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Research Article

QSAR STUDY ON SOME NEWLY SYNTHESIZED PYRIMIDOBENZIMIDAZOLE DERIVATIVES AS ANALGESIC AGENTS

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ABSTRACT

All the drugs used as analgesic agent have some systemic side effects. For the researchers, the prospects of overcoming the side effects of a drug, achieving an effect at a much lower dose is very attractive. Modification of the structure of a known drug is one way to develop new drugs. For this purpose, we have optimized the pyrimidobenzimidazole derivatives using molecular modeling studies. QSAR analysis has been carried out on a series of pyrimidobenzimidazole derivatives using the physicochemical parameter and molecular descriptors. The database was subjected to QSAR studies using Chemsketch software version 10.0 and all the parameter & descriptors were calculated using TSAR 3D version 3.3 for windows. The regression analysis has shown that SFI (Shape flexibility index), R (Randic index), B (Balaban index) and W (Wiener index) in combination with atom indices TA (Total atom), THA (Total hetero atom) HD (H-donar) and HA (H- acceptor) gives significant improvement in the statistics. On the basis of MLR analysis the possible position and substituent on the lead molecule have been predicted for the good analgesic activity. The output of present research work is very interesting, the result of QSAR study suggested that molecule must contain at least one substituent on R_1 and R_2 position should be NO_2 for good analgesic activity.

Keywords: QSAR, Physicochemical properties, Molecular indices, MLR analysis, Analgesic activity, Pyrimidobenzimidazole.

INTRODUCTION

Analgesics are agents which relives the pain without disturbing consciousness. Various analgesic drugs available in the market exhibit several side effects, such as centrally mediated tolerance, dependence, decreased gastrointestinal motility leading to constipation and respiratory depression and hence can not be used continuously for long time[1]. It is therefore, desirable to have potent and safer analgesic drugs which produces minimum or no side effect. As such various laboratories all over the world are involved in the synthesis of a variety of compounds and their evaluation for analgesics activity[2-4]. Pyrimidine derivatives are biologically interesting molecules that have established utility for the treatment of neurodegenerative and proliferative disorders[5,6]. They are also capable of showing anti-cancer activity[7], as antimicrobial agents[8] and as fungicides[9]. Along with these activities numerous research paper have shown that pyrimidine derivatives have other diverse pharmacological activities such as H_1-antihistamine, as selective type 4-phosphodiesterase inhibitors, as anti-inflammatory and analgesic agent[10-16].

The Quantitative structure activity relationship (QSAR) of substance is an important aspect of modern chemistry, biochemistry, medicinal chemistry and drug discovery[17-21]. The QSAR research field provides, medicinal chemists with the ability to predict drug activity by mathematical equations which construct a relationship between the chemical structure and the biological activity[22-24]. Once a correlation between structure and activity/property is found, any number of compounds including those not synthesized, yet can readily be screened for the selection of structures with desire properties. In continuation of our previously reported work on the synthesis and biological evaluation of some pyrimidobenzimidazole derivatives[25,26], a QSAR studies have been investigated. The aim of the our present study is to build QSAR models using multiple regression method for synthesized pyrimidobenzimidazole derivatives to explore the substitutional requirement essential for the improved analgesic activity.

MATERIALS AND METHODS

Analgesic activity of 36 pyrimidobenzimidazole derivatives was used to develop QSAR models. Percent analgesic activity (%AA) has been considered as biological activity parameter[25,26] for QSAR studies. All these activities are calibrated to the logarithmic values. The lead compound with the positions of various substitutions is given in (Figure 1). In the present study, 10 pyrimidobenzimidazole derivatives synthesized using (Scheme 1), were used as trainee set and 26 new possible pyrimidobenzimidazole derivatives were used as test set for obtaining the suitable substitutional requirement for the desired activity. The structure of compounds was generated using Chemsketch software version 10.0.

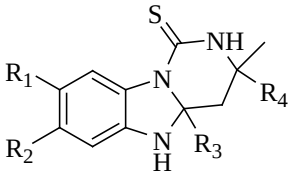
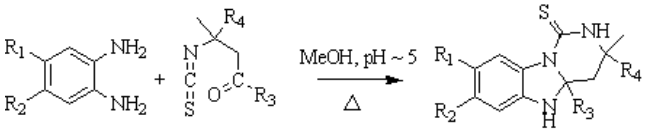


Fig. 1: Lead compound for the present study [R_1, R_2, R_3 and R_4 represents various positions of substituents on basic skeleton]



Scheme 1: Synthesis of different derivatives of pyrimidobenzimidazole

Physicochemical parameters and descriptor used

The following molecular attributes - MV (Molar volume), MSA (molar surface area), MR (Moral refractivity) and Log P were used. In molecular indices - SFI (Shape flexibility index), R (Randic index), B (Balaban index) and W (Wiener index) were used. TA (Total atom), THA (Total hetero atom) HD (H-donar) and HA (H- acceptor) were taken as atom counts indices in present study. All the parameters and descriptors were calculated using TSAR 3D, version 3.3 for windows.

Statistical analysis

Maximum R^2 method together with stepwise regression[27] was carried for arriving at statistically significant models. In present study multiple linear regression models are developed for the QSAR study of pyrimidobenzimidazole derivatives.

RESULTS AND DISCUSSION

To identify the substitutional requirement for the analgesic activity of pyrimidobenzimidazole derivatives, QSAR studies were

performed. The substituents present, observed, calculated activities and residual values of trainee set are reported in the (Table 1), whereas the possible substituents and calculated activities of test set are reported in the (Table 2). The physicochemical parameters molecular indices and atom indices, which were used to develop the QSAR are listed in the (Table 3).

Table 1: Substituents, observed, calculated activity (log%AA) and residual values for trainee set, used in present study

S.No.	R_1	R_2	R_3	R_4	Obs. log %AA	Cal. log %AA (model-6)	Residual
1	H	H	H	H	1	1.000765	-0.00076
2	H	CH_3	H	H	1	1.001528	-0.00153
3	NO_2	H	H	H	1.69897	1.700192	-0.00122
4	COOH	H	H	H	1.30103	1.306339	-0.00531
5	H	Cl	H	H	1	1.005155	-0.00516
6	C_6H_5CO	H	H	H	1.30103	1.303577	-0.00255
7	CH_3	CH_3	H	H	1.477121	1.468836	0.008285
8	CH_3	CH_3	CH_3	CH_3	1.77815	1.788162	-0.01001
9	H	Cl	CH_3	CH_3	1.30103	1.29795	0.00308
10	COOH	H	CH_3	CH_3	1.60206	1.59957	0.00249

Table 2: Possible substituent and calculated activity (log%AA) for test set used in present study

S. No.	R_1	R_2	R_3	R_4	Cal. log % AA (model-6)
11	CH_3	H	H	H	1.133894
12	H	NO_2	H	H	1.48023
13	H	COOH	H	H	1.086377
14	Cl	H	H	H	1.137521
15	H	C_6H_5CO	H	H	1.271588
16	H	COOH	CH_3	CH_3	1.357612
17	Cl	H	CH_3	CH_3	1.431598
18	H	CH_3	CH_3	CH_3	1.344549
19	NO_2	H	CH_3	CH_3	2.005312
20	H	H	CH_3	CH_3	1.219764
21	CH_3	H	CH_3	CH_3	1.478197
22	H	NO_2	CH_3	CH_3	1.763354
23	NO_2	NO_2	H	H	3.637736
24	NO_2	NO_2	CH_3	CH_3	3.822275
25	COOH	NO_2	H	H	3.251205
26	COOH	NO_2	CH_3	CH_3	3.424158
27	NO_2	COOH	H	H	3.251205
28	NO_2	COOH	CH_3	CH_3	3.424158
29	Cl	NO_2	H	H	2.277951
30	Cl	NO_2	CH_3	CH_3	2.476411
31	NO_2	Cl	CH_3	CH_3	2.613977
32	NO_2	Cl	H	H	2.399822
33	NO_2	CH_3	CH_3	CH_3	2.625383
34	NO_2	CH_3	H	H	2.361648
35	CH_3	NO_2	H	H	2.239778
36	CH_3	NO_2	CH_3	CH_3	2.487817

Table 3: Molecular attributes, molecular indices and atom indices of pyrimidobenzimidazole derivatives

S.	Molecular attributes				Molecular Indices				Atom counts			
No.	MSA	MV	logP	MR	SFI	R	B	W	TA	THA	HD	HA
1	134.85	80.58	2.35	64.14	2.10	7.27	1.59	318	28	4	2	1
2	148.30	89.46	2.82	68.97	2.33	7.65	1.56	394	31	4	2	1
3	140.60	87.85	2.31	71.26	2.72	8.56	1.55	559	30	7	2	3
4	142.91	87.87	2.05	70.69	2.76	8.56	1.55	559	31	6	3	3
5	143.98	88.59	2.87	68.74	2.49	7.65	1.56	394	28	5	2	1
6	180.83	110.15	3.57	94.51	3.58	11.13	1.26	1164	40	5	2	2
7	154.97	96.89	3.29	74.01	2.56	8.06	1.58	464	34	4	2	1
8	158.67	101.70	3.99	83.67	2.68	8.72	1.67	606	40	4	2	1
9	152.71	93.55	3.57	78.40	2.60	8.31	1.66	522	34	5	2	1
10	155.71	96.84	2.75	80.35	2.87	9.22	1.65	719	37	6	3	3
11	146.69	89.68	2.82	68.97	2.33	7.65	1.58	391	31	4	2	1
12	142.56	87.92	2.31	71.26	2.72	8.56	1.53	568	30	7	2	3
13	152.44	91.83	2.05	70.69	2.76	8.56	1.53	568	31	6	3	3
14	142.32	88.45	2.87	68.74	2.49	7.65	1.58	391	28	5	2	1
15	190.13	110.26	3.57	94.51	3.58	11.13	1.25	1188	40	5	2	2
16	160.74	96.69	2.75	80.35	2.87	9.22	1.62	728	37	6	3	3
17	148.52	93.55	3.57	78.40	2.60	8.31	1.68	519	34	5	2	1

18	156.39	94.57	3.52	78.63	2.45	8.31	1.66	522	37	4	2	1
19	146.71	92.98	3.00	80.92	2.83	9.22	1.65	719	36	7	2	3
20	147.57	86.35	3.05	73.59	2.23	7.91	1.68	438	34	4	2	1
21	152.17	94.72	3.52	78.63	2.45	8.31	1.68	519	37	4	2	1
22	148.88	89.55	3.00	80.92	2.83	9.22	1.62	728	36	7	2	3
23	140.92	88.67	2.26	78.58	3.36	9.88	1.61	842	32	10	2	5
24	150.25	96.88	2.96	88.24	3.45	10.53	1.69	1048	38	10	2	5
25	151.34	94.65	2.00	78.01	3.40	9.88	1.61	842	33	9	3	5
26	158.99	100.50	2.70	87.67	3.49	10.54	1.69	1048	39	9	3	5
27	151.91	95.58	2.00	78.01	3.40	9.88	1.61	842	33	9	3	5
28	161.06	102.35	2.70	87.67	3.49	10.54	1.69	1048	39	9	3	5
29	142.90	91.74	2.82	76.06	3.12	8.97	1.57	646	30	8	2	3
30	152.13	97.57	3.52	85.72	3.22	9.63	1.67	820	36	8	2	3
31	157.24	101.15	3.52	85.72	3.12	9.63	1.67	814	36	8	2	3
32	151.86	96.10	2.82	76.06	3.22	8.97	1.58	640	30	8	2	3
33	157.81	102.53	3.47	85.96	3.06	9.63	1.67	814	39	7	2	3
34	153.84	97.55	2.77	76.30	2.95	8.97	1.58	640	33	7	2	3
35	146.89	89.90	2.77	76.30	2.95	8.97	1.56	646	33	7	2	3
36	153.37	96.68	3.47	85.96	3.06	9.63	1.65	820	39	7	2	3

From the (Table 2), it is clear that the molecule 24 can be use as a very good analgesic compound. The results have suggested that for the good analgesic activity, pyrimidobenzimidazole derivatives must contain substituents on both the R_1 & R_2 positions and one of which must be an NO_2 group. Further the presence of CH_3 group at R_3 & R_4 position will slightly increase the activity, suggested that this portion of the molecule must interact with the hydrophobic region of the receptor.

Table 4: Correlation matrix demonstrating correlation of the physicochemical parameters molecular indices and atom indices used and their correlation with the activity (log%aa)

	log (%AA)	MSA	MV	logP	MR	SFI	R	B	W	TA	THA	HD	HA
log (%AA)	1												
MSA	0.276	1											
MV	0.451	0.976	1										
logP	0.290	0.720	0.767	1									
MR	0.463	0.952	0.962	0.705	1								
SFI	0.383	0.836	0.821	0.332	0.876	1							
R	0.401	0.863	0.840	0.368	0.913	0.981	1						
B	0.215	- 0.582	- 0.459	- 0.033	- 0.470	-0.701	-0.681	1					
W	0.353	0.875	0.842	0.380	0.914	0.975	0.998	-0.706	1				
TA	0.596	0.876	0.929	0.747	0.931	0.703	0.770	-0.210	0.764	1			
THA	0.380	- 0.140	- 0.103	- 0.504	0.032	0.382	0.309	-0.102	0.270	-0.117	1		
HD	0.192	- 0.084	- 0.062	- 0.462	0.003	0.197	0.182	0.152	0.152	0.082	0.500	1	
HA	0.437	- 0.002	0.026	- 0.537	0.141	0.482	0.454	-0.198	0.415	0.076	0.889	0.722	1

The correlation of the used parameters and their correlation with the activity are shown in (Table 4). The results (Table 4) show that all the four physicochemical parameters (MSA, MV, logP & MR) are mutually correlated and three molecular indices (SFI, R & W) are mutually correlated. Thus, if any two, three or all of them are present in the regression expression then the model may suffer from the defect due to collinearly. However, their occurrence will be dealt with according to the recommendations made by Randic[28].

The MLR analysis was started with mono variable and then the multi variables using two variables, three variables and so on. In the multi variable MLR analyses two sets of combination for the parameters were studied, the first set was the combination of physicochemical parameter with atom indices and the second was molecular indices with atom indices. The mono variable equations showed poor regression coefficient values but on increase in the number of variables, good regression coefficient values were obtained, the maximum number of variables in both type of sets were eight. Stepwise selection and elimination of variables produced MLR models with combination of six, seven and eight variables which showed good regression coefficient values and the equations of the same models are given below.

Set-1 (Physicochemical parameters with atom indices)

Model-1 (Six variables)

BA (log % AA) = 3.05207 -0.2031 x THA (±0.09396) -0.2845 x HD (±0.12623) +0.62047 x HA (±0.18773) -0.05242 x MSA (±0.01432) +0.05459 x MV (±0.03283) +0.58149 x logP (±0.23531)

N = 10, r =0.98354, SD = 0.0909, F = 14.81611

Model-2 (Seven variables)

BA (log % AA) =1.05595 +0.09453 x TA (±0.0511) +0.10398 x THA (±0.14543) -0.30199 x HD (±0.14274) +0.11633 x HA (±0.13797) -0.04316 x MSA (±0.02477) +0.06138 x MV (±0.03352) -0.02794 x MR (±0.03285)

N = 10, r =0.986727, SD = 0.10006, F = 10.54814

Model-3 (Eight variables)

BA (log % AA) =1.85397 +0.05755 x TA (±0.32636) -0.02722 x THA (±1.14784) -0.30665 x HD (±0.20448) +0.37832 x HA (±2.26388) -0.04038 x MSA (±0.04223) +0.05104 x MV (±0.10067) +0.33212 x logP (±2.85923) -0.02506 x MR (±0.05235)

N = 10, r =0.986904, SD = 0.14056, F = 4.67876

Set-2 (Molecular indices with atom indices)

Model-4 (Six variables)

BA (log % AA) = -3.46481 -0.44088 x THA (±0.09018) -0.91957 x HD (±0.13562) +0.7861 x HA (±0.1269) +1.94454 x SFI (±0.49077) -0.40698 x R (±0.16721) +3.82382 x B (±0.39211)

N = 10, r =0.988893, SD = 0.07477, F = 22.13954

Model-5 (Seven variables)

BA (log % AA) = -10.81065 -0.1741 x TA (±0.04142) -1.14482 x THA (±0.17116) -1.4943 x HD (±0.14665) +1.3126 x HA (±0.13472)

+3.69002 x SFI (±0.45742) -0.00204 x R (±0.1164) +9.53556 x B (±1.36763)

N = 10, r =0.998874, SD = 0.0292, F = 126.90681

Model-6 (Eight variables)

BA (log % AA) = -8.63341-0.19534 x TA (±0.02318) -1.28401 x THA (±0.10493) -1.6553 x HD (±0.09961) +1.48154 x HA (±0.09707) +4.30757 x SFI (±0.34186) -0.66767 x R (±0.27088) +10.67727 x B (±0.84468) +0.00268 x W (±0.00106)

N = 10, r =0.999845, SD = 0.01523, F = 409.29164

The results obtained for the calculated biological activity using model-6 summarized in (Table 1) and (Table 2) for test and trainee set respectively and the graph of observed activity versus predicted activities of training set molecules from model-6 analysis is illustrated in (Figure 2).

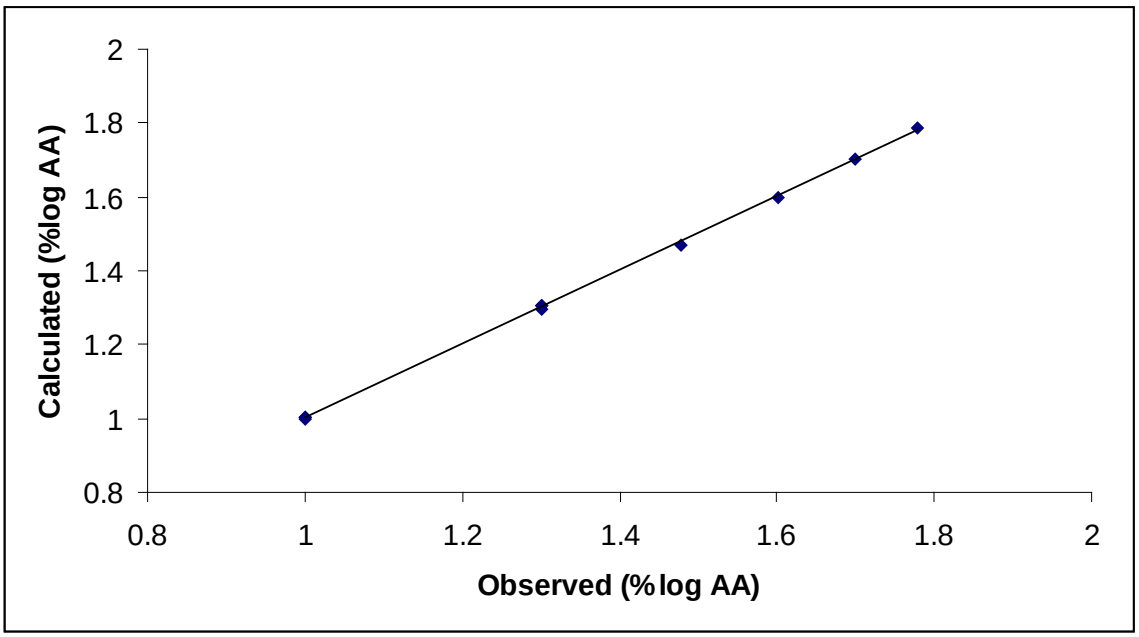


Fig. 2: Graph of observed versus predicted activities of the training set from model 6.

CONCLUSION

The MLR study of the compounds suggested that the pyrimidobenzimidazole derivatives can be successfully modeled by using molecular indices and atom indices (Model-6) for obtaining good analgesic activity. The QSAR study suggested that molecule must contain substituents on both the R_1 & R_2 positions and one of which must be an NO_2 group for good activity which possibly help in electrostatic interaction with the receptor site. It is noticeable that R_1 & R_2 disubstituted compound having at least one NO_2 group will show good analgesic activity even if R_3 & R_4 is H and/or CH_3. Further the presence of CH_3 group at R_3 & R_4 position will slightly increase the activity suggested possible receptor ligand interaction through hydrophobic forces and this prediction will definately help to select substituents for future synthesis of this type of compounds.

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