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In Silico Prediction of Biological Activity, Selected Pharmacokinetic and Toxicity Profile of Some 2,4,6-Trisubstituted Pyrimidines Derived from Guanabenz and Guanfacine

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ABSTRACT

This present work involves the evaluation of drug-likeness of some 2,4,6-Trisubstituted Pyrimidines. Guanabenz and guanfacine were selected as lead molecules and a series of drug-like pyrimidines were generated by virtual condensation of chalcones with the leads. The biological activity, pharmacokinetic and toxicity properties of those molecules were calculated by using PASS, ACD labs Chem Sketch software version 12.0,Molinspiration and Osiris property explorer.All drug-like 2,4,6-Trisubstituted Pyrimidines were predicted to be safe with the exception of GBD-10A and GFD-4A. From this study, it can be concluded that all the drug-like 2, 4, 6-Trisubstituted Pyrimidines possess marked lipophilicity and antihyperlipidimic (HMGCS2 expression enhancer) activity.

Keywords: 2, 4, 6-Trisubstituted Pyrimidines, Biological activity, Pharmacokinetic &Toxicity properties, *In silico* methods.

INTRODUCTION

The biological significance of the pyrimidine derivatives has led us to select the present work. As pyrimidine is a basic nucleus in DNA & RNA, it has been found to be associated with diverse biological activities. Guanidine readily reacts with β-diketones, β-ketoesters, α, β-unsaturated carbonyl compounds and cyano acetic esters to give 2-amino pyrimidines usually in good yields (Ghoneim KM *et al*., 1986, Kenner GW *et al*., 1957, Brown DJ, 1962). It is usual to start with molecules that appear to be drug-like at the outset rather than to make a hit drug-like later (Lester AM *et al*., 2002). Therefore, in this study, we generated 2,4,6-trisubstituted pyrimidines by virtual condensation of guanabenz and guanfacine (synthetic equivalents of guanidine) with substituted chalcones (α,β-unsaturated carbonyl compounds).

Failure of promising lead(s) to exhibit desirable ADME/T profile is now regarded as the major reason for the late-stage drug attrition rate. According to a recent report, poor pharmacokinetics (39%) and preclinical toxicity (11%) were the major reasons for failures in the drug development, in addition to the lack of efficacy, adverse effects in man and commercial reasons. This scenario has changed in the current decade with more efforts focused on the early-stage ADME/T profiling. In addition to the experimental evaluation of ADME/T, *in silico* predictions of these properties have gained popularity in the industry in recent years for the obvious reasons. The sole purpose of all these recently evolved experimental and predictive ADME/T approaches is to reduce late-stage failures by focusing on the most promising lead(s) with desired ADME/T properties (Prashant SK, 2010).

The application of computational technology during drug discovery and development offers considerable potential for reducing the number of experimental studies required for compound selection and development and for improving the success rate. In this context, *in silico* approaches are being used today in drug discovery to assess the ADME properties of compounds at the early stages of discovery and development. This early assessment of ADME properties will help pharmaceutical scientists to select the best

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candidates for development as well as to reject those with a low probability of success (Venkatesh S *et al*., 2000).

In the present study, guanabenz and guanfacine were selected as lead molecules and some drug like substituted pyrimidine molecules, with anticipated biological activity were generated. Biological activity, selected pharmacokinetic and toxicity properties such as Clog P, solubility, TPSA, drug-likeness, drug score, molar refractivity, molar volume, parachor, index of refraction, surface tension, density, polarisability, mutagenicity, tumorogenicity, irritant action and toxicity on reproductive system were predicted using software like ACD labs chemsketch version12.0,Osiris property Explorer, Molinspiration and prediction of activity spectrum of substances PASS online program.

MATERIALS AND METHODS

Selection of lead molecule

The phrase "drug-like" is becoming more widespread. Drug-like compounds are molecules which contain functional groups and / or have physical properties consistent with the majority of known drugs, and hence can be inferred as compounds which might be active biologically or might show therapeutic potential. For a drug, properties like synthetic ease, stability, oral availability, good pharmacokinetic properties, lack of toxicity and minimum addictive potential are of utmost importance. Many of these properties depend on the inherent biological and physicochemical parameters of the molecule (Walters WP *et al*., 1998&1999). Considering these factors, we selected guanabenz and guanfacine as lead molecules to generate some drug-like substituted pyrimidine molecules with anticipated biological activity.

Generation of drug-like substituted pyrimidines

Some drug-like substituted pyrimidines were generated from guanabenz and guanfacine by virtual condensation with substituted chalcones. Structures of these drug-like substituted pyrimidines were drawn through Chemsketch software. Each 2D chemical structure was systematically built according to the Topliss decision tree (Topliss JG, 1972). All these chemical structures were saved and exported to Osiris Property Explorer, Molinspiration and PASS.

ACD labs Chemsketch

ACD labs Chemsketch v 12.0 is a chemical drawing software package from Advanced Chemistry Development Inc, developed in order to help chemists to quickly and easily draw chemical structures of organic molecules, IUPAC names, 3D structures, molecular properties , physicochemical properties, reactions and schematic diagrams and design professional reports and presentations(ACD labs Chem sketch v 12.0. 2008).

Osiris Property Explorer

The Osiris Property Explorer is an integral part of Actelion's in-house substance registration system. It lets you draw chemical structures and calculates on-the-fly various drug-relevant properties whenever a structure is valid. Prediction results are valued and color coded. Properties with high risks of undesired effects like mutagenicity or a poor intestinal absorption are shown in red. Whereas a green color indicates drug conform behavior (Actelion's property explorer, 2001).

Molinspiration

Molinspiration supports internet chemistry community by offering free on-line services for calculation of important molecular properties like molinspiration Log P (miLogP), polar surface area, number of hydrogen bond donors (HBD) and acceptors(HBA) and others, as well as prediction of bioactivity score for the most important drug targets like GPCR ligands, kinase inhibitors, ion channel modulators, enzymes and nuclear receptors (Ertl P *et al*., 2000).

PASS (Prediction of Activity Spectrum of Substances)

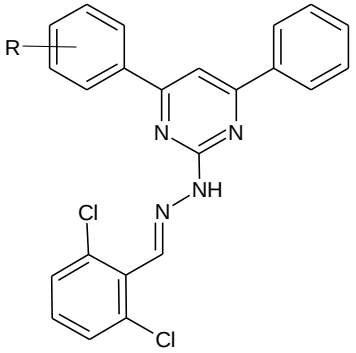
Novel pharmacological actions can be found for title compounds on the basis of an online program PASS. Its application to the title compounds was done in order to identify prospective pharmacological properties that could be confirmed by experimental studies. PASS compares the structure of a new compound with structures of well known biologically active substance and therefore it is possible to estimate if a new compound may have a particular effect. It operates with many thousands of substances from the training set, and provides more objective estimation. Since only the structural formula of chemical compound is necessary to obtain PASS predictions, this approach can be used at the earliest stage of investigation. Structures of the title compounds were drawn through Chem Sketch software, submitted to the PASS online program and predicted the possible mechanisms of action as well as biological activities (http:// www.ibmc.msk.ru/PASS).

RESULTS AND DISCUSSION

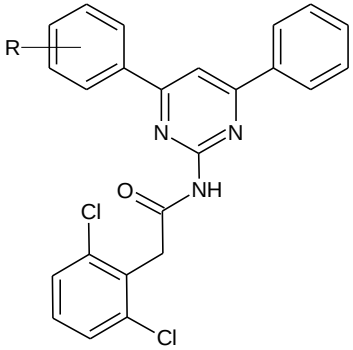
Some selected pharmacokinetic properties, which are of high importance to drug discovery process were predicted using Chemsketch v 12.0 (Table 1). Incorporation of both guanabenz and guanfacine in to pyrimidine structure shows great impact on pharmacokinetic properties. This is reflected in some lipophilic parameters like parachor and molar refractivity. Derivatives containing dimethylamino, iodo and nitro substituents (GFD-11, GFD-7, GFD-9, GFD-13 and GBD-4) show greater parachor and molar refractivity. Lipophilicity affects drug absorption, bioavailability, hydrophobic drug-receptor interactions, metabolism of molecules, as well as their toxicity.

Some selected toxicological properties and drug score values were predicted using Osiris (Tabl 2). Only two derivatives show toxicity (GBD-10A and GFD-4A). It seems that drug score is not favored with nitro (GBD-10A, 0.08) and dimethylamino substitution (GBD-4A, 0.13 and GFD-4A, 0.14). The remaining derivatives have good drug scores, which is maximum in amino substituted derivatives (GFD-5A, 0.28 and GFD-6A, 0.31). Drug likeness, may be defined as a complex

Table.1 Structural details and selected pharmacokinetic properties of 2,4,6-trisubstituted pyrimidines(Chemsketch)



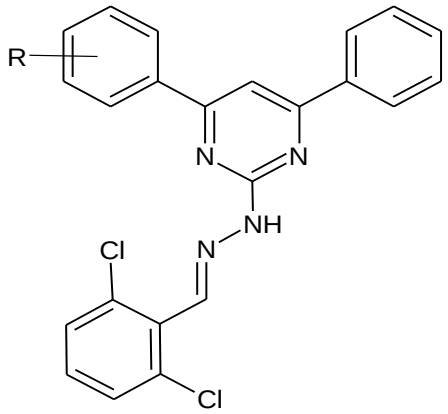
GBD 1 - 8



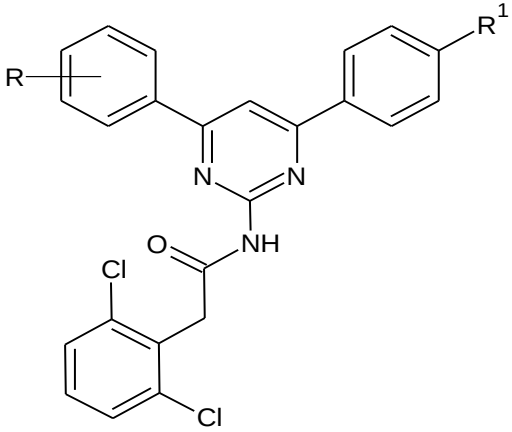
GFD 1 -14

S.No	Code	R	Molecular Weight	Molar Refractivity	Molar Volume	Parachor	Refractive Index	Surface Tension	Density	Polarizability
1	GBD-1	4-H	419.30	119.76	326.0	859.9	1.655	48.3	1.28	47.48
2	GBD-2	4-Cl	453.75	124.36	335.3	888.7	1.663	49.3	1.35	49.30
3	GBD-3	3,4-Cl	488.19	128.96	344.5	917.6	1.671	50.2	1.41	51.12
4	GBD-4	4-I	545.20	132.42	343.6	922.6	1.697	51.9	1.58	52.49
5	GBD-5	4-CF_3	487.30	124.52	356.0	913.9	1.616	43.4	1.36	49.36
6	GBD-6	4-Br	498.20	127.32	338.5	903.4	1.675	50.7	1.47	50.47
7	GBD-7	2,4-Cl	488.19	128.96	344.5	917.6	1.671	50.2	1.41	51.12
8	GBD-8	4-NO_2	464.30	125.42	331.2	905.4	1.681	55.7	1.40	49.72
9	GFD-1	4-H	434.31	120.16	324.1	889.9	1.663	56.8	1.339	47.63
10	GFD-2	4-Cl	468.76	125.06	336.0	925.7	1.666	57.5	1.394	49.57
11	GFD-3	4-OCH_3	464.34	126.84	348.1	946.5	1.649	54.6	1.333	50.28
12	GFD-4	3-Cl	468.76	125.06	336.0	925.7	1.666	57.5	1.394	49.57
13	GFD-5	3-CF_3	502.31	125.14	357.6	947.1	1.617	49.1	1.404	49.61
14	GFD-6	3-Br	513.21	127.85	340.3	940.4	1.674	58.3	1.508	50.68
15	GFD-7	3-I	560.21	133.07	346.2	965.5	1.695	60.4	1.618	52.75
16	GFD-8	3,5-Cl	503.20	129.95	348.0	961.6	1.669	58.2	1.445	51.51
17	GFD-9	3-NO_2	479.31	126.71	335.9	945.3	1.678	62.6	1.426	50.23
18	GFD-10	4-CH_3	448.34	124.99	340.4	927.5	1.655	55.1	1.317	49.55
19	GFD-11	3-$N(CH_3)_2$	477.38	134.48	362.1	991.9	1.665	56.2	1.318	53.31
20	GFD-12	2-Cl	468.76	125.06	336.0	925.7	1.666	57.5	1.394	49.57
21	GFD-13	4-NO_2	479.31	126.71	335.9	945.3	1.678	62.6	1.426	50.23
22	GFD-14	4-F	452.30	120.16	328.3	897.0	1.652	55.7	1.377	47.63

Table.2 Structural details and selected toxic properties and drug scores of 2,4,6-trisubstituted pyrimidines(Osiris)



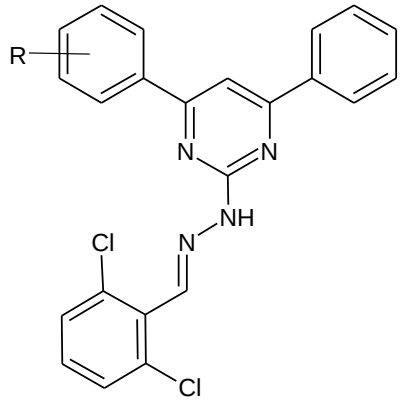
GBD 1A - 11A



GFD 1A - 6A

S.No	Code	R	R^1	Muta--genicity	Tumoro--genicity	Irritant effect	Reproductive toxicity	C log P	Aqueous Solubility	TPSA	Drug likeness	Drug score
1	GBD-1A	4-H	-	---	---	---	---	8.36	-7.44	50.17	3.47	0.24
2	GBD-2A	4-Cl	-	---	---	---	---	8.97	-8.18	50.17	4.35	0.22
3	GBD-3A	4-OCH_3	-	---	---	---	---	8.29	-7.46	59.4	3.47	0.23
4	GBD-4A	4-$N(CH_3)_2$	-	---	---	---	---	8.26	-7.48	53.41	2.41	0.13
5	GBD-5A	4-NH_2	-	---	---	---	---	7.68	-7.52	76.19	3.56	0.24
6	GBD-6A	4-CH_3	-	---	---	---	---	8.7	-7.79	50.17	1.97	0.22
7	GBD-7A	3-Cl	-	---	---	---	---	8.97	-8.18	50.17	3.36	0.21
8	GBD-8A	3-$N(CH_3)_2$	-	---	---	---	---	8.26	-7.48	53.41	4.29	0.22
9	GBD-9A	2-Cl	-	---	---	---	---	8.97	-8.18	50.17	3.84	0.21
10	GBD-10A	4-NO_2	-	+++	---	---	+++	7.76	-8.08	93.87	2.96	0.08
11	GBD-11A	4-F	-	---	---	---	---	8.46	-7.76	50.17	2.63	0.22
12	GFD-1A	-H	-H	---	---	---	---	6.39	-7.39	54.88	1.7	0.26
13	GFD-2A	-Cl	-H	---	---	---	---	6.93	-8.12	54.88	2.72	0.23
14	GFD-3A	-OCH_3	-H	---	---	---	---	6.25	-7.41	64.11	2.16	0.25
15	GFD-4A	-$N(CH_3)_2$	-H	---	+++	---	---	6.22	-7.42	58.12	1.06	0.14
16	GFD-5A	-NH_2	-H	---	---	---	---	5.65	-7.46	80.9	2.07	0.28
17	GFD-6A	-NH_2	-NH_2	---	---	---	---	4.97	-7.54	106.9	2.0	0.31

Table.3 Selected Molecular properties of 2,4,6-trisubstitutedpyrimidines (Molinspiration)



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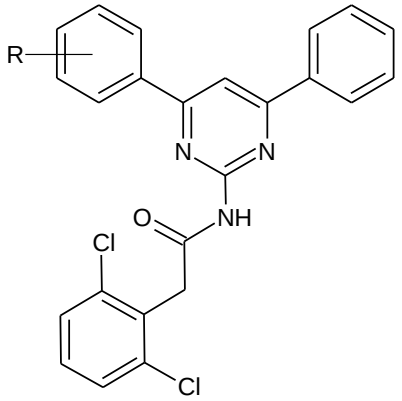
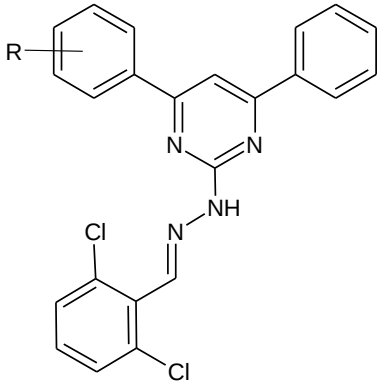


GFD 1 -14

S.No	Code	miLog*P*	TPSA	Number of atoms	Molecular weight	HBA	HBD	LRO5 violation	Number of rotatable bond	Volume
1	GBD-1	6.47	50.17	29	419.31	4	1	1	5	352.69
2	GBD-2	7.15	50.17	30	453.76	4	1	1	5	366.23
3	GBD-3	7.76	50.17	31	488.20	4	1	1	5	379.76
4	GBD-4	7.56	50.17	30	545.21	4	1	2	5	376.68
5	GBD-5	7.37	50.17	33	487.31	4	1	1	6	383.99
6	GBD-6	7.28	50.17	30	498.21	4	1	1	5	370.58
7	GBD-7	7.76	50.17	31	488.20	4	1	1	5	379.76
8	GBD-8	6.43	96	32	464.31	7	1	1	6	376.02
9	GFD-1	6.58	54.88	30	434.33	4	1	1	5	365.22
10	GFD-2	7.26	54.88	31	468.77	4	1	1	5	378.75
11	GFD-3	6.64	64.12	32	464.35	5	1	1	6	390.76
12	GFD-4	7.26	54.88	31	468.77	4	1	1	5	378.75
13	GFD-5	7.48	54.88	34	502.32	4	1	2	6	396.51
14	GFD-6	7.39	54.88	31	513.22	4	1	2	5	383.10
15	GFD-7	7.67	54.88	31	560.22	4	1	2	5	389.21
16	GFD-8	7.87	54.88	32	503.22	4	1	2	5	392.29
17	GFD-9	6.52	100.71	33	479.32	7	1	1	6	388.55
18	GFD-10	7.01	54.88	31	448.35	4	1	1	5	381.78
19	GFD-11	6.66	58.12	33	477.39	5	1	1	6	411.12
20	GFD-12	7.21	54.88	31	468.77	4	1	1	5	378.75
21	GFD-13	6.52	100.71	33	479.32	7	1	1	6	388.55
22	GFD-14	6.75	54.88	31	452.32	4	1	1	5	370.15

Table.4 Bioactivity scores of 2,4,6-trisubstituted pyrimidines (Molinspiration)



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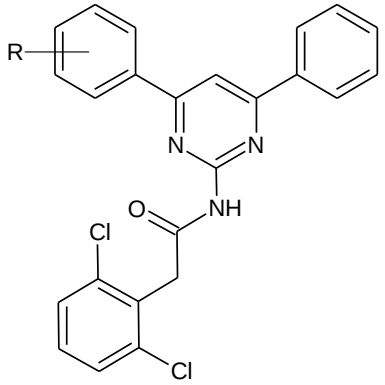

GFD 1 -14

S.No	Code	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	GBD-1	-0.21	-0.51	-0.08	-0.61	-0.56	-0.23
2	GBD-2	-0.21	-0.50	-0.07	-0.59	-0.54	-0.23
3	GBD-3	-0.21	-0.50	-0.07	-0.59	-0.54	-0.23
4	GBD-4	-0.20	-0.50	-0.06	-0.57	-0.60	-0.27
5	GBD-5	-0.14	-0.39	-0.03	-0.43	-0.47	-0.21
6	GBD-6	-0.29	-0.56	-0.11	-0.68	-0.64	-0.29
7	GBD-7	-0.71	-0.47	-0.04	-0.54	-0.50	-0.23
8	GBD-8	-0.32	-0.52	-0.19	-0.64	-0.63	-0.31
9	GFD-1	0.10	-0.12	0.17	-0.08	-0.17	-0.09
10	GFD-2	0.10	-0.12	0.16	-0.08	-0.16	-0.09
11	GFD-3	0.05	-0.18	0.13	-0.09	-0.21	-0.13
12	GFD-4	0.09	-0.13	0.17	-0.06	-0.18	-0.08
13	GFD-5	0.15	-0.04	0.21	0.06	-0.12	-0.07
14	GFD-6	0.00	-0.17	0.12	-0.18	-0.28	-0.14
15	GFD-7	0.17	-0.15	0.20	-0.09	-0.21	-0.10
16	GFD-8	0.09	-0.12	0.16	-0.06	-0.17	-0.08
17	GFD-9	-0.03	-0.16	0.06	-0.16	-0.27	-0.17
18	GFD-10	0.08	-0.17	0.15	-0.07	-0.20	-0.12
19	GFD-11	0.09	-0.14	0.19	-0.07	-0.19	-0.09
20	GFD-12	0.12	-0.11	0.20	-0.06	-0.14	-0.10
21	GFD-13	-0.03	-0.16	0.04	-0.16	-0.27	-0.18
22	GFD-14	0.10	-0.13	0.19	-0.07	-0.19	-0.11

Table.5 Predicted Biological Activity Spectrum of 2,4,6-trisubstitutedpyrimidines (PASS)

Guanabenz

Pa	Pi	Activity
0.962	0.000	CYP2C3 substrate
0.865	0.003	HMGCS2 expression enhancer
0.843	0.002	Monoamine uptake inhibitor
0.527	0.010	Antituberculosic
0.548	0.036	Insulysin inhibitor
0.521	0.031	Anticonvulsant
0,442	0.017	Cardioprotectant
0.434	0.019	Diabetic neuropathy treatment
0.409	0.003	α-adrenoreceptor agonist
0.424	0.032	Antiprotozoal (*Trypanosoma*)

Guanfacine

Pa	Pi	Activity
0.696	0.002	CYP2C3 substrate
0.248	0.183	HMGCS2 expression enhancer
0.375	0.028	Monoamine uptake inhibitor
0.000	0.000	Antituberculosic
0.549	0.036	Insulysin inhibitor
0.218	0.177	Anticonvulsant
0.397	0.027	Cardioprotectant
0.384	0.058	Diabetic neuropathy treatment
0.270	0.004	α-adrenoreceptor agonist
0.388	0.043	Antiprotozoal (*Trypanosoma*)

GBD-1

Pa	Pi	Activity
0.541	0.004	CYP2C3 substrate
0.970	0.001	HMGCS2 expression enhancer
0.460	0.013	Monoamine uptake inhibitor
0.403	0.030	Antituberculosic
0.577	0.029	Insulysin inhibitor
0.248	0.154	Anticonvulsant
0.220	0.160	Cardioprotectant
0.000	0.000	Diabetic neuropathy treatment
0.132	0.014	α-adrenoreceptor agonist
0.373	0.050	Antiprotozoal (*Trypanosoma*)

GBD-2

Pa	Pi	Activity
0.505	0.004	CYP2C3 substrate
0.969	0.001	HMGCS2 expression enhancer
0.469	0.012	Monoamine uptake inhibitor
0.405	0.030	Antituberculosic
0.557	0.034	Insulysin inhibitor
0.278	0.135	Anticonvulsant
0.218	0.163	Cardioprotectant
0.439	0.017	Diabetic neuropathy treatment
0.119	0.017	α-adrenoreceptor agonist
0.365	0.053	Antiprotozoal (*Trypanosoma*)

GBD-3

Pa	Pi	Activity
0.414	0.009	CYP2C3 substrate
0.964	0.001	HMGCS2 expression enhancer
0.476	0.011	Monoamine uptake inhibitor
0.373	0.040	Antituberculosic
0.461	0.064	Insulysin inhibitor
0.360	0.083	Anticonvulsant
0.000	0.000	Cardioprotectant
0.378	0.066	Diabetic neuropathy treatment
0.095	0.027	α-adrenoreceptor agonist
0.291	0.103	Antiprotozoal (*Trypanosoma*)

GBD-4

Pa	Pi	Activity
0.388	0.012	CYP2C3 substrate
0.959	0.001	HMGCS2 expression enhancer
0.292	0.067	Monoamine uptake inhibitor
0.454	0.019	Antituberculosic
0.291	0.145	Insulysin inhibitor
0.000	0.000	Anticonvulsant
0.268	0.111	Cardioprotectant
0.327	0.156	Diabetic neuropathy treatment
0.097	0.026	α-adrenoreceptor agonist
0.290	0.104	Antiprotozoal (*Trypanosoma*)

GBD-5

Pa	Pi	Activity
0.388	0.012	CYP2C3 substrate
0.959	0.001	HMGCS2 expression enhancer
0.292	0.067	Monoamine uptake inhibitor
0.454	0.019	Antituberculosic
0.291	0.145	Insulysin inhibitor
0.000	0.000	Anticonvulsant
0.268	0.111	Cardioprotectant
0.327	0.156	Diabetic neuropathy treatment
0.097	0.026	α-adrenoreceptor agonist
0.290	0.104	Antiprotozoal (*Trypanosoma*)

GBD-6

Pa	Pi	Activity
0.388	0.012	CYP2C3 substrate
0.964	0.001	HMGCS2 expression enhancer
0.292	0.067	Monoamine uptake inhibitor
0.457	0.018	Antituberculosic
0.487	0.054	Insulysin inhibitor
0.292	0.125	Anticonvulsant
0.000	0.000	Cardioprotectant
0.327	0.156	Diabetic neuropathy treatment
0.138	0.013	α-adrenoreceptor agonist
0.348	0.062	Antiprotozoal (*Trypanosoma*)

GBD-7

Pa	Pi	Activity
0.414	0.009	CYP2C3 substrate
0.964	0.001	HMGCS2 expression enhancer
0.476	0.011	Monoamine uptake inhibitor
0.373	0.040	Antituberculosic
0.461	0.064	Insulysin inhibitor
0.360	0.083	Anticonvulsant
0.000	0.000	Cardioprotectant
0.378	0.066	Diabetic neuropathy treatment

0.095	0.027	α-adrenoreceptor agonist
0.291	0.103	Antiprotozoal (*Trypanosoma*)

GBD-8

Pa	Pi	Activity
0.364	0.016	CYP2C3 substrate
0.965	0.001	HMGCS2 expression enhancer
0.442	0.015	Monoamine uptake inhibitor
0.525	0.010	Antituberculosic
0.292	0.145	Insulysin inhibitor
0.225	0.170	Anticonvulsant
0.248	0.129	Cardioprotectant
0.323	0,164	Diabetic neuropathy treatment
0.083	0.038	α-adrenoreceptor agonist
0.493	0.020	Antiprotozoal (*Trypanosoma*)

GFD-1

Pa	Pi	Activity
0.306	0.032	CYP2C3 substrate
0.301	0.112	HMGCS2 expression enhancer
0.209	0.136	Monoamine uptake inhibitor
0.000	0.000	Antituberculosic
0.292	0.145	Insulysin inhibitor
0.000	0.000	Anticonvulsant
0.000	0.000	Cardioprotectant
0.373	0.073	Diabetic neuropathy treatment
0.000	0.000	α-adrenoreceptor agonist
0.000	0.000	Antiprotozoal (*Trypanosoma*)

GFD-2

Pa	Pi	Activity
0.287	0.042	CYP2C3 substrate
0.315	0.099	HMGCS2 expression enhancer
0.215	0.130	Monoamine uptake inhibitor
0.000	0.000	Antituberculosic
0.275	0.160	Insulysin inhibitor
0.000	0.000	Anticonvulsant
0.000	0.000	Cardioprotectant
0.384	0.059	Diabetic neuropathy treatment
0.000	0.000	α-adrenoreceptor agonist
0.000	0.000	Antiprotozoal (*Trypanosoma*)

GFD-3

Pa	Pi	Activity
0.192	0.153	CYP2C3 substrate
0.294	0.119	HMGCS2 expression enhancer
0.000	0.000	Monoamine uptake inhibitor
0.000	0.000	Antituberculosic
0.278	0.157	Insulysin inhibitor
0.000	0.000	Anticonvulsant
0.000	0.000	Cardioprotectant
0.341	0.127	Diabetic neuropathy treatment
0.000	0.000	α-adrenoreceptor agonist
0.000	0.000	Antiprotozoal (*Trypanosoma*)

GFD-4

Pa	Pi	Activity
0.268	0.054	CYP2C3 substrate
0.298	0,115	HMGCS2 expression enhancer
0.188	0,163	Monoamine uptake inhibitor
0.000	0.000	Antituberculosic
0.271	0.164	Insulysin inhibitor
0.000	0.000	Anticonvulsant
0.000	0.000	Cardioprotectant
0.364	0.087	Diabetic neuropathy treatment
0.000	0.000	α-adrenoreceptor agonist
0.000	0.000	Antiprotozoal (*Trypanosoma*)

GFD-5

Pa	Pi	Activity
0.250	0.069	CYP2C3 substrate
0.334	0.086	HMGCS2 expression enhancer
0.000	0.000	Monoamine uptake inhibitor
0.000	0.000	Antituberculosic
0.000	0.000	Insulysin inhibitor
0.000	0.000	Anticonvulsant
0.000	0.000	Cardioprotectant
0.311	0.191	Diabetic neuropathy treatment
0.000	0.000	α-adrenoreceptor agonist
0.000	0.000	Antiprotozoal (*Trypanosoma*)

GFD-6

Pa	Pi	Activity
0.205	0.128	CYP2C3 substrate
0.561	0.021	HMGCS2 expression enhancer
0.000	0.000	Monoamine uptake inhibitor
0.243	0.0118	Antituberculosic
0.000	0.000	Insulysin inhibitor
0.000	0.000	Anticonvulsant
0.000	0.000	Cardioprotectant
0.000	0.000	Diabetic neuropathy treatment
0.000	0.000	α-adrenoreceptor agonist
0.000	0.000	Antiprotozoal (*Trypanosoma*)

GFD-7

Pa	Pi	Activity
0.205	0.128	CYP2C3 substrate
0.000	0.000	HMGCS2 expression enhancer
0.000	0.000	Monoamine uptake inhibitor
0.245	0.116	Antituberculosic
0.000	0.000	Insulysin inhibitor
0.000	0.000	Anticonvulsant
0.000	0.000	Cardioprotectant
0.000	0.000	Diabetic neuropathy treatment
0.000	0.000	α-adrenoreceptor agonist
0.000	0.000	Antiprotozoal (*Trypanosoma*)

GFD-8

Pa	Pi	Activity
0.251	0.068	CYP2C3 substrate
0.349	0.076	HMGCS2 expression enhancer
0.000	0.000	Monoamine uptake inhibitor
0.000	0.000	Antituberculosic
0.279	0.156	Insulysin inhibitor
0.200	0.200	Anticonvulsant
0.000	0,000	Cardioprotectant

0.343	0.122	Diabetic neuropathy treatment
0.000	0.000	α-adrenoreceptor agonist
0.000	0.000	Antiprotozoal (*Trypanosoma*)

GFD-9

Pa	Pi	Activity
0.192	0.154	CYP2C3 substrate
0.512	0.028	HMGCS2 expression enhancer
0.201	0.146	Monoamine uptake inhibitor
0.269	0.091	Antituberculosic
0.000	0.000	Insulysin inhibitor
0.000	0.000	Anticonvulsant
0.200	0.189	Cardioprotectant
0.000	0.000	Diabetic neuropathy treatment
0.000	0.000	α-adrenoreceptor agonist
0.273	0.122	Antiprotozoal (*Trypanosoma*)

GFD-10

Pa	Pi	Activity
0.281	0.045	CYP2C3 substrate
0.274	0.142	HMGCS2 expression enhancer
0.198	0.151	Monoamine uptake inhibitor
0.000	0.000	Antituberculosic
0.334	0.117	Insulysin inhibitor
0.000	0.000	Anticonvulsant
0.000	0.000	Cardioprotectant
0.326	0.158	Diabetic neuropathy treatment
0.000	0.000	α-adrenoreceptor agonist
0.000	0.000	Antiprotozoal (*Trypanosoma*)

GFD-11

Pa	Pi	Activity
0.247	0.073	CYP2C3 substrate
0.309	0.105	HMGCS2 expression enhancer
0.000	0.000	Monoamine uptake inhibitor
0.000	0.000	Antituberculosic
0.309	0.132	Insulysin inhibitor
0.000	0.000	Anticonvulsant
0.000	0.000	Cardioprotectant
0.351	0.108	Diabetic neuropathy treatment
0.000	0.000	α-adrenoreceptor agonist
0.000	0.000	Antiprotozoal (*Trypanosoma*)

GFD-12

Pa	Pi	Activity
0.268	0.054	CYP2C3 substrate
0.270	0.148	HMGCS2 expression enhancer
0.243	0.103	Monoamine uptake inhibitor
0.000	0.000	Antituberculosic
0.000	0.000	Insulysin inhibitor
0.206	0.192	Anticonvulsant
0.000	0.000	Cardioprotectant
0.332	0.144	Diabetic neuropathy treatment
0.000	0.000	α-adrenoreceptor agonist
0.000	0.000	Antiprotozoal (*Trypanosoma*)

GFD-13

Pa	Pi	Activity
0.205	0.128	CYP2C3 substrate
0.481	0.033	HMGCS2 expression enhancer
0.198	0.150	Monoamine uptake inhibitor
0.275	0.087	Antituberculosic
0.000	0.000	Insulysin inhibitor
0.000	0.000	Anticonvulsant
0.200	0.189	Cardioprotectant
0.000	0.000	Diabetic neuropathy treatment
0.000	0.000	α-adrenoreceptor agonist
0.255	0.143	Antiprotozoal (*Trypanosoma*)

GFD-14

Pa	Pi	Activity
0.235	0.086	CYP2C3 substrate
0.248	0.183	HMGCS2 expression enhancer
0.000	0.000	Monoamine uptake inhibitor
0.000	0.000	Antituberculosic
0.000	0.000	Insulysin inhibitor
0.000	0.000	Anticonvulsant
0.000	0.000	Cardioprotectant
0.380	0.064	Diabetic neuropathy treatment
0.000	0.000	α-adrenoreceptor agonist
0.000	0.000	Antiprotozoal (*Trypanosoma*)

balance of various molecular properties and structure features which determine whether a particular molecule is similar to the known drugs. These properties, mainly hydrophobicity, electronic distribution, hydrogen bonding characteristics, molecule size and flexibility and of course presence of various pharmacophoric features influence the behavior of molecule in a living organism, including bioavailability, transport properties, affinity to proteins, reactivity, toxicity, metabolic stability and many others.

Table 3 shows the selected molecular properties predicted using Molinspiration. All the derivatives were found to violate Lipinski's rule of 5 regarding clog *P* and a few regarding molecular weight. Number of hydrogen bond donors and acceptors were within the limit. The number of rotatable bonds indicated that all derivatives are flexible. Number of rotatable bonds is a simple topological parameter and has been shown to be a very good descriptor of oral bioavailability of drugs. Rotatable bond is defined as any single non-ring bond, bounded to nonterminal heavy (i.e., non-hydrogen) atom. TPSA is a very useful parameter for the prediction of drug transport properties and is defined as a sum of surfaces of polar atoms (usually oxygens, nitrogens and attached hydrogens) in a molecule. This parameter has been shown to correlate very well with the human intestinal absorption, Caco-2 monolayer's permeability, and blood-brain barrier penetration.

Molinspiration was also used to predict the bioactivity scores of each derivative (Table 4). Guanfacine derivatives showed enhanced kinase inhibitory and GPCR ligand activity than guanabenz derivatives.

Table 5 shows the biological activity spectra predicted using PASS computer program. PASS is based on a robust analysis of structure-activity relationships in a heterogeneous training set currently including about sixty thousand of biologically active compounds from different chemical series with about four thousand five hundred types of biological activity. The biological activity spectrum for a substance is a list of biological activity types for which the probability to be revealed (Pa) and the probability not to be revealed (Pi) are calculated. Pa and Pi values are independent and their values vary from 0.000-1.000.It is reasonable that only those types of activities may be revealed by the compound, where Pa>Pi and so they are put into the biological activity spectrum. If Pa>0.7, the compound is likely to reveal its activity in experiments, but in this case, the chance of being the analogue of the known pharmaceutical agent is high. If 0.5<Pa>0.7, the compound is likely to reveal this activity in experiments, but this is less and the compound is not so similar to the known pharmaceutical agent. If Pa <0.5, the compound is unlikely to reveal this activity in experiments, but if the presence of this activity is confirmed in the experiment, the compound might be a new chemical entity. Incorporation of guanabenz in to pyrimidine seems to be more beneficial than guanfacine regarding certain biological activities like antitubercular, anticonvulsant, cardioprotectant, and antiprotozoal (Trypanosoma) and α-adreno receptor agonist. But it is interesting to note that all the derivatives except GFD-7 were predicted to have antihyperlipidemic (HMGCS2 expression enhancer) activity.

CONCLUSION

From this study, it can be concluded that all the title molecules except GBD-10A and GFD-4A were predicted to be safe regarding mutagenicity, tumorogenicity, irritant effect and effect on reproductive system. All molecules possessed significant lipophilicity, molecular flexibility, drug score, drug-likeness and bioactivity score. Further studies including Synthesis, evaluation of biological activity, QSAR and Molecular modeling are necessary to establish their efficacy as bioactive agents.

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