Chemical Sciences Journal
ISSN: 2150-3494

Lungu, Chem Sci J 2017, 8:2
DOI: 10.4172/2150-3494.1000159

Research Article Open Access

Inhibitors of cGMP 3',5'-Cyclic Phosphodiesterase 10A: A QSAR Study

Claudiu Lungu*

Department of Chemistry, Faculty of Chemistry and Chemical Engineering, Babes-Bolyai University, Romania

Abstract

A series of compounds with known experimental IC_{50} (nM) targeting phosphodiesterase10A (PDE10A) was studied. Recently PDE10A was proposing as a colon cancer drug target. A QSAR model was build using the compounds having as target variable their inhibitory effect on PDE10A expressed as IC_{50} (nM). A multiple correlation technique was used in order to select the appropriate descriptors for building a regression model. Descriptors used were functional group base descriptors and some centrality descriptors. The regression model was build using artificial neural network regression (ANN). A model with, r^2=0.9769, and a standard error deviation of 0.41 was build. Model was used to predict IC_{50} (nM) for a series of screening resulted compound. Template used for screening was established by generating a hypothesis using the common pharmacophore. The pharmacopohore hypothesis was build using functional groups displacement criteria. Hypothesis resulted was used for virtual screening. Compounds resulted were classified using a score. Best 17 compounds where chosen (when score decreased with 1/3 of best value). A comparison between best PDE10A inhibitor cited in the literature, best dataset compound with inhibitory effect on PDE10A and best compound resulted after screening with best IC_{50} predicted were analyzed. All three structures were analyzed in complex with PDE10A. Poses were generated using docking. Results demonstrated the importance of Pi-Pi bounds with Phe 696 as being crucial in PDE10A inhibition. The conclusion is sustained by both QSAR model and the common pharmacophore hypothesis.

Keywords: Colon tumor; PDE10A inhibitors; QSAR; Common pharmacophore; TAK-063

Introduction

Phosphodiesterase10A (PDE10A) is under evaluation or a several psychiatric and neurodegenerative diseases [1]. Recently phophodiesterase 10A was proposed as a novel target for inhibition of tumor cell growth [2]. It was found that PDE 10 A has elevated expression levels in human colon tumor cell lines compared with normal colonocytes [3]. Evidence was provided that PDE10A is involved in colon tumorigenesis. PDE10 was found to be essential for colon tumor cell growth as evident by experiments showing anti-proliferative and pro-apoptotic effects from small molecule inhibitors and genetic silencing. Consistent with the differential expression of PDE10 in colon tumor cells compared with colonocytes, the growth inhibitory effects resulting from PDE10 inhibition were only observed in tumor cells. An oncogenic function of PDE10 was also evident by experiments demonstrating increased mitogenesis resulting from ectopic expression of PDE10 in normal or precancerous colonocytes. A novel pathway by which PDE10 inhibition and activation of cGMP/PKG signaling can inhibit colon tumor cell growth by attenuating β-catenin-dependent TCF transcriptional activity was described [4]. A series of compounds are known and further studied for their capability of inhibiting PDE10A. Some of those compounds have a quantitative determination of their ability of PDE10A inhibition expressed using IC_{50}. In this respect compound 96 has a IC_{50}=700 pM (0.7nM) and is high selective against all other members of PDE family [5]; TAK-063 is another compound with IC_{50}=300 pM (0.3nM) [6]. Other compounds with known PDE10A inhibitory effect are Papaverine [7], PF-2545920 [8] and AMG 579 [9]. Purpose of this study is to search for novel PDE10A inhibitors. In this respect two strategies were adopted: (I) a pharmacophore model was used to screen for novel compounds; (II) a QSAR model was built in order to evaluate and predict the IC_{50} of the novel compounds; (III) binding site analysis using molecular docking and dynamic methods.

Methods

In order to build a pharmacophore model a data set of experimentally determine inhibitory activities on PDE10A compound was used [10]. The compounds were used to generate several common pharmacophore hypotheses. LigPrep was used for preparing ligands using OPLS_2005 force field, Ph set to 7.4 In building the pharmacophore compounds that have the IC50 above 100 nM were consider inactive in order to hypothesis to have dicriminant power i.e., being able to favor compounds that act specifically on PDE10A and have inhibitory effect in contrast with other compound that inhibit all PDEs. Hypothesis was validated using a bank of deckois [11]. The best rank hypothesis was chosen for screening novel PDA10 specific inhibitors. ZINC data base was used with an MRSD constrain of 0.7, 10 rotable bounds cut -off and molecular weight between 100-500 Daltons. The resulted structures were represented in a table together with their predicted IC_{50} (nM). Phase vector score was used to evaluate the ligands [12]. QSAR prediction model was build using the same set of compounds with the target variable IC_{50} (nM). Giving the nature of the compounds used: conformational isomers, partial charges, halogenated isomers, a special set of descriptors based on distance matrix property weighted was chosen along with indices that characterized functional groups. Descriptors evaluated for model building were: number of H, C, N, O atoms, molecular weight, number of heavy atoms, number of flexible points, number of H acceptor groups, number of aromatic rings, number of sp^2 and sp^3 C, Andrews charges, mean distance between two H acceptor groups, mean

***Corresponding author:** Claudiu Lungu, Department of Chemistry, Faculty of Chemistry and Chemical Engineering, Babes-Bolyai University, Romania, Tel: +40264591998; E-mail: lunguclaudiu5555@gmail.com

Received May 28, 2017; **Accepted** June 07, 2017; **Published** June 12, 2017

Citation: Lungu C (2017) Inhibitors of cGMP 3',5'-Cyclic Phosphodiesterase 10A: A QSAR Study. Chem Sci J 8: 159. doi: 10.4172/2150-3494.1000159

distance between the average distance and distance of a H acceptor group, max distance between to h acceptor group, C[LM[Density]], CS[LM[Electronegativity]], CS[LM[Density]], C[Sh[Distance]], CS[Sh[Distance]], PD^2S[Sh[Distance]], C[LM{Electronegativity]], PDS[LM[Electronegativity]], PDS[LM[Density]], PDS[Sh[Distance]], PDS1[LM[density]]. A future selection method in correlation with target variable was used in building the model. In order to emphasize the correlation of descriptors the correlation matrix based on Pearson r^2 was represented, together with detail descriptors values for each structure. The regression method used was artificial neural network (ANN). Model was internal validated using leave one out technique and external validated by splitting the set in training and a test set. Docking studies were performed using PDB id 2OUN which represent the computationally obtained crystallographic structure of PDE10A2 in complex with AMP [13]. The binding site used was the same as AMP. Structure was energetically minimized, protonated at 310.15 K°, pH 7.4 at NaCl salt concentration of 0.1M. In order to validate the docking procedure AMP was redocked and superimposed with the original structure PDB retrieved structure, also all ligands were represented in the binding site to ensure no defective docking position is present. TAK-063 and the best predicted IC_{50} compound resulted after screening were docked with 2OUN. Three complexes were compared: the TAK-063, the best IC_{50} compound used in the tada set (#1) and the best IC_{50} compound resulted after screening.

Results

The pharmacophore hypothesis (Figure 1) retrieved by Prime selected after ranking the 12 hypothesis resulted was ARRRH 67. Pharmacophore cartesian coordinates are: A1 x -1.40; y2.12; z -2.79; R7 x-2.79; y 2.37; z -0.68; R8 x 0.55; y -1.33; z 1.37; R10 x 1.36, y -2.73, z 3.04; H4 x 1.11; y -3.19; z 5.80. Ligands used are shown in Table 1. Multiple correlation method applied returned the results showed in Table 2. In Figure 2 a surface plot represents the increase of r^2 with increase in descriptors number. The QSAR model, built by ANN 9-4-1, after analyzing the descriptor correlation with the target, was built using the following descriptors: (1) total number of hydrogen atoms (H); (2) number of H-accepting groups (HA); (3) maximum distance between two H-acceptor groups (HA-HA-Mean); (4) average distance between two H-accepting groups (HA-HA-Mean); (5) maximum distance between two H-accepting groups; (6) C[Sh[Distance]]; (7) PDS[Sh[Distance]]; (8) PDS1[LM[Density]]. By initial computing, the model equation was: y=0.7919x-44.746, where x is a certain variable (descriptor), r^2=0.907, and a standard error deviation of 5.12. By calculating the MSE (medium standard error) it was observed that predicted values for structure 78-84 had a MSE >5. Thus in building final model those points were not computed. The resulted QSAR model has the equation y=0.8445x+9.0311, where x is a certain variable (descriptor), r^2=0.9769, and a standard error deviation of 0.41 represented in Figure 3. The compounds resulted after screening ordered after Phase vector score are represented in Table 3 together with the predicted values for IC_{50} (nM). Docking procedure was successful. None of the compounds docked outside the binding pocket (Figure 4). A superimpose docking was performed on the crystallographic model of (PDB id 2OUN) PDE10a in complex with AMP that confirmed the reliability of poses (Figures 4-7).

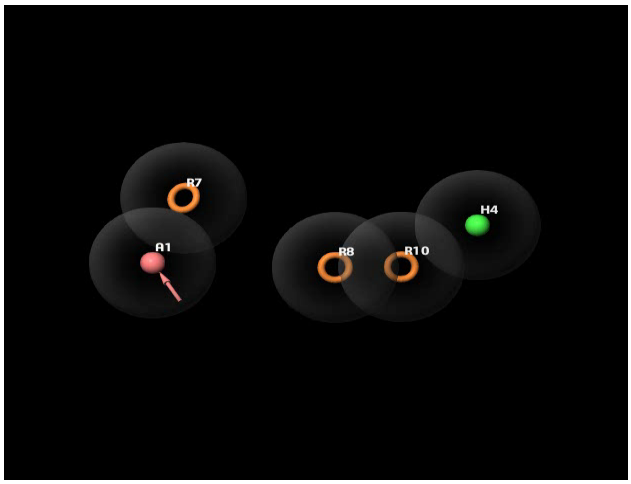

Figure 1: Common pharmacophore A –H accepting group, R –aromatic ring, H –hydrophobic group.

Conclusions

Both QSAR model and pharmacophore showed the major role of HA groups in compounds its biological action as selective inhibitors of

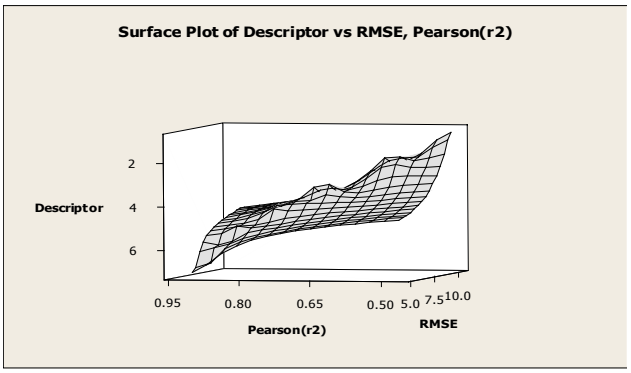

Figure 2: Surface plot of number of descriptors in respect to r^2 and RMSE.

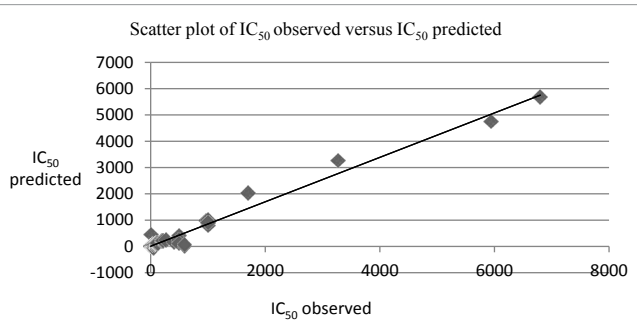

Figure 3: Scatter plot of observed IC_{50} versus predicted IC_{50}.

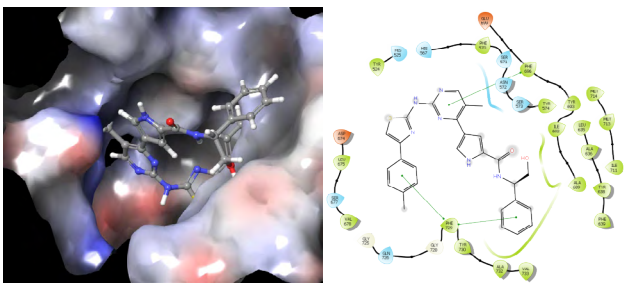

Figure 4: #14 resulted (predicted IC_{50} 5.96 nM) after screening docked with PDE10A. Pi-Pi bounds are formed with Phe 696 and Phe 729.

No.	Molecules	IC_{50}	$IC_{50}p$
1	ClC(C=C1)=CC=C1C=2C=CC=NC=2OCCC=3C=NC=4N(C)C5=CC=CC=C5C=4C=3	0.0033	0.01
2	CN1C2=CC=CC=C2C(C=3)=C1N=CC=3C4(CC4)COC5=NC=CC=C5C=6C=NC=NC=6	0.1	0.2
3	BrC(C(=C1)OC)=C(OC)C=C1C(N=2)=COC=2C(=O)C(OC)C(C=C3)=CC=C3C(O4)=NN=C4C	0.37	0.37
4	BrC(C(=C1)OC)=C(OC)C=C1C(N=2)=CSC=2C(=O)C(OC)C(C=C3)=CC=C3N4CCOCC4	0.5	0.7
5	BrC(C(=C1)OC)=C(OC)C=C1C(O2)=CC=C2C(=O)C(OC)C(C=C3)=CC=C3C(S4)=NN=C4C	1	1.7
6	O=C(C(C=2C=CC(=CC=2)C1=NN=C(O1)C)OC)C(O3)=CC=C3C(C=4)=CC(OC)=C(OC)C=4OC	1	1
7	CC(N=1)=C2C=CC=CN2C=1CCC=3NC4=CC=C(OC)C=C4N=3	1.3	1.34
8	CN1C2=CC=CC=C2C(C=3)=C1N=CC=3CCCOC4=NC=CC=C4C=5C=NC=NC=5	1.4	1.6
9	FC1=NC=CC=C1C=2C=CC=NC=2OCCCC=3C=NC=4N(C)C5=CC=CC=C5C=4C=3	4.1	4.3
10	CC(C=1)=CC=C(N3C=2C=CC=CC=2)C=1N=C3CCC4=NC=C5C=CC=CN45	5.7	6.7
11	FC(F)(F)C(C=C1)=CC(=N2)C1=NC(C)=C2C=CC(=N3)N=C(N4CCCC4)C=C3NC(C5)CCS5(=O)=O	6.3	-6.7
12	O=C(N1CCC1)C=2C=NN(C)C=2C(=O)NC(=C3)C=CN(C=4)C3=NC=4C5=CC=CC=C5	6.7	6.8
13	CN(N=1)C=C(C2=CC=NC=C2)C=1C(C=C3)=CC=C3OCC4=NC5=CC=CC=C5C=C4	7.3	7.5
14	COC1=NC=2C=CC=NC=2N1C(C=C3)=CC=C3NC=4NC5=CC=CC=C5N=4	8.3	8.6
15	O=C(NC2=CC(=NN2(CCOC))C=1C=CC=CN=1)C3=NC(C4CC4)=CC=C3NC=5C=NC=NC=5	9.1	9.4
16	O=C(C=2C(NC3=CN=CN=C3)=CC=C(N=2)C1CC1)NC(=C4)N(C)N=C4C=5C=CC6=CC=CC=C6N=5	9.2	9.8
17	CN(N=1)C=C(C2=CC=NC=C2)C=1C(C=C3)=CC=C3OCC4=NC5=CC=CC=C5C=C4	9.5	9.8
18	FC(F)(F)CN(N=1)C=C(C2=CC=NC=C2)C=1C(C=C3)=CC=C3OCC4=NC5=CC=CC=C5C=C4	10	10.22
19	COC1=NC=2C=CC=NC=2N1C(C=C3)=CC=C3NC4=NC=C(C)C=C4	10	11.19
20	COC1=NC=2C=CC=NC=2N1C(C=C3)=CC=C3NC=4SC5=CC=CC=C5N=4	10	12.4
21	O=C1N(C)C=2C=CC=NC=2N1CCC3=NC4=CC(OC)=CC=C4N3C5=CC=CC=C5	10	11
22	CC(C=N1)=CC=C1NC(C=C2)=CC=C2N3C=4N=CC=CC=4N=C3CCC	10	11
23	O=C1N(C)C=2C=CC=NC=2N1CCC3=NC4=C(OC)C=CC=C4N3C5=CC=CC=C5	10	-10
24	CC(C=1)=CC=C(N3C=2C=CC=CC=2)C=1N=C3CCN(N=4)C=5N=CC=CC=5C=4C	10	11.7
25	CC(C=1)=CC=C(N3C=2C=CC=CC=2)C=1N=C3CCC(=N4)N5N=CC=CC5=C4C	10	11.5
26	O=C1N(C)C=2C=CC=NC=2N1CCC3=NC4=CC(C)=CC=C4N3C5=CC=CC=C5	10	451.11
27	O=C1N(C)C=2C(C)=CC=NC=2N1CCC3=NC=4C(OC)=CC=NC=4N3C5=CC=CC=C5	10	10.720
28	COC(C=1)=C(OC)C=C(C=32)C=1CCN2C(C)=NC=3C(=C4)C=NC=C4N5C=CC=6C=CC=CC5=6	11	-11.7
29	COC(=C(C=1)OC)C=C(C=32)C=1CCN2C=NC=3C(S4)=CN=C4N5CCOCC5	15	16.14
30	O=C(NCCCC=2NC=1C(N=2)=CC=CC=1)C(=C3)C4=NN=C(C(C)(C)C)N4C=C3C5=CC=C(O)C=C5	21	22.33
31	O=S(CC=1C=CC=CC=1)(=O)C(C=C2)=CC=C2C(=O)N(C)CCC(CC3)CCN3CC4=CC=CC=C4	22	25.02
32	CN1CCCC1CC(C=3C=2)=CNC=3C=CC=2OC	24	25.05
33	COC(C=1)=C(OC)C=C(C=32)C=1CCN2C=NC=3C(=C4)C=NC=C4OC	25	27.83
34	CN1C2=CC=CC=C2C(C=3)=C1N=CC=3CCOC4=NC=CC=C4C=5C=CN=CC=5	25	25.53
35	BrC(C=1)=CN2N=C(C3CC3)N=C2C=1C(=O)NCCC=4NC5=CC=CC=C5N=4	28	31.21
36	ClC(C=1)=CC=CC=1N2N=CC=C2C(=N3)C(=O)C(OC)=CN3C(C=C4)=C(F)C=C4N5N=CC=C5	28	29.28
37	BrC(C=1)=CN2C(C(C)(C)C)=NN=C2C=1C(=O)NCCC=3SC4=CC=CC=C4N=3	33	34.51
38	CN1C2=CC=CC=C2C(C=3)=C1N=CC=3CCOC4=NC=CN=C4C=5C=CN=CC=5	36	35.78
39	O=C(C=2NC=1C(N=2)=CC=CC=1)C(C=C3)=CC=C3N4C=5N=CC=CC=5N=C4OC	37	66.24
40	CCCC1=NC=2C=CC=NC=2N1C(C=C3)=CC=C3NC=4SC5=CC=CC=C5N=4	37	56.53
41	CCC1=NC=2C=CC=NC=2N1C(C=C3)=CC=C3NC=4SC5=CC=CC=C5N=4	40	71.59
42	CN1C2=CC=CC=C2C(C=3)=C1N=CC=3CCOC4=NC=CC=C4C=5C=NC=NC=5	42	50.143
43	N(=C2N1CCOCC1)C=CN=C2OC(C=C3)=CC=C3NC=4NC5=CC=CC=C5N=4	47	50.95
44	FC(F)(F)C(C=1)=NC=CC=1C2=NC=CN=C2OC(C=C3)=CC=C3C(=O)C=4NC5=CC=CC=C5N=4	50	51.16
45	O=C1N(C)C=2C=CC=NC=2N1CCC3=NC=4C(OC)=CC=NC=4N3C5=CC=CC=C5	50	67.63
46	O=C1C(C)=NC=2C=CC=NC=2N1CCC3=NC4=CC(C)=CC=C4N3C5=CC=CC=C5	50	-65.41
47	FC(F)N1C2=CC=CC=C2C(C=3)=C1N=CC=3CCOC4=NC=CC=C4C=5C=NC=NC=5	50	83.62
48	COC(=C1)C(OC)=CC2=C1C=CN=C2CC(C=3)=CC=C(OC)C=3OC	50	98.29
49	O=C1N(C)C=2C=CC=NC=2N1CCC3=NC4=CC(OC)=CC=C4N3C5=CC=CN=C5	50	51.83
50	CC1=NC=2C=CC=NC=2N1C(C=C3)=CC=C3NC=4SC5=CC=CC=C5N=4	52	53.13
51	ClC(C=N1)=CC=C1NC(C=C2)=CC=C2N3C=4N=CC=CC=4N=C3OC	67	68.49
52	FC(C=C1)=CC=C1C2=NC=CN=C2OCCC=3C=NC=4N(C)C5=CC=CC=C5C=4C=3	69	73.92
53	CC(C=N1)=CC=C1NC(C=C2)=CC=C2N3C=4N=CC=CC=4N=C3CC	92	93.31
54	O=C(NN=CC=2C1=C(C=CC=2)C=NC=C1)C3CC3C(C=C4)=CC=C4C5=CC=CC=C5	97	98.50
55	O=C(C1CC1(C=2C=CC(=CC=2)C(C)(C)C))N(C)N=CC=3C=4C=CN=CC=4C=CC=3	100	100.29
56	O=C(C1CC1(C=2C=CC(=CC=2)C(C)(C)C))NN=CC=3C=4C=CN=CC=4C=CC=3	100	100.03
57	C(=CC=1)C=C(N=2)C=1C=CC=2COC(C=C3)=CC=C3C=4C=CC=CC=4C=5C=CN=CC=5	100	100.61
58	O=C1OC(C)(C)C(C2=CC=NC=C2)=C1C(C=C3)=CC=C3OCC=4C=CC5=CC=CC=C5N=4	100	149.55
59	O=C1N(C)CC(C=2C=CC(=CC=2)OC)=C1C(C=C3)=CC=C3OCC=4C=CC5=CC=CC=C5N=4	100	103.49
60	CC1=NC=2C=CC=NC=2N1C(C=C3)=CC=C3NC4=NC=C(C)C=C4	100	100.20

61	CN1C2=CC=CC=C2C(C=3)=C1N=CC=3CCOC4=NC=CN=C4C=5C=NC=NC=5	100	120.54
62	FC(C=C1)=CC=C1C=2C=CC=NC=2OCCC=3C=NC=4N(C)C5=CC=CC=C5C=4C=3	100	107.76
63	CC(C=1)=CC=C(N3C=2C=CC=CC=2)C=1N=C3CCC4=NC=C5C=CC=NN45	105	107.97
64	O=C1N(C)C=2C=CC=NC=2N1CCC3=NC4=CC(OC)=CC=C4N3C=5C=CN=CC=5	111	113.119
65	FC(F)(F)OC(=CC=21)C=C(C)C1=NC=3NN=C(C)C=3C=2CC(N=4)=CC=NC=4OC	115	124.323
66	CC1=CC(OC)=CC=2C1=NC=3NN=C(C)C=3C=2N(C4)CCNC4C	123	118.93
67	ClC(C=C1)=CC=C1C=C(COC2=CC=NC=C2)C(C=C3)=CC=C3OCC=4C=CC5=CC=CC=C5N=4	188	209.57
68	ClC(C=C1)=CC=C1C=C(CN2N=NC=N2)C(C=C3)=CC=C3OCC=4C=CC5=CC=CC=C5N=4	200	219.19
69	ClC(C=C1)=CC=C1C=2N=C3SC=CN3C=2C(C=C4)=CC=C4OCC(=O)N(C)C=5C=CC=CN=5	210	210.97
70	FC=1C=CC=C(F)C=1CC(=O)N(CC=2C=NC=CC=2)C(C=C3)=CC=C3OCC=4C=CC5=CC=CC=C5N=4	220	221.52
71	ClC(=CC=21)C=C(C)C1=NC=3NN=C(C)C=3C=2N(CC4)CCCN4S(C)(=O)=O	271	250.56
72	O=C(CCC)N(CC=1C=NC=CC=1)C(C=C2)=CC=C2OCC=3C=CC4=CC=CC=C4N=3	404	156.149
73	C1=CC=NC2=C1N=CN2C(C=C3)=CC=C3NC=4SC5=CC=CC=C5N=4	500	420.60
74	O=C1N(C)C2=NC=CN=C2N1CCC3=NC=4C(OC)=CC=NC=4N3C5=CC=CC=C5	500	238.112
75	COC1=NC=2C=CC=NC=2N1C(C=C3)=CC=C3NC4=NC5=CC=CC=C5C=C4	500	113.027
76	CN(C=1)C2=CC3=CC=CC=C3N=C2C=1CCOC4=NC=CN=C4C=5C=NC=NC=5	590	24.62
77	ClC(C=C1)=CC=C1C2=NC=CN=C2OCCC=3C=NC=4N(C)C5=CC=CC=C5C=4C=3	592	73.42
78	O=C1N(C)C=2C=CC=NC=2N1CCC3=NC=4C=C(C)C=NC=4N3C5=CC=CC=C5	971	-81.21
79	CC(C=1)=CC=C(N3C=2C=CC=CC=2)C=1N=C3CCC(=N4)N5C=CC=NC5=C4C	1000	-99.54
80	O=C1N(C)C=2C=CC=NC=2N1CCC3=NC4=CC(OC)=CC=C4N3C=5C=CC=CN=5	1000	16.287
81	COC1=NC=2C=CC=NC=2N1C(CC3)CCC3NC=4SC5=CC=CC=C5N=4	1000	-105.77
82	NC=1C=CC=NC=1NC(C=C2)=CC=C2NC=3SC4=CC=CC=C4N=3	1000	263.467
83	CN1C2=CC=C3N=CC=CC3=C2N=C1CCC=4N=C5C=CC=NC5=CC=4	1700	237.526
84	C(=C1)C=CC(=N2)C1=NC=C2CCC(N3)=NC=C3C4=CC=CC=C4	3271	3451.5
85	O=C(N=1)C=2C=CC=CC=2NC=1CCC(N3)=NC=C3C4=CSC=C4	5937	4749.27
86	CC(N=1)=C2C=CC=CN2C=1CCC3=NC4=CC(C)=CC=C4N3C5=CC=CC=C5	6800	5673.17

Table 1: Compounds used for pharmacophore generation and QSAR model are represented as smiles. Nr-compound number. IC_{50}-observed value, IC_{50}p- model predicted value. Compounds are arranged accordingly to IC_{50} in increasing order.

Pearson (r^2)	RMSE	Descriptor used	Descriptors
0.9066	5.12	7	H, HA, HA-HA Max, HA-Ha-Mean, C[Sh[Distance]], PDS1[LM[Density]], PDS[Sh[Distance]]
0.89509	5.43	7	Atoms, HA, Ha-HA-Max, HA-HA Mean, C[Sh[Distance]], PDS1[LM[Density]], PDS[Sh[Distance]]
0.864741	6.17	6	HA, HA-HA Max, HA-Ha-Mean, C[Sh[Distance]], PDS1[LM[Density]], PDS[Sh[Distance]]
0.856127	6.39	6	HA, HA-HA Max, HA-Ha-Mean, C[LM[Density]], PDS1[LM[Density]], PDS[Sh[Distance]]
0.845931	6.64	5	HA, HA-HA Max, HA-Ha-Mean, PDS1[LM[Density]], PDS[Sh[Distance]]
0.836971	6.67	5	HA, HA-HA Max, HA-Ha-Mean, C[LM[Electronegativity]], PDS1[LM[Density]]
0.824227	6.99	5	HA, HA-HA Max, HA-Ha-Mean, C[Sh[Distance]], PDS1[LM[Density]]
0.818655	7.07	5	HA, HA-HA Max, HA-Ha-Mean, C[LM[Density]], PDS1[LM[Density]]
0.81772	7.19	5	HA, HA-HA Max, HA-Ha-Mean, PDS1[LM[Density]], Andrewes
0.785367	7.67	4	HA, HA-HA Max, HA-Ha-Mean, PDS1[LM[Density]]
0.745622	8.07	4	HA, HA-HA Max, HA-Ha-Mean, C[LM[Electronegativity]]
0.725038	8.38	4	HA, HA-HA Max, HA-Ha-Mean, C[Sh[Distance]]
0.703133	8.65	3	HA, HA-HA Max, HA-Ha-Mean
0.57351	9.90	2	HA, HA-HA Max
0.466729	10.63	1	HA-HA Max

Table 2: Descriptors contribution to the model.

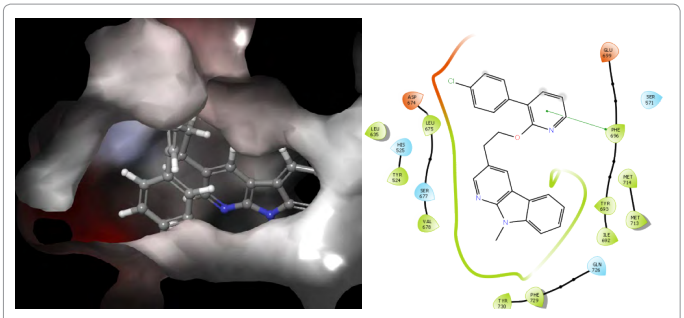

Figure 5: #1 in the data set (experimental IC_{50} 0.0033nM) docked with PDE10A Pi-Pi bounds are formed with Phe 696.

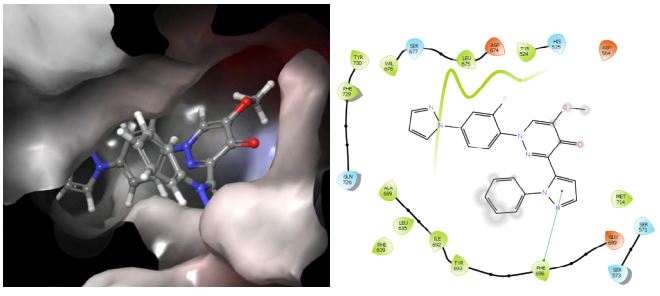

Figure 6: TAK-069 (experimental IC_{50}=0.3nM) docked with PDE10A Pi-Pi bounds are formed with Phe 696.

Nr	Compounds	P HV	IC_{50} p
1	OCC(C1=CC=CC=C1)NC(=O)C(=C2)NC=C2C(=N3)C(C)=CN=C3NCC=4C=CC=CN=4	0.961084	157.482
2	BrC(C=1)=C2C=C(C(N)=N)C=CC2=CC=1C=CC=3C=C(OCC)C(OCC)=CC=3OCC	0.933503	4290.1
3	O=C(OC)C1CCCN1C(=O)C(C=2)=CC=C(NC4=C3)C=2NC(=O)C4=CC=C3C(C=5)=CC=C(O)C=5OC	0.855927	280.621
4	OC(=C(C=1)OC)C=CC=1C(=CC=2)C=CC=2C3=NNC4=C3CC(C=5)=C4C=CC=5C(=O)NC6CCC(O)CC6	0.850775	459.631
5	O=C(O)C(C(=C1)OC)=CC=C1C=2C=C3NC4=CC=CC=C4NC(=O)C3=CC=2	0.843352	87.7343
6	OC(=C1)C=CC2=C1CC3=C2NN=C3C(=CC=4)C=CC=4C(=C5)C=CNC5=O	0.816614	342.438
7	BrC(=CC=1)C=CC=1C2=NNC3=C2CC(=C4)C3=CC(OC)=C4OCC=5C=CC(OC)=CC=5	0.814371	127.702
8	COC(=C(OC)C=1)C=C2C=1CC3=C2NN=C3C(=CC=4)C=CC=4C5=NN=NN5	0.812519	270.854
9	O=C(N1)C=C(C)N=C1NC(=N2)N=C3C=C(OC)C=CC3=C2C	0.811566	42.1176
10	BrC(C=1(C))=CC=CC=1NC(=N2)N=CC(C)=C2C(C=3)=CNC=3C(=O)NC(CO)C=4C=CC=CC=4	0.784309	52.5271
11	ClC(=C1)C=CC=C1C(CO)NC(=O)C(=C2)NC=C2C(=N3)C(C)=CN=C3NC4CC[NH2]CC4	0.78415	68.5334
12	ClC(C=1)=CC=CC=1C(CO)NC(=O)C(=C2)NC=C2C(=N3)C(C)=CN=C3NC=4C=CC=C(F)C=4C	0.772989	76.7807
13	OCC(C1=CC=CC=C1)NC(=O)C(=C2)NC=C2C3=NC(C)=NC=C3C	0.772806	77.2612
14	O=C(NC(C1=CC=CC=C1)CO)C(=C2)NC=C2C(N=3)=C(C)C=NC=3NC(=N4)SC=C4C=5C=CC(C)=CC=5	0.771981	5.96891
15	OC(=C(C=1)OC)C=CC=1C(=CC=2)C=CC=2C(=C43)NN=C3C=5C=CC=CC=5C4=O	0.750745	188.328
16	OC(=CC=1)C(OC)=CC=1C#CC=2NN=C3C=2CC(=C4)C3=CC(OC)=C4OC	0.689424	258.259
17	OC(=C(C=1)OC)C=CC=1C(=CC=2)C=CC=2C3=NNC4=C3CC(C=5)=C4C=CC=5CNC6CCC(O)CC6	0.612074	469.609

Table 3: Compounds resulted after screening arrange after phase vector score-PHV, IC_{50}p –$IC_{50\ predicted}$.

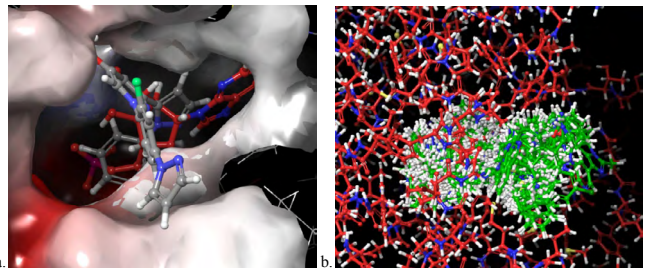

Figure 7: a. PDE10A binding poket containing AMP (red) superpose with TAK-069 b. All compounds in PDE10A binding pocket.

PDE10A. QSAR model supports this assumption by 0.7 r^2 contribution of HA (HA, HA-HA-Max, HA-HA-Mean) to the model and by the model correlation of predicted values versus experimental values. The centrality descriptors explained the rest of the correlation. The pharmacophore retrieved the same hypothesis where the HA group plays a major role. The docking study emphasizes the role of Pi-Pi interactions with Phe 696.

References

1. Siuciak JA, Chapin DS, Harms JF (2006) Inhibition of the striatum-enriched phosphodiesterase PDE10A: a novel approach to the treatment of psychosis. Neuropharmacology 51: 386-396.
2. Li N, Lee K, Xi Y, Zhu B, Gary BD, et al. (2015) Phosphodiesterase 10A: a novel target for selective inhibition of colon tumor cell growth and β-catenin-dependent TCF transcriptional activity. Oncogene 19: 1499-509.
3. Ashley SL, Kevin L, Joel A, Wen-Chi L (2017) PDE10A overexpression in colon cancer cells and tumors relative to normal colonocytes and colon mucosa, proceedings of the AACR Special Conference on Colorectal Cancer: From Initiation to Outcomes. Cancer Res.
4. Nan L, Yaguang X, Heather NT, Evrim G, Bernard DG, et al. (2013) Sulindac selectively inhibits colon tumor cell growth by activating the cGMP/PKG pathway to suppress Wnt/β-catenin signaling. Mol Cancer Ther 12: 1848-1859.
5. Malamas MS (2011) Highly potent, selective, and orally active phosphodiesterase 10A inhibitors. J Med Chem 54: 7621-7638.
6. Kunitomo J, Yoshikawa M, Fushimi M, Akira K, John FQ, et al. (2014) Discovery of 1-[2-Fluoro-4-(1H-pyrazol-1-yl)phenyl]-5-methoxy-3-(1-phenyl-1H-pyrazol-5-yl)pyridazin-4(1H)-one (TAK-063), a Highly Potent, Selective, and Orally Active Phosphodiesterase 10A (PDE10A) Inhibitor. J Med Chem 57: 9627-9643.
7. Siuciak JA, Chapin DS, Harms JF (2006) Inhibition of the striatum-enriched phosphodiesterase PDE10A: a novel approach to the treatment of psychosis. Neuropharmacology 51: 386-396.
8. Verhoest PR, Chapin DS, Corman M (2009) Discovery of a novel class of phosphodiesterase 10A inhibitors and identification of clinical candidate 2-[4-(1-methyl-4-pyridin-4-yl-1H-pyrazol-3-yl)-phenoxymethyl]-quinoline (PF-2545920) for the treatment of schizophrenia. J Med Chem 52: 5188-5196.
9. Essa H, Ning C, Matthew PB, Paul EH, Kaustav B, et al. (2014) Discovery of Clinical Candidate1-(4-(3-(4-(1Hbenzo[d]imidazole-2-carbonyl)phenoxy) pyrazin-2-yl)piperidin-1-yl)ethanone (AMG 579), a Potent, Selective, and Efficacious Inhibitor of Phosphodiesterase 10A (PDE10A). J Med Chem 57: 6632-6641.
10. Liu T, Lin Y, Wen X, Jorrisen RN, Gilson MK (2007) Binding DB: a web-accessible database of experimentally determined protein-ligand binding affinities. Nucleic Acids Res 35: 98-201.
11. Bauer MR, Ibrahim TM, Vogel SM, Boeckler FM (2013) Evaluation and optimization of virtual screening workflows with DEKOIS 2.0-a public library of challenging docking benchmark sets. J Chem Inf Model 24: 1447-1462.
12. Murugesan R, Natchimuthu S, Vembu B (2014) Pharmacophore and Virtual Screening of JAK3 inhibitors. Bioinformation 10: 157-163.
13. Wang H, Liu Y, Hou J, Zheng M, Robinson H, et al. (2007) Structural insight into substrate specificity of phosphodiesterase. Proc Natl Acad Sci USA 104: 5782-5787.