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CoMFA Study of Some Benzoic Acid Derivatives as Antibacterial Agents

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ABSTRACT

Forty-six β-Ketoacyl-acyl carrier protein (ACP) synthase III (FabH) inhibitors with antibacterial activity were selected to develop a three-dimensional quantitative structure-activity relationship (3D-QSAR) using comparative molecular field analysis (CoMFA) models. A training set of 40 compounds were used to build up the models which were then evaluated by a series of internal and external cross-validation techniques. A test set of 6 compounds was used for the external validation. The best CoMFA model predicted a *q2* value of 0.446 and an *r2* value of 0.681 based on a combination of steric, electrostatic effects. The analysis of the contour maps from each model provided the structural requirements for the development of more active FabH inhibitors and on the basis of the analysis new FabH inhibitors were designed and predicted.

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INTRODUCTION

β-ketoacyl-acyl carrier protein synthase III (FabH) is an emerging target for the design and development of novel antibacterial agent. FabH is key enzyme to discovering inhibitors with broad spectrum antibacterial activity. Fatty acid biosynthesis (FAB) is an essential metabolic process for prokaryotic organisms and is required for cell viability and growth these are the essential for organism survival.[1,2,3] *β-Ketoacyl- acyl carrier protein (ACP) synthase III* also known as FabH or KAS III plays an important and regulatory role in bacterial fatty acid biosynthesis.[4, 5] FabH enzyme is responsible for initiates the fatty acid elongation cycles[6, 7] and is involve in the feedback regulation of the biosynthetic pathway via product inhibition.[8]One is the most attractive biochemical pathways that is targeted for new antibacterial agents for fatty acid biosynthesis (FAS). This pathway has been demonstrated to be essential for the bacteria cell survival.[9] β-ketoacyl-acyl carrier protein synthase III (KAS III) which is encoded by the FabH gene.[10, 11] The 3D structures of KAS III and co-complex structures with their inhibitors have been identified in different bacteria by x-ray crystallography. The first x-ray structure of KAS III was identified in E. coli by Rock et al. by using a coenzyme A (CoA) substrate.[12]

Infectious diseases caused by bacteria affect many people and are leading causes of death worldwide treatment of infectious diseases still remains an important and challenging problem because of a combination of factors including emerging and increasing number of multi drug resistant microbial pathogens. Considering the antimicrobial resistance phenomenon as one of the greatest challenges in modern medicine system discovery of new substances with potential effectiveness against several pathogenic microorganisms becomes highly desirable.[13, 14, 15.]

The emergence of bacterial resistance to most of all antibiotics poses a threat to health care and novel therapeutics is needed. Nowadays the research has been focused on discovered and development of new antibacterial agents with novel target. Therefore it represents a promising target for the design of novel antimicrobial agents.[16]

In this research work, various kinds of compounds were design by CoMFA (drug design methods).

MATERIALS AND METHODS

COMPOUNDS AND BIOLOGICAL DATA

Compounds 1-46 which can inhibit FabH receptor were taken from the literatures and served as the training set and test set in the CoMFA counter map study.[17]

The structures and inhibitory activities of the compounds are described in table. 1, 2, 3, 4 and 5. The chemical structures were drawn in CHEM-Draw software and saved in mol format. All the 2D structures were converted to 3D structures by SYBYL X-1.2.1 software.

MODELING TOOL

All the CoMFA study was performed using TRIPOS module of SYBYL-X 2.1.1 software. The tasks were running on Intel R core-2 Duo RAM: 4GB Memory: 560GB Graphic card: NVIDIA under the Windows Vista 32 bit system.

CoMFA (COMPARATIVE MOLECULAR FIELD ANALYSIS)

The CoMFA molecular modelling studies were performed using TRIPOS module of SYBYL-X 2.1.1 software.

The compounds of benzoylaminobenzoic acid derivatives were randomly divided into training set and a test set by SYBYL-X 2.1.1. The training set comprises 40 compounds and test set comprises of 6 compounds. CoMFA models were developed using 40 compounds as training set and externally validated using 6 compounds as test set.

The CoMFA (comparative molecular field Analysis) approach which has two fields steric and electrostatic potential field's effects were calculated using the TRIPOS force field.

Five different kinds of partial charges are considered:

(1) Gasteiger charges

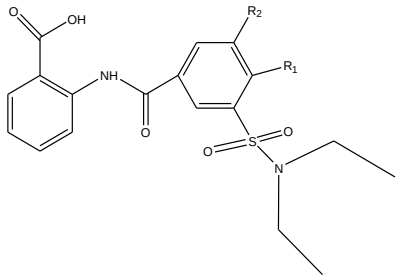
(2) Gasteiger Huckel charges

(3) Huckel charges

(4) Pullman charges and

(5) MMFF94 charges

Table No. 1: Derivatives of Diethyl sulfonamide as FabH inhibitors.



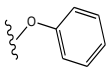
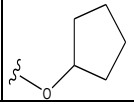
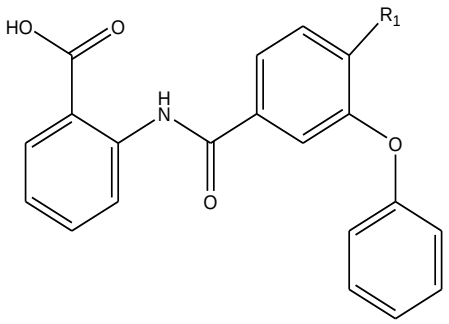
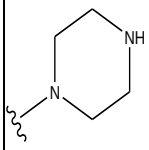
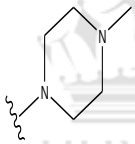
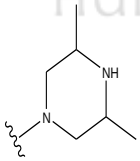
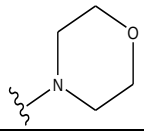
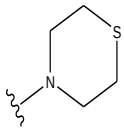
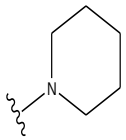
Compounds	R1	R2	IC50	pIC50
13a	Br	H	1.6	5.796
13b	Ph	H	1.6	5.796
13c	Br	Me	160	5.796
13d	O-Me	H	11.4	4.943
13e	F	H	8.4	5.079
13f		H	2.2	5.658
13g		H	6.1	5.215
13h		H	2.1	5.678

Table No. 2: Derivatives of [3-Phenoxybenzoylamino] benzoic acid as FabH inhibitors



Compounds	R1	IC50	pIC50
15	H	2.7	5.569
23a	F	3.8	5.420
23b	Br	1.1	5.959
23c		185	3.733
23d		25	4.602
23e		38	4.420
23f		3.2	5.495
23g		1.2	5.921
23h		0.29	6.538

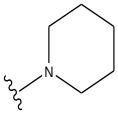
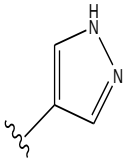
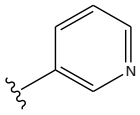
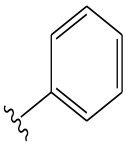
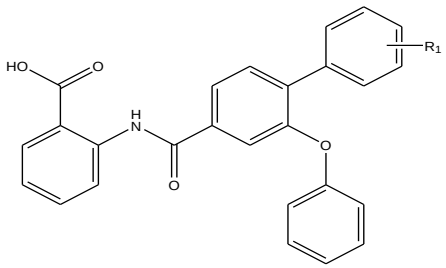
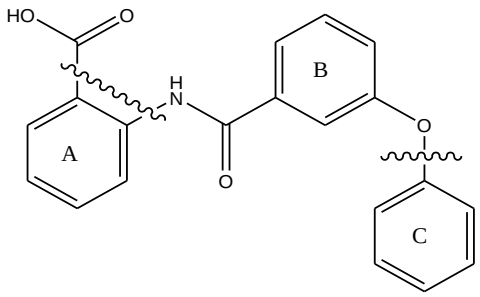
23i		0.27	6.569
24a		22	4.658
24b		0.11	6.959
24c		0.056	7.252

Table No. 3: Derivatives of [3-Phenoxybenzoylamino] benzoic acid. Substitutions on the Para position



Compounds	R1	IC50	pIC50
24d	4-CF_3	0.096	7.018
24e	4-Me	0.16	6.796
24f	4-CO_2	2.1	5.678
24g	4-OH	0.41	6.387
24h	4-OEt	0.22	6.658
24i	4-SO_2	0.028	7.553
24j	3-iPr	0.79	6.102
24k	3-OCF_3	0.47	6.328
24l	3-Me-4-F	0.24	6.620
24m	3-Cl-4-F	0.57	6.244
24n	3,4-di-F	0.33	6.481
24o	3-Me-4-Cl	0.25	6.602
24p	2,4-di-F	0.16	6.796

Table No. 4: Derivatives of [3-Phenoxybenzoylamino] benzoic acid as FabH inhibitors.



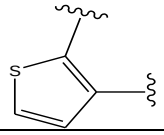
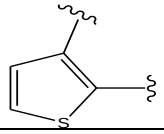
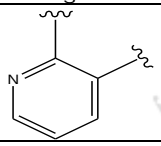
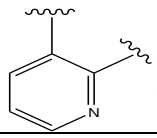
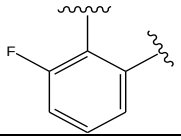
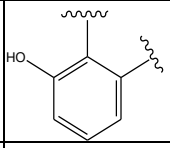
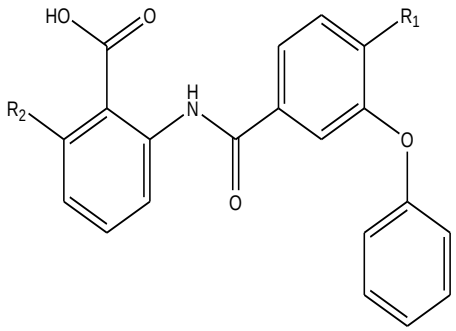
Compounds	A	C	IC50	pIC50
28a		Ph	10.1	4.996
28b		Ph	43.0	4.367
28c		Ph	290	3.533
28d		Ph	>1000	3.00
28e		Ph	6.0	5.222
28f		Ph	0.41	6.387
28g	Ph	4-Pyr	10	5.00
28h	Ph	3-CO_2H-Ph	3.7	5.432
28i	Ph	4- CO_2H-Ph	4.4	5.356
28j	Ph	4-F-Ph	5.0	5.301

Table No. 5: Potent inhibitors of FabH: Effect of adding OH Ortho to the carboxylic acid



Compounds	R1	R2	IC50	pIC50
31	Br	OH	0.062	7.208
33	Ph	OH	0.004	8.398

RESULTS AND DISCUSSION

COMFA MODEL PREDICTIVITY

A CoMFA model was generated from a training set of 40 molecules and test sets of 6 molecules with pIC_{50} values ranging from 4.606 to 5.5145 automatically by TRIPOS modules. The predictable power of resulting molecule was evaluating using a test set of 6 molecules. The predicted pIC_{50} values and experimental pIC_{50} values of the training set and test set are summarises in table 6, 7. The statistical parameters related to CoMFA models are described in Table 8. The CoMFA model by both steric and electrostatic fields gives a correlation coefficient (r^2) 0.681, standard error estimates (SEE) 0.6578, Q^2 value 4.46, steric contribution 19.26, Electrostatic contribution of positive charge desirable 25.41 and negative charge desirable 14.9.

Table No. 6: The experimental pIC_{50} values and predicted pIC_{50} values of the training set compounds.

Sr. No.	Compound Name	Experimental pIC_{50}	Predicted pIC_{50}
			Gasteiger
1	13b	5.796	5.3682
2	13c	3.796	4.6914
3	13e	5.076	4.7048
4	13f	5.658	5.061
5	13g	5.215	4.8606
6	13h	5.678	5.1273
7	15	5.569	5.5368
8	23b	5.959	5.6063
9	23c	3.733	5.1864
10	23e	4.420	5.3065
11	23f	5.495	4.9199
12	23g	5.921	5.2723
13	23h	6.538	5.4466
14	23i	6.569	5.5269
15	24a	4.658	4.9623
16	24c	7.252	6.6338
17	24d	7.018	6.1018
18	24e	6.796	6.6704
19	24f	5.678	5.6778
20	24g	6.387	6.7326
21	24h	6.658	6.741
22	24j	6.102	5.5551
23	24k	6.328	6.389
24	24l	6.620	6.6872
25	24m	6.244	6.5219
26	24n	6.481	6.6761
27	24o	6.602	6.6021
28	24p	6.796	6.434
29	28a	4.996	5.1486
30	28b	4.367	4.7582
31	28c	3.533	4.7832
32	28d	3.000	4.5609
33	28e	5.272	4.992
34	28f	6.387	5.3787
35	28g	5.000	4.8923
36	28h	5.432	4.9593
37	28i	5.356	5.1045
38	28j	5.301	5.2608
39	31	7.208	7.6302
40	33	8.348	8.5145

Table No. 7: The experimental pIC50 values and predicted pIC50 values of the test set compounds.

Sr. No.	Compound Name	Experimental pIC_{50}	Predicted pIC_{50}
			Gasteiger
1	13	5.796	4.7299
2	13d	4.943	4.6086
3	23a	5.420	5.5291
4	23d	4.602	5.3672
5	24b	6.569	6.2782
6	24i	6.959	6.4603

TEST VALIDATION

Test validation is the precise validation of model where the activity prediction of those compounds is made which are not include in training set. external predictive ability of generated CoMFA model of benzoylaminobenzoic acid derivative was evaluate for the test set of 6 molecule which are include 13, 13d,23a,23d,24b and 24i where they obtained predictive r^2 value (r^2 pred) 0.681 supported the high predictive ability of the generated model.

The coefficient from the CoMFA were used to generated 3D counter maps which determine the critical physicochemical properties responsible for charge in activity and also explore the critical importance of varies substituent's in their 3D orientation.

The physicochemical properties of benzoylaminobenzoic acid molecules responsible for FabH inhibitory activity. The total contribution of steric field are 19.26 and electrostatic field of positive charge and negative charge are 25.41, 14.93 respectively obtained from CoMFA study of benzoylaminobenzoic acid based series. It showed an r^2 value 0.681 with a standard error 0.657.

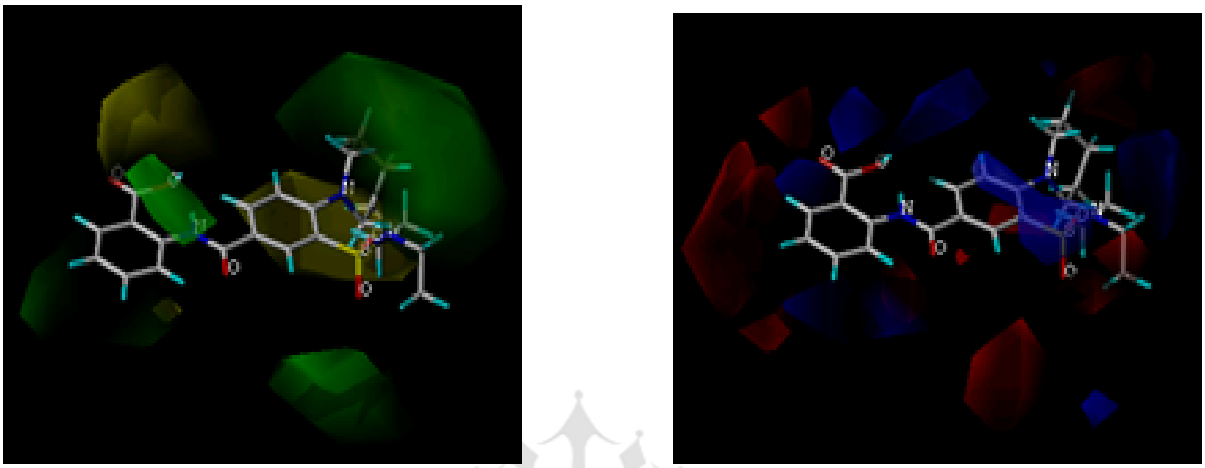
CoMFA CONTOUR MAPS

The results obtained from CoMFA indicate that steric and electrostatic properties play a major role in inhibition activity described in table 8.

Table No. 8: Statistical parameters related to CoMFA models

S.n	Q^2	R^2	Std. Error	Steric Contribution %		Electrostatic Contribution %	
				Steric Bulk Desirable	Steric Bulk Undesirable	PC	NC
K2	0.446	0.681	0.657981	19.26	20.39	25.41	14.93

*K2- Gasteiger charge



a **b**

Figure No. 1: CoMFA contour maps for Gasteiger charge (a) Steric contribution (b) Electrostatic contributions.

As shown in the figure 1 CoMFA contour maps of compound 33 which is the most active compound the green contour was favoured around the benzene ring attached to amino indicates that bulky substituents at the R_2 increases activity like OH and green contour around the benzene ring attached to phenoxy ring indicates that bulky substituents at the R_1 increases activity like phenyl etc. sterically unfavorable contour in yellow color were found near in benzin ring attached to phenoxy ring and around the of amino group. Thus bulky substituents decrease activity. Blue contour near amino on benzene ring attached to amino group and phenoxy ring attached to benzene ring indicates that substituents with electropositive group enhance activity. While red colour on substituent R_2 i.e. 2-hydroxybenzoic acid indicates that electronegative group at this position enhances activity.

CONCLUSION

FabH inhibitors provide a promising approach to treat bacterial infection. We have successfully generated 3D-QSAR models using CoMFA was utilized to investigate structural requirements for improving potency of benzoylaminobenzoic acid derivatives as FabH inhibitors. Authentic CoMFA model ($q2$ = 0.446, $r2$ = 0.681 contribution of steric filed 19.26 and electrostatic contribution of positive charge and negative charge are 25.41, 14.93 respectively) was developed and validated. Analysis of model parameters and contour maps provided details of the structure-activity relationship and the information for structural modifications to design analogs with better activity were obtained. These models are also used to design and predict the FabH inhibitory activity of newly designed compounds. CoMFA counter maps analysis show in figure 1 to suggest these inhibitors bind to FabH there by acting as inhibitor of fatty acid biosyntheses in bacteria.

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