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Research Article

ADME SCREENING OF NOVEL 1,4-DIHYDROPYRIDINE DERIVATIVES

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ABSTRACT

ADME screening of N^3, N^5-diphenyl-1,4-dihydropyridine-3,5-dicarbohydrazides [2A-2D'] and 2,6-dimethyl-1,4-dihydropyridine-3,5-yl-bis[carbonyl-2-(phenyl)]pyrazolidine-3,5-diones] [3A-3D'] was carried out. Absorption, Distribution, Metabolism and Excretion properties along with Human Intestinal Absorption (HIA) and Blood Brain Barrier (BBB) plots were studied. The profiles of these compounds were generated by using DS Accord for Excel (ADME screening) .The chemical structure of the derivatives were given as an input and a desired predictor was selected. DS Accord for Excel provides methods for assessing the disposition and potential toxicity of a ligand within an organism. In addition, we can apply specific rules to remove ligands that are not likely drug-like, unsuitable leads, etc. based on the presence or absence and frequency of certain chemical groups.

Keywords: 1,4-Dihydropyridine, Pyrazolidine-3,5-Diones, ADME screening, Accord for Excel.

INTRODUCTION

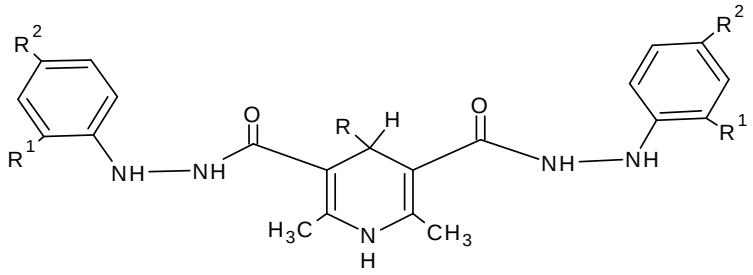
Absorption, Distribution, Metabolism and Excretion properties of molecules are most important in developing good lead molecules. DS Accord for Excel helps to compute and analyze ADME properties of the query chemicals. Various groups which are substituted on a molecule have a profound effect on the biological activity. Different biological as well as toxicological properties of molecules can be manipulated by a mere change of substituents[1]. Development of drugs through Drug design has brought a ground breaking change in the conventional method of drug synthesis and their biological, toxicological, physicochemical profile development. It has reduced the cost of synthesis and *invivo* studies which are carried out only after extensive study of different profiles using Computer Aided Drug Design (CADD). The rationale of this work is to focus mainly on the development of ADME profile, HIA and BBB plots for the derivatives containing 1, 4-Dihydropyridines and pyrazolidine-3,5-dione moieties(2A-2D')[2] and (3A-3D')[3].

MATERIALS AND METHODS[4,5]

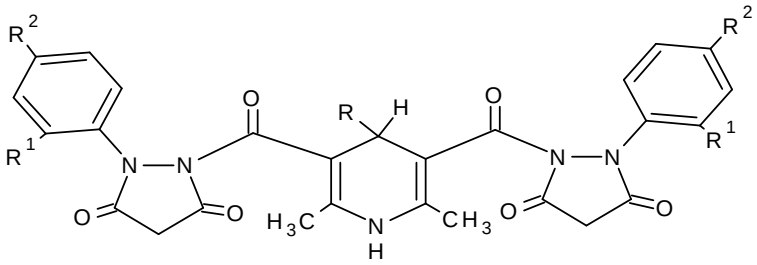
Computer aided ADME studies have been done by using Accord for Excel, Accelrys Discovery studio software. These studies are solely based on the chemical structure of the molecule. ADME-Aqueous solubility model uses linear regression to predict the solubility of each compound in water at 25 ^{o}C. Blood Brain Barrier (BBB) model predicts blood-brain penetration after oral administration which contains a quantitative linear regression model for the prediction of blood-brain penetration, as well as 95% and 99% confidence ellipses in the ADME_PSA_2D, ADME_AlogP98 plane. They were derived from over 800 compounds that are known to enter the CNS after oral administration. The cytochrome P450 2D6 model predicts CYP2D6 enzyme inhibition using 2D chemical structure as input. The model was developed from known CYP2D6 inhibition data on a diverse set of 100 compounds. Human Intestinal Absorption (HIA) model predicts HIA after oral administration. Intestinal absorption is defined as a percentage absorbed rather than as a

ratio of concentrations . A well-absorbed compound is one that is absorbed at least 90% into the bloodstream in humans. The intestinal absorption model includes 95% and 99% confidence ellipses in the ADME_PSA_2D, ADME_AlogP98 plane.

The following structures are drawn using DS Viewer Pro Suite software and are appended into Accord for Excel and the parameters have been calculated. Substitutions for the derivatives are given in Table 1.



2A-2D'



3A-3D'

RESULTS AND DISCUSSION

16 derivatives (2A-2D' and 3A-3D') were subjected to extensive ADME screening, their HIA and BBB plots were developed. A LogP values of all the 16 derivatives is more than 1 and Fast Polar Surface Area is above 100 for all the compounds other than 2A, 2C.Results in Table 2.

Categorical HIA level of derivatives 2A, 2C, 2C', 3A, 3C, 3C' has shown zero prediction level indicating good absorption. Derivatives 2A', 2B', 3A', 3B' has shown prediction level 2 indicating poor intestinal absorption. Derivatives 2B, 2D, 2D', 3B, 3D, 3D' has shown prediction level 3 indicating very poor intestinal absorption. Results in Table 2.

In HIA plot, compounds 2A, 2B, 2C, 3B, 3B' have fallen inside the 99% confidence ellipse, where as the remaining compounds have fallen outside the 99% ellipse (undefined). Hence the compounds 2a, 2B, 2C, 3B and 3B' are expected to posses good Human Intestinal Absorption when compared to other compounds of the class. Figures 1 and 3.

BBB plot has shown that all the derivatives have fallen inside the 99% ellipse (undefined). Hence these derivatives may be able to penetrate the Blood Brain Barrier and the chances of CNS side effects are relatively more. On the contrary, as all these compounds exhibit anti-microbial activity [2, 3], they can be used to treat CNS infections like meningitis, encephalitis etc. Results in Table 2 and figures 2 and 4.

ADME aqueous solubility logarithmic level of most of the synthesized compounds was found to be more than 1 or 0 which indicates better aqueous solubility. Results in Table 3

All the derivatives has shown good Plasma Protein Binding. Among all the derivatives 2A' and 3A' has shown greater than 95% and rest others of the class has shown 90%. All the compounda are predicted to bind to carrier proteins in the blood level of 90-95%. Hence there is high probability that these compounds can reach the desired targets. Results in Table 3

Derivative 2A' is likely to inhibit CytochromeP, Where as all the other derivatives are unlikely to inhibit.So except 2A', all the derivatives are non-inhibitors of CytochromeP.Results in Table 4

Hepato toxicity probability values of derivatives lie in the range of 0.83-0.95. Hence all the derivatives are likely to cause dose dependant liver injuries. So, further studies are necessary to determine the hepatotoxic dose levels. Results in Table 4.

CONCLUSION

From the developed ADME profile, HIA and BBB plots, it is evident that the derivatives

possess optimum to good values for chosen predictors. Most of the drugs showed good logarithmic and categorical values of aqueous solubility, fast polar surface area, plasma protein binding. From the obtained data and interpreted results, it is evident that these derivatives are likely hepatotoxic, but the compounds can be further explored to arrive at better molecules. As the derivatives possess good plasma protein binding and are non-inhibitors of CytochromeP, they can reach desired targets. All the derivatives penetrate blood brain barrier. Hence, these can be used for the treatment of CNS infections like meningitis, encephalitis etc.

ACKNOWLEDGEMENTS

I am grateful to express my sincere thanks to the GEF (medical), the Management and staff of M.S.Ramaiah College of Pharmacy, Bangalore for providing all the facilities and encouragement for carrying out the work.

Table 1: Set of compounds for ADME screening

Compound	R^1	R^2	R
2A	H	H	H
2B	NO_2	NO_2	H
2C	H	Cl	H
2D	H	NO_2	H
2A'	H	H	C_6H_4OH
2B'	NO^2	NO_2	C_6H_4OH
2C'	H	Cl	C_6H_4OH
2D'	H	NO_2	C_6H_4OH
3A	H	H	H
3B	NO_2	NO_2	H
3C	H	Cl	H
3D	H	NO_2	H
3A'	H	H	C_6H_4OH
3B'	NO^2	NO_2	C_6H_4OH
3C'	H	Cl	C_6H_4OH
3D'	H	NO_2	C_6H_4OH

Table 2: Computer aided ADME screening

Compound	FST. ALOGP98	ADME.2D. FPSA	ADME.HIA. LEV	ADME.BBB.LOG	ADME.BBB.LOG.LEV
2A	2.2912	98.652	0	-100	3
2B	2.0687	269.94	3	-100	4
2C	3.82	98.65	0	-100	4
2D	2.28	184.29	3	-100	4
2A'	3.533	119.46	2	-100	4
2B'	3.110	290.76	2	-100	4
2C'	4.862	109.43	0	-100	4
2D'	3.32	205.11	3	-100	4
3A	2.229	130.024	0	-100	4
3B	1.806	301.317	3	-100	4
3C	3.558	130.024	0	-100	4
3D	2.018	215.67	3	-100	4
3A'	3.271	150.84	2	-100	4
3B'	2.849	322.13	2	-100	4
3C'	4.600	150.840	0	-100	4
3D'	3.06	236.486	3	-100	4

ADME: Absorption, Distribution, Metabolism, Excretion
FST ALOGP: Atom based Logp from fast desc
FPSA: Fast polar surface area
HIA.LEV: Categorical Human Intestinal Absorption level
BBB.LOG: Logarithmic value of Blood Brain Barrier
BBB.LOG.LEV: Categorical base 10 Logarithm of Blood Brain Barrier

Table 3: Computer aided ADME screening

Compound	ADME. AQ.SOL. LOG	ADME. AQ.SOL. LOG.LEV	ADME.PROT.BIND.LEV	ADME.PROT.BIND.LEV. LOG	PROT.BIND.LEV Description
2A	-3.067	3	0	0	>= 90%
2B	-5.637	2	0	0	>= 90%
2C	-5.076	2	0	1	>= 90%
2D	-4.379	2	0	0	>= 90%
2A'	-3.993	3	2	1	>= 95%
2B'	-6.762	1	0	0	>= 90%
2C'	-6.089	1	1	0	>= 90%
2D'	-5.38	2	0	0	>= 90%
3A	-4.051	2	0	0	>= 90%
3B	-3.317	3	0	0	>= 90%
3C	-5.281	2	0	1	>= 90%
3D	-3.681	3	1	0	>= 90%
3A'	-4.967	2	2	0	>= 95%
3B'	-4.161	2	0	0	>= 90%
3C'	-6.01	1	2	0	>= 90%
3D'	-4.406	2	0	0	>= 90%

AQ.SOL.LOG: Base 10 logarithm of molar solubility as predicted by the regression
AQ.SOL.LOG.LEV: Categorical logarithmic solubility level
PROT.BIND.LEV: Categorical protein binding level
PROT.BIND.LEV.LOG: Base 10 logarithm of categorical protein binding level
PROT.BIND.LEV. Description: Categorical protein binding level description

Table 4: Computer aided ADME screening

Compound	ADME. CYP2D6	ADME. CYP2D6. PROB	CYP450 2D6 Level Description	ADME. HEPATO TOX	ADME. HEPATO TOX.PROB
2A	0	0.287	Non-inhibitor	1	0.841
2B	0	0.158	Non-inhibitor	1	0.8344
2C	0	0.227	Non-inhibitor	1	0.933
2D	0	0.168	Non-inhibitor	1	0.847
2A'	1	0.544	Non-inhibitor	1	0.907
2B'	0	0.089	Non-inhibitor	1	0.807
2C'	0	0.455	Non-inhibitor	1	0.953
2D'	0	0.198	Non-inhibitor	1	0.927
3A	0	0.267	Non-inhibitor	1	0.940
3B	0	0.138	Non-inhibitor	1	0.801
3C	0	0.198	Non-inhibitor	1	0.933
3D	0	0.198	Non-inhibitor	1	0.940
3A'	0	0.405	Non-inhibitor	1	0.973
3B'	0	0.059	Non-inhibitor	1	0.960
3C'	0	0.257	Non-inhibitor	1	0.966
3D'	0	0.168	Non-inhibitor	1	0.986

CYP2D6: 2 Dimensional Cytochrome P (unlikely to inhibit)
CYP2D6.PROB: Cytochrome probability (likely inhibition)
HEPATO TOX: hepatotoxicity
HAPATO TOX.PROB: Probability of hepatotoxicity

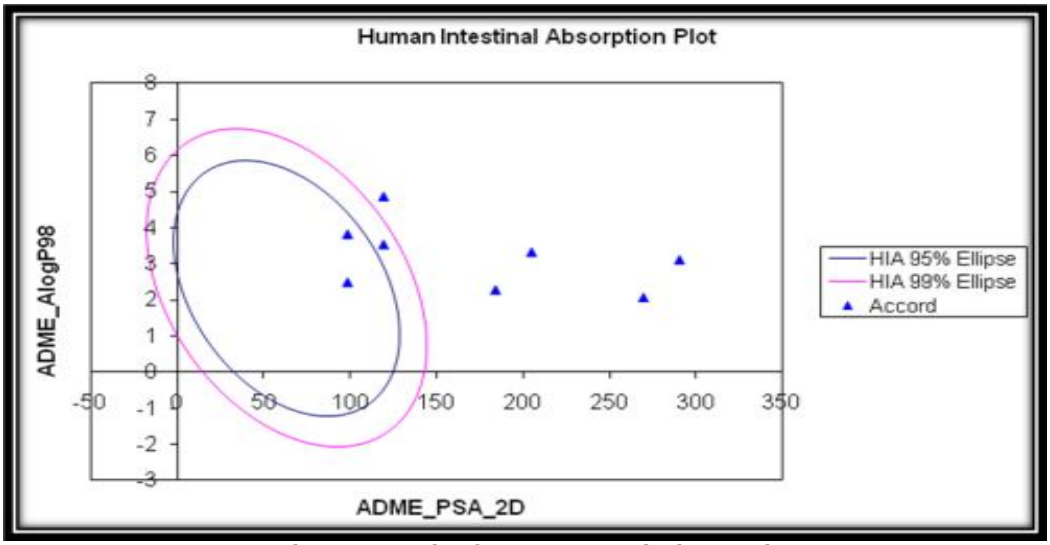


Fig. 1: HIA plot for compounds (2A-2D')

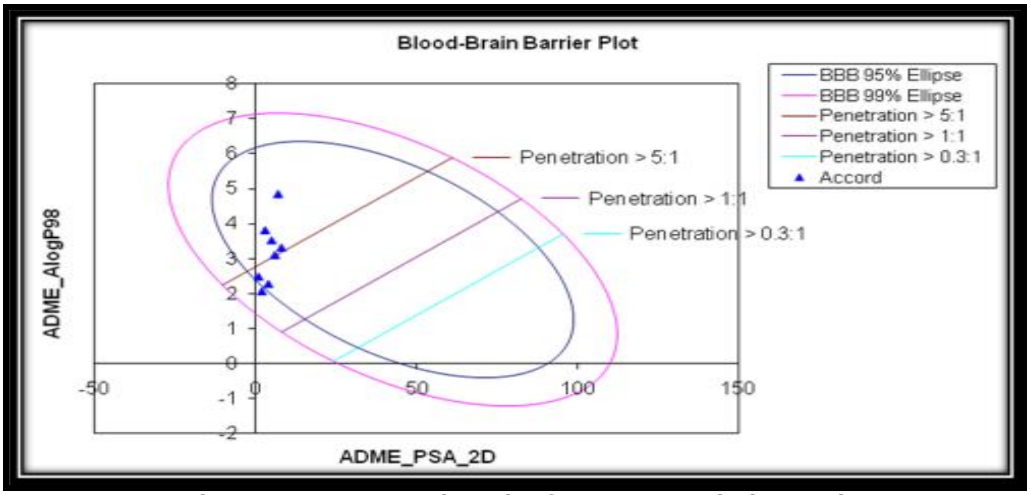


Fig. 2: BBB Penetration plot for compounds (2A-2D')

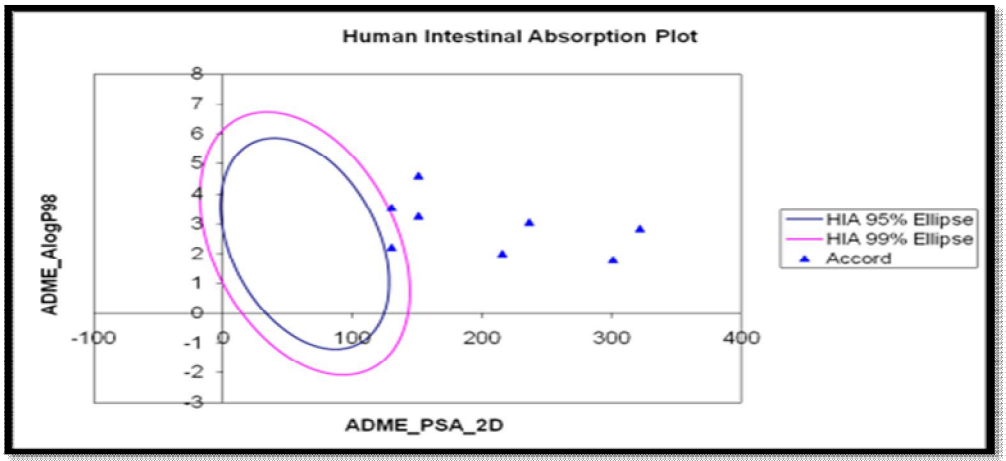


Fig. 3: HIA plot for compounds (3A-3D')

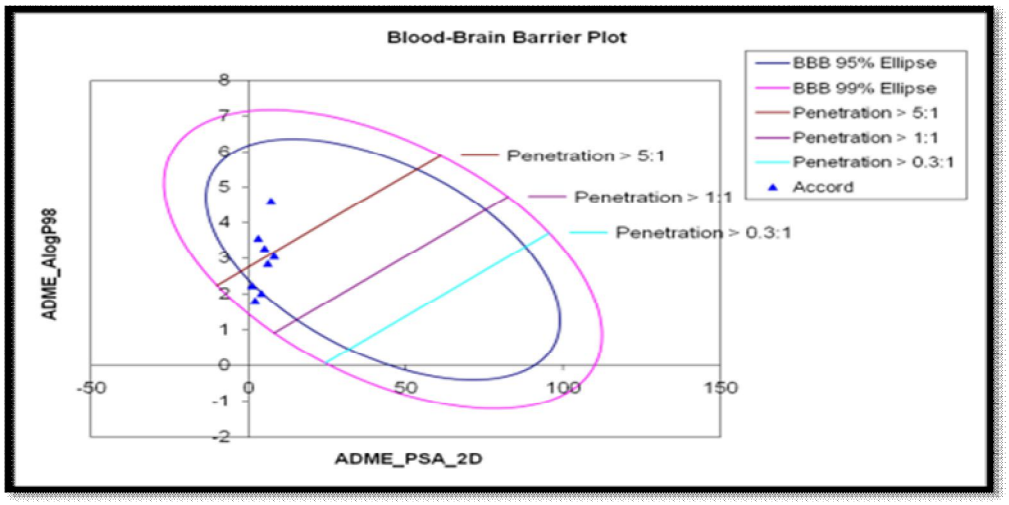


Fig. 4: BBB Penetration plot for compounds (3A-3D')

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