correlate the activity with I_{arom} and $I_{x\text{-OH}}$. The positive sign in I_{arom} indicates that aromatic substituents should be preferred over aliphatic ones. $I_{x\text{-OH}}$ shows that hydroxyl group at this position is favorable for better enzyme inhibitory activity. I_{N_4} denotes the presence of N atom in the ring (aromatic/aliphatic ring) at R_1 substituents (Fig. 2). The negative sign in I_{N_4} indicates that nitrogen atom in ring is not favorable for activity.

3.4. Study of compd nos. *21–46*

Eqs. (7) and (8) resulted from the QSAR study of fourth set of compound (compd nos. **21–46**)

$$-\log IC_{50} = 4.9.9(\pm 0.375) + 1.694(\pm 0.460) I_{arom} + 1.856(\pm 0.693) I_{x\text{-OH}}$$
$$n = 25, r = 0.880, r^2 = 0.774, s = 0.530,$$
$$F = 37.771, q^2 = 0.711, S_{press} = 0.600,$$
$$S_{DEP} = 0.563, \text{ICAP} = 0.201, \text{Chance} \leq 0.001 \quad (7)$$

$$-\log IC_{50} = 5.218(\pm 0.370) + 1.404(\pm 0.426) I_{arom} - 1.368(\pm 0.620) I_y + 1.576(\pm 0.516) I_{x\text{-R}}$$
$$n = 25, r = 0.926, r^2 = 0.858, s = 0.430,$$
$$F = 42.380, q^2 = 0.799, S_{press} = 0.512,$$
$$S_{DEP} = 0.469, \text{ICAP} = 0.452, \text{Chance} \leq 0.001 \quad (8)$$

Table 5
Statistically significant QSAR models of benzoylaminobenzoic acid derivatives with their FabH inhibitory activity

Eq. No.	Equations
Compd nos. **2–21**	
1	$-\log IC_{50} = 5.679(\pm 0.307) - 1.326(\pm 0.633) I_{N_4} + 0.988(\pm 0.709) I_{arom}$
2	$-\log IC_{50} = 5.492(\pm 0.463) - 1.217(\pm 0.662) I_{N_4} + 0.956(\pm 0.709) I_{arom} + 0.164(\pm 0.305)\pi$
Compd nos. **9–34**	
3	$-\log IC_{50} = 5.924(\pm 0.175) - 1.571(\pm 0.291) I_{N_4} + 0.707(\pm 0.213) I_{arom}$
4	$-\log IC_{50} = 5.725(\pm 0.264) - 1.687(\pm 0.312) I_{N_4} + 0.011(\pm 0.011)\text{MR} + 0.560(\pm 0.56) I_{arom}$
4a	$-\log IC_{50} = 5.848(\pm 0.869) - 2.110(\pm 0.674) I_{N_4} + 0.020(\pm 0.029)\text{MR} + 0.290(\pm 0.496) I_{arom}$
Compd nos. **9–46**	
5	$-\log IC_{50} = 5.158(\pm 0.309) + 1.478(\pm 0.456) I_{arom} + 1.679(\pm 0.827) I_{x\text{-OH}}$
6	$-\log IC_{50} = 5.36(\pm 0.313) - 1.01(\pm 0.693) I_{N_4} + 1.28(\pm 0.433) I_{arom} + 1.53(\pm 0.753) I_{x\text{-OH}}$
Compd nos. **21–46**	
7	$-\log IC_{50} = 4.909(\pm 0.375) + 1.694(\pm 0.460) I_{arom} + 1.856(\pm 0.693) I_{x\text{-OH}}$
8	$-\log IC_{50} = 5.218(\pm 0.37) + 1.404(\pm 0.42) I_{arom} - 1.368(\pm 0.62) I_y + 1.576(\pm 0.51) I_{x\text{-R}}$
Compd nos. **9**, **35–46**	
9	$-\log IC_{50} = 5.275(\pm 0.606447) + 2.05517(\pm 1.05) I_x - 0.900167(\pm 1.0504) I_{x\text{-OH}}$
Compd nos. **2–46**	
10	$-\log IC_{50} = 5.212(\pm 0.127) + 1.376(\pm 0.200) I_{arom} + 1.660(\pm 0.386) I_{x\text{-OH}}$
11	$-\log IC_{50} = 5.371(\pm 0.125) - 1.018(\pm 0.316) I_{N_4} + 1.224(\pm 0.186) I_{arom} + 1.552(\pm 0.350) I_{x\text{-OH}}$
12	$-\log IC_{50} = 5.532(\pm 0.118) - 1.179(\pm 0.280) I_{N_4} + 1.070(\pm 0.168) I_{arom} + 1.443(\pm 0.307) I_{x\text{-OH}} - 1.156(\pm 0.316) I_y$
13	$-\log IC_{50} = 5.577(\pm 0.114) - 1.224(\pm 0.267) I_{N_4} + 1.026(\pm 0.161) I_{arom} + 1.412(\pm 0.293) I_{x\text{-OH}} - 0.851(\pm 0.381) I_x - 0.918(\pm 0.319) I_y$
14	$-\log IC_{50} = 1.248(\pm 0.924) + 0.383(\pm 0.065) X1_{sol} - 0.029(\pm 0.004) T$ (N···O)
15	$-\log IC_{50} = 3.987(\pm 0.254) + 0.013(\pm 0.002)\text{MPC}_{10} - 1.896(\pm 0.277) I_{N_4} + 1.786(\pm 0.315) I_{x\text{-OH}}$

Table 6
QSAR statistics of significant equations

Eq. no.	n	r	r^2	s	F	q^2	S_{press}	S_{DEP}	ICAP	Chance
1	20	0.822	0.676	0.522	17.76	0.508	0.6439	0.593	0.210	<0.001
2	20	0.816	0.666	0.547	10.636	0.437	0.710	0.635	0.328	<0.001
3	26	0.878	0.771	0.464	38.636	0.707	0.524	0.493	0.497	<0.001
4	26	0.884	0.781	0.475	26.129	0.698	0.544	0.500	0.498	<0.001
4a	21	0.867	0.752	0.505	17.163	0.567	0.660	0.594	0.493	<0.001
5	37	0.792	0.628	0.674	26.769	0.575	0.721	0.691	0.059	<0.001
6	37	0.840	0.706	0.607	26.536	0.645	0.668	0.631	0.303	<0.001
7	25	0.880	0.774	0.530	37.771	0.711	0.600	0.563	0.201	<0.001
8	25	0.926	0.858	0.430	42.380	0.799	0.512	0.469	0.452	<0.001
9	12	0.889	0.790	0.644	16.99	0.541	0.953	0.825	0.333	<0.001
10	44	0.782	0.611	0.644	32.191	0.563	0.682	0.658	0.029	<0.001
11	44	0.831	0.691	0.581	29.811	0.636	0.630	0.601	0.250	<0.001
12	44	0.877	0.770	0.508	32.618	0.681	0.597	0.562	0.250	<0.001
13	44	0.893	0.797	0.484	29.764	0.713	0.574	0.534	0.373	<0.001
14	44	0.769	0.592	0.660	29.752	0.530	0.707	0.683	0.286	<0.001
15	44	0.868	0.753	0.520	40.570	0.701	0.571	0.545	0.168	<0.001

Eqs. (7) and (8) correlate the activity with I_{arom}, $I_{x\text{-OH}}$ and $I_{x\text{-R}}$. The positive sign in I_{arom} indicates that aromatic substituents should be preferred over aliphatic ones. $I_{x\text{-OH}}$ and $I_{x\text{-R}}$ show that hydroxyl group at this position is favorable for better enzyme inhibitory activity.

I_y parameter indicates the presence of a heteroatom in place of carbon at y positions (Fig. 2). The negative sign associated with this indicator parameter shows that heterocyclic ring system at this position is unfavorable for activity.

3.5. Study of compd nos. 9, 35–46

The study of the fifth set (compd nos. **9**, **35–46**) resulted in Eq. (9):

$$\begin{aligned}-\log IC_{50} = {} & 5.275(\pm 0.606447) + 2.05517(\pm 1.0504) I_x \\ & - 0.900167(\pm 1.0504) I_{x\text{-OH}} \\ & n = 12, r = 0.889, r^2 = 0.790, s = 0.644, \\ & F = 16.99, q^2 = 0.541, S_{press} = 0.953, \\ & S_{DEP} = 0.825, \text{ICAP} = 0.333, \text{Chance} \le 0.001 \end{aligned} \quad (9)$$

Eq. (9) shows the correlation of activity for these compounds with dummy parameters $I_{x\text{-OH}}$ and I_x. I_x indicates the presence of a heteroatom in place of carbon at x positions (Fig. 2). $I_{x\text{-OH}}$ is an indicator parameter for the presence of hydroxyl group attached at x; the negative sign associated with these indicator parameters shows that heterocyclic ring system is unfavorable for activity. The positive sign of this parameter shows that at this position it favors for better enzyme inhibitory activity.

3.6. Study of compd nos. 2–46

Finally all the compounds were taken together in a single set and the correlation was established to observe the effect of physicochemical properties on the biological activity.

$$\begin{aligned}-\log IC_{50} = {} & 5.212(\pm 0.127) + 1.376(\pm 0.200) I_{arom} \\ & + 1.660(\pm 0.386) I_{x\text{-OH}} \\ & n = 44, r = 0.782, r^2 = 0.611, s = 0.644, \\ & F = 32.191, q^2 = 0.563, S_{press} = 0.682, S_{DEP} = 0.658, \\ & \text{ICAP} = 0.029, \text{Chance} \le 0.001 \end{aligned} \quad (10)$$

$$\begin{aligned}-\log IC_{50} = {} & 5.371(\pm 0.125) - 1.018(\pm 0.316) I_{N_4} \\ & + 1.224(\pm 0.186) I_{arom} + 1.552(\pm 0.350) I_{x\text{-OH}} \\ & n = 44, r = 0.831, r^2 = 0.691, s = 0.581, \\ & F = 29.811, q^2 = 0.636, S_{press} = 0.630, \\ & S_{DEP} = 0.601, \text{ICAP} = 0.250, \text{Chance} \le 0.001 \end{aligned} \quad (11)$$

$$\begin{aligned}-\log IC_{50} = {} & 5.532(\pm 0.118) - 1.018(\pm 0.316) I_{N_4} \\ & + 1.070(\pm 0.168) I_{arom} + 1.443(\pm 0.307) I_{x\text{-OH}} \\ & - 1.156(\pm 0.316) I_y \\ & n = 44, r = 0.877, r^2 = 0.770, s = 0.508, \\ & F = 32.618, q^2 = 0.681, S_{press} = 0.597, S_{DEP} = 0.562, \\ & \text{ICAP} = 0.250, \text{Chance} \le 0.001 \end{aligned} \quad (12)$$

$$\begin{aligned}-\log IC_{50} = {} & 5.577(\pm 0.114) - 1.224(\pm 0.267) I_{N_4} \\ & + 1.026(\pm 0.161) I_{arom} + 1.412(\pm 0.293) I_{x\text{-OH}} \\ & - 0.851(\pm 0.381) I_x - 0.918(\pm 0.319) I_y \\ & n = 44, r = 0.893, r^2 = 0.797, s = 0.484, \\ & F = 29.764, q^2 = 0.713, S_{press} = 0.574, S_{DEP} = 0.534, \\ & \text{ICAP} = 0.373, \text{Chance} \le 0.001 \end{aligned} \quad (13)$$

Eq. (10) correlates the activity with I_{arom} and $I_{x\text{-OH}}$. I_{arom} indicates that aromatic substituents should be preferred over aliphatic ones. $I_{x\text{-OH}}$ shows that hydroxyl group at this position

is favorable for better enzyme inhibitory activity. Eqs. (10), (11) and (13) have been derived by successive addition of I_{N_4}, I_y and I_x to Eq. (9). I_{N_4} denotes the presence of N atom in the ring (aromatic/aliphatic ring) at R_1 substituents. The negative sign in I_{N_4} indicates that nitrogen atom in ring is not favorable for activity. The I_x and I_y parameters indicate the presence of a heteroatom in place of carbon at x and y positions, respectively (Fig. 2). The negative sign associated with these indicator parameters shows that heterocyclic ring system is unfavorable for activity.

The correlation was also established to observe the effect of topological parameters on the biological activity. Statistically significant di- and tri-variant expressions were selected.

$$\begin{aligned}-\log \mathrm{IC}_{50} &= 1.248(\pm 0.924) + 0.383(\pm 0.065)X1_{\mathrm{sol}} \\ &\quad -0.029(\pm 0.004)T(\mathrm{N}\cdots\mathrm{O}) \\ &\quad n=44, r=0.769, r^2=0.592, s=0.660, \\ &\quad F=29.752, q^2=0.530, S_{\mathrm{press}}=0.707, \\ &\quad S_{\mathrm{DEP}}=0.683, \mathrm{ICAP}=0.286, \mathrm{Chance}\leq 0.001 \qquad (14)\end{aligned}$$

$$\begin{aligned}-\log \mathrm{IC}_{50} &= 3.987(\pm 0.254) + 0.013(\pm 0.002)\mathrm{MPC}_{10} \\ &\quad -1.896(\pm 0.277)I_{N_4} + 1.786(\pm 0.315)I_{x\text{-OH}} \\ &\quad n=44, r=0.868, r^2=0.753, s=0.520, \\ &\quad F=40.570, q^2=0.701, S_{\mathrm{press}}=0.571, \\ &\quad S_{\mathrm{DEP}}=0.545, \mathrm{ICAP}=0.168, \mathrm{Chance}\leq 0.001 \qquad (15)\end{aligned}$$

Study suggested that topological parameters alone are not adequate to explain the activity, therefore indicator variables were incorporated in equation development. Di-variant expression (Eq. (14)) solely depends on the topological parameters and it has explained moderate variance in the activity. Incorporation of indicator variable(s) causes significant improvement in the correlation (Eq. (15)). Eq. (14) has also improved significantly by the addition of indicator parameter $I_{x\text{-OH}}$ ($r = 0.846$, $Q^2 = 0.657$, $F = 33.51$). $X1_{\mathrm{sol}}$ and T (N···O) contributed positively and negatively to Eq. (14), respectively. $X1_{\mathrm{sol}}$ is solvation connectivity index and T (N···O), sum of topological distances between nitrogen and oxygen, is a simple molecular descriptor calculated by summing topological distances between all pairs of nitrogen and oxygen. The negative contribution of T (N···O) suggests that increase in the topological distance between nitrogen and oxygen would decrease the enzyme inhibitory activity.

Tri-variant expression (Eq. (15)) showed better correlation coefficient, which explains more than 75% variance in the activity. Eq. (15) contributed positively by MPC and indicator variable $I_{x\text{-OH}}$ while another indicator variable I_{N_4} contributed negatively. MPC, molecular path counts, is obtained from H-depleted molecular graph, based on the graph path, which is a walk without any repeated vertices or edges. The molecular path count MPC_k of order k is the total number of paths of length k in the graph. The positive contribution of MPC_{10} suggests that increase in the total number of paths of length 10 is favorable for better enzyme inhibitory activity.

3.7. Study of benzoylaminobenzoic acid derivatives against some pathogenic bacteria

In the continuation of the QSAR study, the correlation between the inhibitory activity in some pathogenic bacteria and physicochemical parameter has also been established. Eqs. (18)–(21), shown in Table 7, have been derived with the *in vitro* antibacterial activity of 10 most potent compounds. Interestingly π (hydrophobicity) is the common descriptor in all the equations (Eqs. (16)–(19)) derived with the antibacterial activity against *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Enterococcus faecalis*, *Neisseria meningitidis* and *Escherichia coli*. The statistics for Eqs. (16)–(19) has been given in Table 8. The value of calculated and predicted inhibitory activity data has been given in Table 9.

The coefficient of π in all these equations is in a narrow range ($\pi = 0.239$–0.474). It shows that π is the major physicochemical property related to the antibacterial activity. Its positive sign shows that the antibacterial activity in these analogues will increase with the hydrophobicity. The hydrophobicity of compound increases the passage of compound

Table 7
Statistically significant QSAR models of some benzoylaminobenzoic acid derivatives against some pathogenic bacteria

Eq. No.	Equations
16	$-\log \mathrm{MIC}_{S.\,aureus} = 4.415(\pm 0.301) + 0.323(\pm 0.131)\pi - 0.587(\pm 0.259)I_{x\text{-R}}$
17	$-\log \mathrm{MIC}_{S.\,pneumoniae} = 4.626(\pm 0.342) + 0.474(\pm 0.149)\pi - 1.109(\pm 0.294)I_{x\text{-R}}$
18	$-\log \mathrm{MIC}_{N.\,meningitidis} = 4.912(\pm 0.300) + 0.265(\pm 0.101)\pi + 0.477(\pm 0.199)I_{\mathrm{arom}}$
19	$-\log \mathrm{MIC}_{E.\,coli} = 4.780(\pm 0.309) + 0.258(\pm 0.104)\pi + 0.588(\pm 0.205)I_{\mathrm{arom}}$

Table 8
QSAR statistics of significant equations

Eq. no.	n	r	r^2	s	F	q^2	S_{press}	S_{DEP}	ICAP	Chance
16	10	0.952	0.907	0.134	34.167	0.629	0.267	0.223	0.0171	<0.002
17	10	0.883	0.779	0.372	12.357	0.052	0.771	0.645	0.017	<0.007
18	10	0.776	0.602	0.247	5.296	0.0028	0.390	0.327	0.195	<0.019
19	10	0.796	0.633	0.254	6. 059	−0.039	0.428	0.358	0.195	<0.02

Table 9
Observed and calculated inhibitory activity data of some selected benzoylaminobenzoic acid derivatives against some given microbes

Compd no.	−log MIC											
	S. aureus			*S. pneumoniae*			*N. meningitidis*			*E. coli*		
	Obsd.	Calc.	Pred. (Loo)	Obsd.	Calc.	Pred. (Loo)	Obsd.	Calc.	Pred. (Loo)	Obsd.	Calc.	Pred. (Loo)
18	5.252	5.306	5.320	5.553	5.929	6.018	5.553	5.923	5.738	5.252	5.489	5.744
21	4.947	4.957	4.959	5.854	5.417	5.337	5.854	5.906	5.828	5.854	5.799	5.789
22	5.252	5.242	5.240	6.155	5.834	5.776	5.854	5.986	6.109	6.155	6.025	5.999
27	4.347	4.429	4.796	4.347	4.645	5.982	5.252	5.262	5.945	5.252	5.378	5.845
28	5.252	5.208	5.199	5.854	5.784	5.771	5.854	5.716	6.070	5.553	5.998	6.078
30	5.252	5.216	5.210	6.155	5.796	5.736	6.155	5.956	6.024	6.155	6.005	5.977
33	5.252	5.400	5.454	5.553	6.066	6.250	6.155	5.945	6.213	6.155	6.152	6.151
34	5.252	5.047	5.017	5.553	5.550	5.550	6.444	5.969	5.829	6.155	5.871	5.830
45	4.347	4.502	4.658	4.347	4.502	4.658	5.553	5.932	5.368	5.553	5.316	5.060
46	4.658	4.502	4.347	4.658	4.502	4.347	5.854	5.932	5.953	5.854	5.904	5.912

through the lipid membrane of microbes so that more drugs are available to the target receptor and shows better activity. $I_{x\text{-OH}}$ is an indicator parameter for the presence of hydroxyl group attached at x (N). This hydroxyl group has favorable interaction with the target enzyme. The positive $I_{x\text{-OH}}$ shows that hydroxyl group at this position is favorable for better activity against given microbes and acts as potent inhibitor of that enzyme. Also the positive sign in the I_{arom} indicates that aromatic substituents should be preferred over aliphatic ones.

4. Conclusion

The present study provides important structural insights in designing better inhibitors of β-ketoacyl-acyl carrier protein synthase III. QSAR study revealed that parameters hydrophobicity (π), aromaticity, molar refractivity, and presence of hydroxyl group in A ring contribute significantly to inhibitory activity. The substituents that increase the lipophilicity, aromaticity and molar refractivity at both positions R_1 and R_2 will enhance the inhibitory activity. Whereas the presence of nitrogen and any other electronegative substituents at 4th position in R_1 ring, and the presence of heteroatom in A ring at x and y positions is not favorable for inhibitory activity. The parameter $I_{x\text{-R}}$, represents the presence of hydroxyl group at position R, increases the biological activity indicating hydrogen bond interaction with the receptor. Thus substitution of more bulky group at R_1 position and substitution with electronegative group capable of forming hydrogen bond interaction with receptor at the $I_{x\text{-R}}$ position are conducive for the inhibitory activity. The hydrophobic character of compound is also important for the inhibitory activity.

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