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SCREENING OF NEWLY SYNTHESIZED SPIROAZETIDIN-2-ONES FOR ORAL ACTIVITY

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ABSTRACT

For eight compounds 1-(substituted phenyl)-3-chloro-5,9-bis(furan-2-ylmethylidene)-1-azaspiro[3.5] nonan-2-ones (3a - 3h) in set, Lipinski parameters were calculated. 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 providing a relationship between the structure and its activity.

KEYWORDS: Spiro, azetidin-2-ones, Furan, Lipinski parameters, ADME screening.

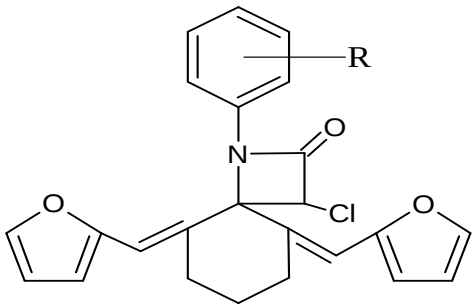
INTRODUCTION

Spiroazetidin-2-ones and their analogues have been known through many decades for treating a number of health conditions and possess varied activities like antibacterial, anti-fungal, anti-inflammatory, anti-tubercular, anti-convulsant, anthelmintic, hypoglycemic, hypnotic, insecticidal, anti-parkinsonism etc.[1-7] Although there are many Spiroazetidin-2-one derivatives in existence for a variety of ailments, search for new 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'.

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. 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 moderately lipophilic molecules.[8] So totally eight derivatives 1-(substituted phenyl)-3-chloro-5,9-bis(furan-2-ylmethylidene)-1-azaspiro[3.5]nonan-2-ones (3a - 3h) in set,[9] were screened and their Lipinski parameters were obtained.

MATERIALS AND METHODS

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.



3a - 3h

Table 1: Set of compounds for screening.

Compound	R
3a	H
3b	4-NO_2
3c	4-Cl
3d	4-Br
3e	2-NO_2
3f	3,4-diCl
3g	4-F
3h	2,6-diCl

RESULTS AND DISCUSSION

Totally 8 derivatives of 3a-3h were extensively subjected to screening, to study their Lipinski parameters. The results are listed in table 2 & table 3.

Table 2: Calculated Lipinski parameters.

Compound	Log P	Molar Refractivity	Polar Surface area	Molecular Weight
3a	4.06	112.13	100.97	405.88
3b	4.11	119.46	188.42	450.87
3c	4.53	116.94	90.02	440.32
3d	4.64	119.76	80.15	484.78
3e	4.11	119.46	132.60	450.87
3f	5.01	121.74	87.99	474.77
3g	4.43	112.35	86.18	423.87
3h	5.01	121.74	101.18	474.77

Table 3: Calculated Lipinski parameters.

Compound	Hydrogen bond donor	Hydrogen bond acceptor	No. of rotatable bonds	Total No. of atoms
3a	0	4	3	49
3b	0	7	4	51
3c	0	4	3	49
3d	0	4	3	49
3e	0	7	4	51
3f	0	4	3	49
3g	0	4	3	49
3h	0	4	3	49

Log P values of all 8 derivatives are well below 5.6. So Log P parameter of all the derivatives obey Lipinski's rule and fall well within the range of -0.4 to +5.6.

Molar refractivity of all 8 derivatives was in the range of 40 to 130. So Molar refractivity parameter of all the derivatives obey Lipinski's rule and fall well within the range. Polar surface area of all eight compounds was present well below 140 $Å^2$ and obey Lipinski's stated limit. And molecular weights of all 8 derivatives are in between 180 to 500 daltons. So molecular weight of all the derivatives obey Lipinski's rule and fall well within the range.

All the derivatives have hydrogen bond donors less than 5 and hydrogen bond acceptors less than 10, there by obeying Lipinski rule. All the derivatives have rotatable bonds less than 10, there by obeying Lipinski rule. And the total number of atoms of all 8 derivatives ranges from 20 to 70, there by obeying Lipinski rule.

All the derivatives obey all the limits and thus meet the criteria for Lipinski's rule of five and are likely to be orally active.

CONCLUSION

Lipinski parameters for the above mentioned eight derivatives 1-(substituted phenyl)-3-chloro-5,9-bis(furan-2-ylmethylidene)-1-azaspiro[3.5]nonan-2-ones (3a - 3h) 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 eight listed derivatives, all the derivatives obey all the parameters of Lipinski's rule of five. So it can be concluded from the results that all derivatives 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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