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Research Article

SCREENING OF NEWLY SYNTHESIZED 1,4-DIHYDROPYRIDINES FOR ORAL ACTIVITY

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ABSTRACT

For sixteen compounds of two sets, eight in each set, Lipinski parameters were calculated. Two sets are 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']. The chemical structures of the above mentioned derivatives were given as input and desired Lipinski parameters were selected. These studies were carried out using DS accord for excel (ADME screening) provided by Accelrys Discovery studio software. Parameters were calculated based on the chemical structure. From the results obtained, drugs which are likely to be Orally active can be identified. All the calculated parameters depend solely on the chemical structure of the derivatives and determine their oral activity. Thus providing a relationship between the structure and its activity.

Keywords: 1,4-Dihydropyridine, Pyrazolidine-3,5-Diones, Lipinski parameters, ADME screening.

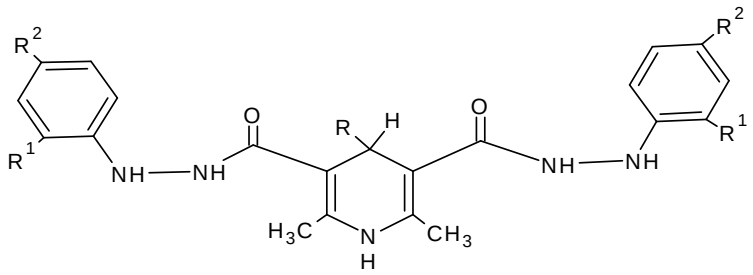
INTRODUCTION

1,4-dihydropyridines and their analogues have been known through many decades for treating a number of health conditions and possess varied activities like antibacterial, antifungal, antihypertensive, anticonvulsant, anti-inflammatory, anticancer [1-6] etc . Although there are many 1,4-dihydropyridine derivatives in existence for a variety of ailments, search for new block buster drugs is on wheels in order to reduce the side effects and for the better therapeutic efficacy. After investigating the compounds using drug design studies, they were selected for synthesis, which maximizes the presence of functional groups or features believed to be responsible for biological activity[7]. The overall objective is to find parameters from experiment or theory that, when substituted into one of the many forms of the equations along with biological activity for a series of molecules, gives a statistically significant correlation. This predictive element is undoubtedly the most exciting aspect of QSAR[8]. Using Accelrys drug design software, DS Accord for Excel, various Lipinski parameters were calculated. These parameters are known to 'evaluate drug likeness, or determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug in human' and this rule was formulated by Christopher A. Lipinski in 1997, based on the assumption that most of the medication drugs are relatively small and lipophilic molecules[9]. So totally sixteen derivatives from two sets, N^3, N^5-diphenyl-1,4-dihydropyridine-3,5-dicarbohydrazides [2A-2D'][10] and 2,6-dimethyl-1,4-dihydropyridine-3,5-yl-bis[carbonyl-2-(phenyl)]pyrazolidine-3,5-diones] [3A-3D'][11] were screened and their Lipinski parameters were obtained.

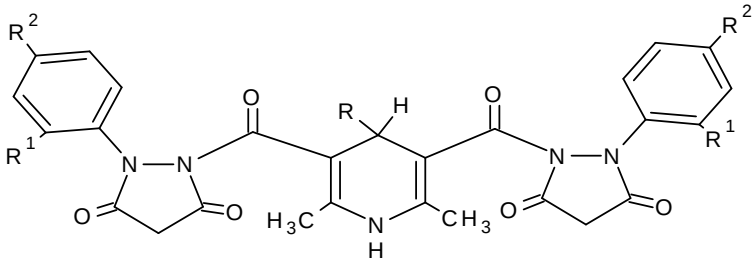
MATERIALS AND METHODS[8, 12]

Lipinski studies have been done by using DS Accord for Excel, Accelrys Discovery studio software. These studies are solely based on the chemical structure of the molecule.

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

Totally 16 derivatives of two sets (2A-2D') and (3A-3D') were extensively subjected to screening, to study their Lipinski parameters. The results are listed in table 2.

LogP values of all 16 derivatives are well below 5.6. So LogP parameter of all the derivatives obey Lipinski's rule and fall well within the range of -0.4 to +5.6.

Molar refractivity of derivatives 2A, 2C (chloro), 2D (nitro) is less than 130 and obey Lipinski's stated limit. Derivatives 2B (dinitro), 2A' (phenyl), 3A has molar refractivity's of 135, 136 and 131 respectively which is slightly above 130, stated by Lipinski. All the other derivatives fall well above 130 there by violating Lipinski's stated limit.

Polar surface area of 2A, 2C (chloro), 2A' (phenyl derivative), 2C' (chloro phenyl), 3A, 3C (chloro) lie well below 140 Å^2 and obey Lipinski's stated limit. Derivatives 3A' (phenyl),3C' (chloro phenyl) has polar surface area of 150 Å^2 which is slightly above the stipulated limit. Derivatives 2B, 2D, 2B', 2D', 3B, 3D, 3B', 3D' show values well greater than 140 Å^2 and do not adhere to the 140 limit stated by Lipinski.

Molecular weights of 2A, 2C (chloro), 2D (nitro), 2A' (phenyl) are below 500 Daltons and obey Lipinski's stated limit. Other derivatives of the class have molecular weights more than 500 Daltons and thus violates Lipinski's stated limit.

All the derivatives except 2A' (phenyl), 2B' (dinitro phenyl), 2C' (chloro phenyl), 2D' (nitro phenyl) has hydrogen bond donors, less than 5, there by obeys Lipinski's rule. Derivatives 2B (dinitro), 2B' (dinitro phenyl), 3B (dinitro), 3D (nitro), 3B' (dinitro phenyl), 3D' (nitro phenyl) has more than 10 hydrogen bond acceptors and violates Lipinski's limits and rest other derivatives of the class has less than 10 hydrogen bond acceptors, thus obeying Lipinski's limit.

Derivatives 2A, 2C (chloro) and 2D (nitro) obey all the limits and thus meet the criteria for Lipinski's rule of five and are likely to be orally active. Remaining other derivatives of the class has more than one violation and do not obey Lipinski's rule of five.

CONCLUSION

Lipinski parameters for the above mentioned sixteen derivatives were generated by using DS accord for excel (ADME screening) provided by Accelrys Discovery studio software and thoroughly studied. From the results it is evident that among the sixteen listed derivatives only three derivatives namely 2A, 2C (chloro), 2D (nitro) obeys all the parameters of Lipinski's rule of five. Other derivatives of the class violate more than one criteria. So it can be concluded from the results that 2A, 2C, 2D are likely to be orally active. Further studies are required to predict the oral activities of these derivatives. Further investigation of these compounds might throw a light on possibly potent and better molecules.

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Table 1: Set of compounds for 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 1: Calculated Lipinski parameters

Compound	LogP	Molar Refractivity	Polar surface area	Molecular Weight	Hydrogen bond donors	Hydrogen bond acceptors
2A	2.2912	109.70	98.652	377.43	5	5
2B	2.0687	135.89	269.94	557.41	5	13
2C	3.82	119.50	98.65	446.32	5	5
2D	2.28	122.80	184.29	467.43	5	9
2A'	3.533	136.03	119.46	469.53	6	6
2B'	3.110	162.21	290.76	649.52	6	14
2C'	4.862	145.82	109.43	538.42	6	6
2D'	3.32	149.12	205.11	559.5	6	10
3A	2.229	131.50	130.024	513.5	1	7
3B	1.806	157.68	301.317	693.49	1	15
3C	3.558	141.29	130.024	582.39	1	7
3D	2.018	144.59	215.67	603.49	1	11
3A'	3.271	157.82	150.84	605.59	2	8
3B'	2.849	184.00	322.13	785.58	2	16
3C'	4.600	167.61	150.840	674.48	2	8
3D'	3.06	170.91	236.486	695.59	2	12

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