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ADME-Toxpredictions of 3-benzimidazol-1-yl-1-(4-phenyl piperazine -1-yl) propan-1-one and their derivatives

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Abstract

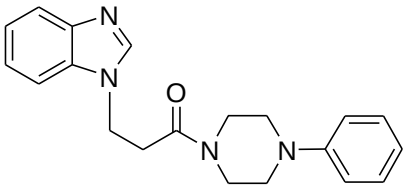
A novel approach introduces early, parallel evaluation of efficacy and biopharmaceutical Properties of drug candidates. Knowledge regarding pharmacokinetics, toxicity would be helpful for producing an effective drug so in early stage of drug development ADMET properties are to be considered. Toxicity determinations of chemicals are essential to recognise deleterious effects on humans, animals, plants, or the environment. Insilco models are used for prediction of ADMET properties for reduction of time, costs and animal experiments. The objective of this study was to obtain drug likeness and low toxicity of 3-benzimidazol-1-yl-1-(4-phenylpiperazine -1-yl) propan-1-one. The 2D structures were generated using the chemdraw application. The Swiss ADME, PkCSM, Lazar and Protox applications were used to predict pharmacokinetics, toxicity properties, and end point carcinogenicity. Compounds are adept to break through the BBB except compound B to affect the CNS and they are predicted for the enzymes of the cytochrome P450. They are predicted to be substrates for the P-gp protein and showing good oral bioavailability. The investigated compounds reveal that carcinogenic potential and hepatotoxicity.

Keywords: Benzimidazole, ADME, Toxicity, Swiss ADME, Boiled egg PkCSM, Lazar.

Introduction

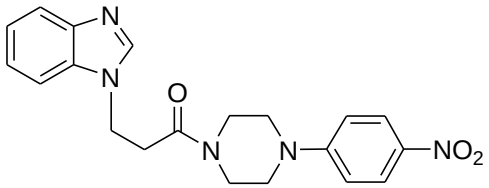
A new strategy to introduce early, parallel evaluation of efficacy and biopharmaceutical Properties of drug candidates. Study of terminated projects discovered that the primary cause for drug failure in the development phase was the poor pharmacokinetic and ADMET properties rather than unacceptableefficacy[1]. In the early stage of drug development ADMET properties are to be considered and it leads to an enormous reduction of number of compounds that failed in clinical trials due to poor ADMET. Pharmacokinetic parameters such as determination of time that drug molecule remains in the blood stream and also determining the binding efficiency with the target protein in the body can be ascertained through ADME. To reduce non-success rate at early stages of drug discovery comprehensive studies of ADMET processes, evaluation of efficiency and biopharmaceutical properties of drug candidate are routinely carried out. ADMET-related research can economize money and cut down much time and also avert even one clinical trial failure. The current experimental methods for ADMET evaluation require a lot of animal testing. When managing hundreds of compounds in the early stage of drug discovery which is animal testing is usually inadequate and are still costly and time-consuming. Several free and commercial computational tools for predicting ADMET properties are currently being used. Incorporation of prediction correctness in the predicted ADMET properties may significantly get better quality of compound choice[2-4]. At different stages of the drug discovery process various pharmacokinetic behaviours are predicted. The predicted data helps us to choose most effective compound with minimum toxicity and maximum efficiency thereby eliminating dissipation of money. By computing the lipophilicity and polarity of numerous molecules brain or intestinal access estimated permeation method (BOILED-Egg) is proposed as an accurate predictive model. The BOILED-Egg be able to functional in a variety of settings, at early stages of drug discovery to filter chemical libraries to evaluate various drug candidates[5,6]. The plan of in silico toxicity models is to complement the existing in vitro toxicity methods to predict toxicity effects of chemicals, thereby minimizing the time, the need of animal testing and cost associated with it[7].

The Benzimidazole scaffold represents the central core model for a huge range of pharmacologically active compounds, and has numerous pharmaceutical activities. We reported the design, molecular docking analysis, properties and synthesis of new benzimidazole 3-(1*H*-benzo [*d*] imidazol-1-yl) propane-1-ones[8,9]. Now we planned to determine the Toxicity of benzimidazole derivatives which is very obligatory to identify their detrimental effects on humans, animals, plants, or the environment. ADME covers the pharmacokinetic issues which are influential, whether a drug molecule will get to the target protein in the body, and how long it will stay in the blood stream.-SDD,./12`12345.



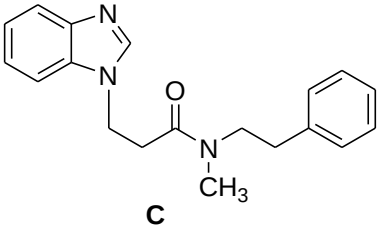
A

3-(1H-Benzo [d] imidazol-1-yl) -1-(4-phenylpiperizin-1-yl) propan-1-one



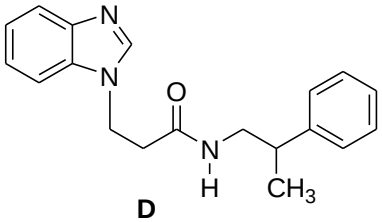
B

3-(1H-Benzo[d]imidazol-1-yl)-1-(4-(4-nitrophenyl) piperazin-1-yl)-propan-1-one



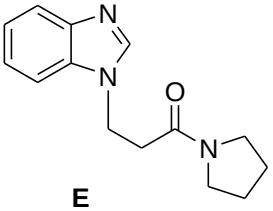
C

3-(1H-Benzo [d] imidazol-1-yl) -N-methyl-N-phenethylpropanamide



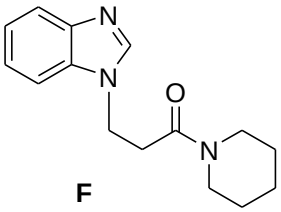
D

3-(1H-Benzo [d] imidazol-1-yl)-N-(2-pheneylpropyl) propanamide



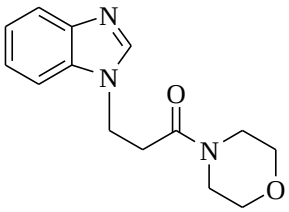
E

3-(1H-Benzo [d] imidazol-1-yl)-1-(pyrrolidin-1-yl) propan-1-one



F

3-(1H-Benzo[d]imidazol-1-yl)-1-(piperidin-1-yl) propan-1-one



G

3-(1H-Benzo[d]imidazol-1-yl)-1-morpholinopropan-1-one

Figure-1: Structures of 3-(1*H*-Benzo [*d*] imidazol-1-yl) -1-(4-phenylpiperizin-1-yl) propan-1-one.

Materials and methods

Exhaustive literature is abundant in computational methods available for predicting ADMET properties. We have selected free handy online computational tools, Swiss ADME, PkCSM, Lazar and Protox for our study. These tools were continuously updated, robust and their correctness of predictions is higher than 70 %. PkCSM, is a user-friendly web interface predict their pharmacokinetic and toxicity properties[10].

The Swiss ADME web tool is accessible and also computation of key physicochemical, pharmacokinetic, drug-like and related parameters for one or multiple molecules. The Bioavailability Radar enables a first glance at the drug-likeness of a molecule. Six physicochemical properties are taken into account: lipophilicity, size, polarity, solubility, flexibility and saturation. The pink area represents the optimal range for each property. The graphical output of Swiss ADME consists of the BOILED-Egg directly implemented to predict passive diffusion through HIA and BBB by position in a WLOGP-*versus*-TPSA physicochemical space. The possibility to visualize the position of the molecules between the different BOILED-Egg compartments and their propensity of being substrate of P-gp by coloured points: blue for substrate (PGP+) and red for non-substrate (PGP−)[5].

These models are in accordance by refine the recognized easy procedure giving PSA thresholds for BBB penetration.

ProTox-II and Lazar: The ProTox-II web servercan create a toxicity prediction. The prediction scheme is classified into different levels of toxicity such as oral toxicity, hepatotoxicity, toxicological endpoints (such as mutagen city, carcinotoxicity, cytotoxicity and immunotoxicity (B cell growth inhibition), toxicological pathways (AOPs) and toxicity targets thereby providing insights into the possible molecular mechanism behind such toxic response[7,11,14].

Results and discussion

Swiss ADME, PkCSM Results: ADMET profiles of 3-(1*H*-benzo [*d*] imidazol-1-yl) propane-1-ones have been obtained using Swiss ADME web tool and PkCSM Data presented in Tables 2 and 3.

Swiss ADME predictions on passive human gastrointestinal absorption (GI), blood-brain barrier (BBB) permeation, skin penetration coefficient, substrate or non-substrate of the permeability glycoprotein (P-gp), interaction of molecules with five major isoforms of the human cytochrome P450 enzymesare involved in the metabolism of several endogenous and exogenous compounds.

Table-1: Predictions of Molar Refractivity, Total Polar Surface Area and Log p Values.

Molecule	Canonical SMILES	MR	TPSA	iLOGP	XLOGP3	WLOGP	MLOGP
Molecule 1	O=C(N1CCN(CC1)c1ccccc1)CCn1cnc2c1cccc2	106.59	41.37	2.72	2.4	2.01	2.29
Molecule 2	O=C(N1CCN(CC1)c1ccc(cc1) N(=O)=O)CCn1cnc2c1cccc2	115.41	87.19	2.52	2.23	2.45	1.3
Molecule 3	CN(C(=O)CCn1cnc2c1cccc2) CCc1ccccc1	92.61	38.13	2.69	2.76	3.13	2.62
Molecule 4	O=C(CCn1cnc2c1cccc2) NCC(c1ccccc1)C	92.52	46.92	2.79	2.91	3.35	2.62
Molecule 5	O=C(N1CCCC1) CCn1cnc2c1cccc2	74.73	38.13	2.39	1.29	1.67	1.64
Molecule 6	O=C(N1CCCCC1) CCn1cnc2c1cccc2	79.54	38.13	2.4	1.65	2.06	1.89
Molecule 7	O=C(N1CCOCC1) CCn1cnc2c1cccc2	75.82	47.36	2.28	0.43	0.9	0.81

Table-2: Solubility predictions.

Molecule	Silicos-IT Log P	Consensus Log P	ESOL Log S	ESOL Solubility (mg/ml)	ESOL Solubility (mol/l)	ESOL	Log S	Solubility (mg/ml)
Molecule A	2.13	2.31	-3.54	9.66E-02	2.89E-04	Soluble	-2.91	4.11E-01
Molecule B	0.34	1.77	-3.6	9.58E-02	2.53E-04	Soluble	-3.7	7.64E-02
Molecule C	3	2.84	-3.51	9.60E-02	3.12E-04	Soluble	-3.22	1.87E-01
Molecule D	3.27	2.99	-3.6	7.73E-02	2.51E-04	Soluble	-3.56	8.54E-02
Molecule E	1.86	1.77	-2.27	1.32E+00	5.41E-03	Soluble	-1.69	4.96E+00
Molecule F	2.1	2.02	-2.56	7.06E-01	2.74E-03	Soluble	-2.06	2.22E+00
Molecule G	1.47	1.18	-1.81	4.06E+00	1.57E-02	Very soluble	-0.99	2.64E+01

Table-3: Gastro Intestinal absorption, Blood Brain Barrier Permeability and Metabolism.

Molecule	GI absorption	BBB per meant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
A	High	Yes	Yes	No	No	Yes	Yes	Yes
B	High	No	No	No	Yes	Yes	Yes	Yes
C	High	Yes	No	Yes	Yes	Yes	Yes	Yes
D	High	Yes	No	Yes	Yes	Yes	Yes	Yes
E	High	Yes	Yes	No	Yes	No	No	No
F	High	Yes	Yes	No	Yes	No	Yes	No
G	High	Yes	Yes	No	No	No	No	No

Table-4: Bioavailability Score, Lipinski Rule, Veber Rule, Ghose Rule predictions.

Molecule	Bioavailability Score	PAINS #alerts	Brenk #alerts	Lead likeness #violations	Synthetic Accessibility	Lipinski #violations	Ghose #violations	Veber #violations
A	0.55	0	0	0	2.45	0	0	0
B	0.55	1	1	1	2.63	0	0	0
C	0.55	0	0	0	2.2	0	0	0
D	0.55	0	0	0	2.65	0	0	0
E	0.55	0	0	1	1.89	0	0	0
F	0.55	0	0	0	1.99	0	0	0
G	0.55	0	0	0	2.1	0	0	0

Prediction of blood–brain barrier (BBB) penetration: In function to the position of the molecules in the WLOGP-*versus*-TPSA passive gastrointestinal absorption (HIA) and blood brain penetration (BBB) of compounds can be referred from The BOILED-Egg.

The white region represents compounds with high probability of passive absorption from gastrointestinal tract, and the yellow region (yolk) is for high probability of compounds to cross blood brain barrier.

In addition the points are coloured in blue if predicted as actively effluxes by P-gp (PGP+) and in red if predicted as non-substrate of P-gp (PGP−). Only Compound 2(B) is predicted well-absorbed but not accessing the brain and PGP+ (blue dot), and Compound A,C,D,E,F and G are predicted as brain-penetrant (in the yolk) and not subject to active efflux (red dot). The Bioavailability Radar enables a first glance at the drug-likeness of a molecule. All compounds are in a range of optimal values as shown in the pink area.

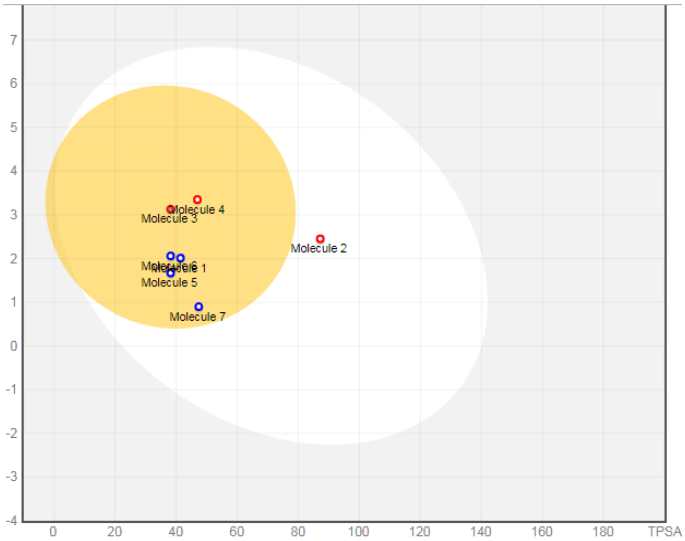


Figure-2: Molecules,1,3,4,5,6,7 (compound A,C,D,E,F and G) are predicted as brain-penetrant (in the yolk).

Toxicity predictions: Toxicity predictions are shown in Table-5, 6, 7. Compound B is hepatotoxic and carcinogenic. Probabilities are B-80% and D-91%. Compound E Toxicity Targets were identified with average similarity of known ligands, 80.26% of Amine Oxidase a, 70.45% of Dopamine receptor D_3 78.21%, Opioid Receptors MU. Compound F Toxicity Targets were identified with average similarity of known ligands, 85.33% of Amine Oxidase A, 74.71% of Dopamine receptor D_3,83.12% Opioid Receptors MU.

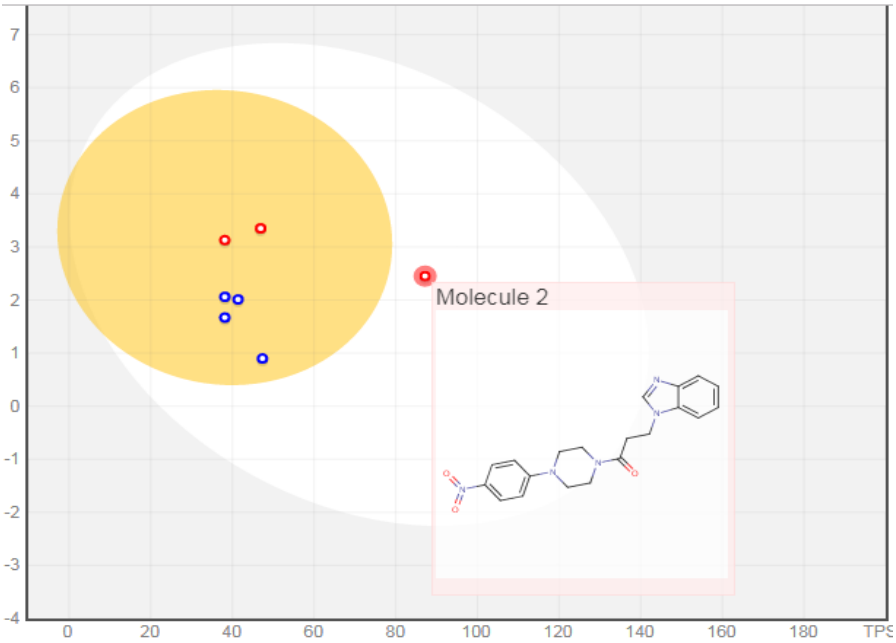


Figure-3: Molecule 2 - (B) is predicted well-absorbed but not accessing the brain and PGP+ (Red dot).

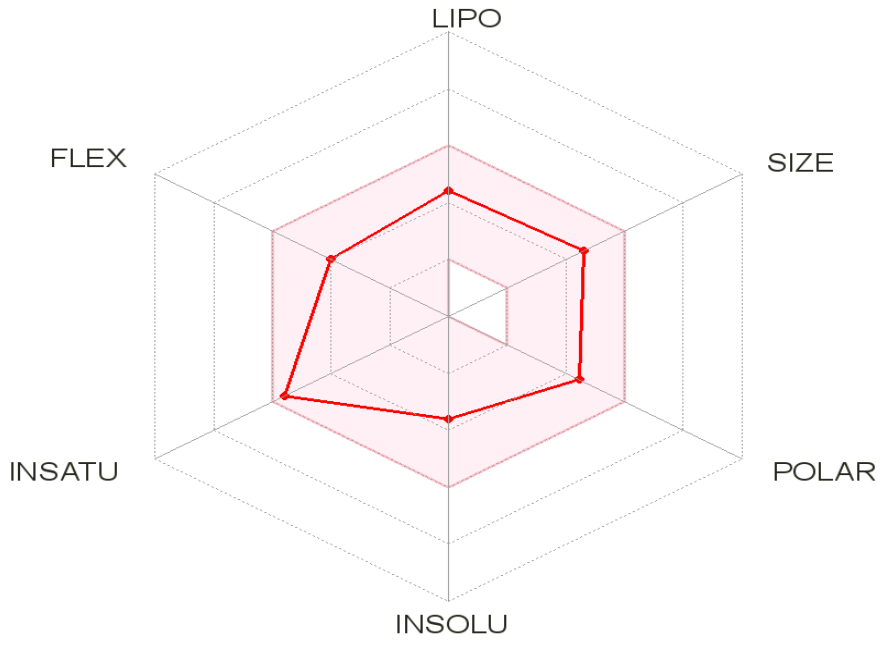


Figure-4: Bioavailability Radar.

Table-5: Toxicity predictions of Molecules A, B, C.

A. Predicted LD50: 500mg/kg, Predicted Toxicity Class (PTC): 4, Average similarity (AS): 60.05%, Prediction accuracy (PA): 68.07%				Predicted LD50: 500mg/kg, PTC; 4., AS: 56.68%, PA: 67.38%		Predicted LD50: 300mg/kg, PTC: 3, AS: 61.98%, PA: 68.07%	
Classification	Target	Prediction	Probability	Prediction	Probability	Prediction	Probability
Organ toxicity	Hepatotoxicity	Non active	0.83	Non active	0.73	Non active	0.9
Tox-EP	Non carcinogenicity	Active	0.64	Active	0.8	Non active	0.69
Tox-EP	Immunotoxicity	Non active	0.99	Non active	0.92	Non active	0.99
Tox-EP	Mutagenicity	Non active	0.6	Active	0.91	Non active	0.52
Tox-EP	Cytotoxicity	Non active	0.84	Non active	0.6	Non active	0.72
Tox21- NRSP	AhR	Non active	0.65	Non active	0.79	Non active	0.79
Tox21- NRSP	AR	Non active	0.91	Non active	0.96	Non active	0.93
Tox21- NRSP	(AR-LBD	Non active	0.95	Non active	0.94	Non active	0.97
Tox21- NRSP	Aromatase	Non active	0.86	Non active	0.95	Non active	0.88
Tox21- NRSP	ER	Non active	0.69	Non active	0.76	Non active	0.89
Tox21- NRSP	ER-LBD	Non active	0.99	Non active	0.98	Non active	0.99
Tox21- NRSP	PPAR-Gamma	Non active	0.99	Non active	0.98	Non active	0.98
Tox21-SRP	Nuclear factor (erythroid-derived 2) -like 2/antioxidant responsive element (nrf2/ARE)	Non active	0.94	Non active	0.9	Non active	0.97
Tox21-SRP	HSE	Non active	0.94	Non active	0.9	Non active	0.97
Tox21-SRP	MMP	Non active	0.94	Non active	0.57	Non active	0.93
Tox21-SRP	Phosphoprotein (Tumour Suppressor) p53	Non active	0.89	Non active	0.86	Non active	0.89
Tox21-SRP	ATAD5	Non active	0.85	Non active	0.86	Non active	0.98

Table-6: Toxicity predictions of Molecules D, E, F, G

Predicted LD50: 300mg/kg, PTC: 3, AS: 61.98%, PA: 68.07%				Predicted LD50: 281mg/kg, AS: 57.02%, PA: 67.38%, PTC: 3		Predicted LD50: 500mg/kg, AS: 58.29%, PA: 67.38%, PTC: 4		Predicted LD50: 300mg/kg, AS: 59.43%, PA: 67.38%, PTC: 3	
Classification	Target	Prediction	Probability	Prediction	Probability	Prediction	Probability	Prediction	Probability
OT	Hepatotoxicity	Non active	0.89	Non active	0.9	Non active	0.9	Non active	0.87
Tox-EP	Carcinogenicity	Non active	0.68	Non active	0.71	Non active	0.72	Non active	0.65
Tox-EP	Immunotoxicity	Non active	0.99	Non active	0.99	Non active	0.99	Non active	0.99
Tox-EP	Mutagenicity	Non active	0.5	Non active	0.58	Non active	0.57	Non active	0.59
Tox-EP	Cytotoxicity	Non active	0.81	Non active	0.82	Non active	0.85	Non active	0.84
Tox21-NRSP	AhR	Non active	0.65	Non active	0.77	Non active	0.72	Non active	0.68
Tox-21NRSP	AR	Non active	0.95	Non active	0.96	Non active	0.96	Non active	0.97
Tox21-NRSP	AR-LBD	Non active	0.96	Non active	0.97	Non active	0.97	Non active	0.98
Tox21-NRSP	Aromatase	Non active	0.83	Non active	0.9	Non active	0.83	Non active	0.9
Tox21-NRSP	ER	Non active	0.83	Non active	0.86	Non active	0.84	Non active	0.83
Tox21-NRSP	ER-LBD	Non active	0.98	Non active	0.99	Non active	0.99	Non active	0.99
Tox21-NRSP	PPAR-Gamma	Non active	0.94	Non active	0.98	Non active	0.99	Non active	0.99
Tox21-SRP	Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)	Non active	0.96	Non active	0.89	Non active	0.88	Non active	0.91
Tox21-SRP	(HSE)	Non active	0.96	Non active	0.89	Non active	0.88	Non active	0.91
Tox21-SRP	(MMP)	Non active	0.9	Non active	0.94	Non active	0.94	Non active	0.94
Tox21-SRP	Phosphoprotein (Tumour Suppressor) p53	Non active	0.9	Non active	0.91	Non active	0.92	Non active	0.94
Tox21-SRP	(ATAD5)	Non active	0.94	Non active	0.96	Non active	0.96	Non active	0.87

Organ toxicity (OT), Toxicity end point (Tox-EP) Nuclear receptor signalling pathways (NRSP), Stress response pathways (SRP), Aryl hydrocarbon Receptor (AhR), Aryl hydrocarbon Receptor (AhR), Androgen Receptor Ligand Binding Domain (AR-LBD), Estrogen Receptor Alpha (ER), Estrogen Receptor Ligand Binding Domain (ER-LBD), Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma), Heat shock factor response element (HSE), Mitochondrial Membrane Potential (MMP), ATPase family AAA domain-containing protein5 (ATAD5)

Table-7: Toxicity predictions of Molecules.

Toxicity	A	B	C	D	E	F	G
AMES toxicity	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Max.tolerated dose (human) (mg/kg/day)	0.252 log	0.284 log	0.379 log	0.415 log	0.249 log	0.242 log	No
hERG I inhibitor	Yes	Yes	Yes	Yes	No	No	No
hERG II inhibitor	Yes	Yes	Yes	Yes	No	No	No
Oral Rat Acute Toxicity (LD50) (mol/kg)	2.823	3	2.568	2.376	2.845	2.869	2.763
Oral Rat Chronic Toxicity (LOAEL) (mg/kg_bw/day)	1.482 log	1.386 log	1.66 log	1.738 log	0.879 log	0.833 log	1.528 log
Hepatotoxicity	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Skin Sensitisation	No	No	No	No	No	No	No
T. Pyriformis Toxicity (ug/L)	0.285 log	0.285 log	0.285 log	0.285 log	0.285 log	0.285 log	0.285 log
Minnow toxicity(mM)	0.115	0.421	0.394	0.536	0.771	0.654	1.083

Conclusion

The title compounds are capable to penetrate the blood brain barrier except compound B and to have an effect on the central nervous system and they are predicted for the enzymes of the cytochrome P450. They are predicted to be substrates for P-gp protein and showing good oral bioavailability. The investigated compounds reveal that carcinogenic potential and hepatotoxicity.

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