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INSILICO SCREENING OF NEWLY SYNTHESIZED SPIRO-1,2,4-THIADIAZOLES FOR ORAL ACTIVITY

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ABSTRACT

1,2,4-thiadiazoles are known to possess varied biological activities like antibacterial, antifungal, antiviral, anti-inflammatory, cardiovascular, antidiabetic, anticancer, antipsychotic, antiplatelet, antidepressant etc. For sixteen compounds N-[3-chloro-2-oxo-1-(substituted)-5-thia-1,6,8-triazaspiro[3.4]oct-6-en-7-yl]acetamide(5a – 5b) and 3-chloro-7-[3-chloro-2-(substituted phenyl)-4-oxoazetidin-1-yl]-1-(substituted)-5-thia-1,6,8-triazaspiro[3.4]oct-6-en-2-one(5c – 5p) in a set, Lipinski parameters were calculated. The chemical structures which were drawn in DS Viewer Pro Suite and 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, all the derivatives except 5e, 5f and 5g obey all the limits and thus meet the criteria for Lipinski's rule of five and are likely to be orally active. All the calculated parameters solely depend on the chemical structure of the derivatives and determine their oral activity.

KEYWORDS: ***Spiro-1,2,4-thiadiazoles, azetidin-2-ones, Lipinski parameters, Oral activity.***

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INTRODUCTION

1,2,4-thiadiazoles and their analogues have been known through many decades for treating a number of health conditions and possess varied activities like antibacterial, antifungal, antiviral, anti-inflammatory, cardiovascular, antidiabetic, anticancer, antipsychotic, antiplatelet, antidepressant etc.[1-3] Although there are many 1,2,4-thiadiazoles derivatives in existence for a variety of ailments, search for new drugs is at a fast pace in order to minimize the side effects and for the better therapeutic efficacy. After investigating the compounds using drug design studies, Spiro-1,2,4-thiadiazoles tethered with azetidin-2-ones were selected for synthesis, as we already knew azetidin-2-ones for their potential to treat various health conditions.[4-10] By using Spiro-1,2,4-thiadiazoles tethered with azetidin-2-ones 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 likeliness, 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 medicines in use are relatively small and moderately lipophilic molecules.[11] So totally sixteen derivatives N-[3-chloro-2-oxo-1-(substituted)-5-thia-1,6,8triazaspiro[3.4] oct-6-en-7-yl]acetamide(5a – 5b) and 3-chloro-7-[3-chloro2(substitutedphenyl)4oxoazetidin1yl]1(substituted) -5-thia-1,6,8-triazaspiro[3.4]oct-6-en-2-one (5c – 5p) in a set, were screened and their Lipinski parameters were obtained.

MATERIALS AND METHODS

As the Lipinski's rule states that, an orally active drug has no more than one violation of the following criteria:

1. Not more than 5 hydrogen bond donors (the total number of nitrogen-hydrogen and oxygen-hydrogen bonds)
2. Not more than 10 hydrogen bond acceptors (all nitrogen or oxygen atoms)
3. A molecular mass less than 500 daltons
4. An octanol-water partition coefficient[12] log *P* not greater than 5

In an attempt to improve the predictions of druglikeness, the rules have spawned many extensions, which are as follows:[13]

1. Partition coefficient log *P* in −0.4 to +5.6 range
2. Molar refractivity from 40 to 130
3. Molecular weight from 180 to 500
4. Number of atoms from 20 to 70 (includes H-bond donors [e.g.;OH's and NH's] and H-bond acceptors [e.g.; N's and O's])
5. Polar surface area no greater than 140 $Å^2$
6. 10 or fewer rotatable bonds[14]

Lipinski studies have been performed by using DS Accord for Excel 6.1, provided by Accelrys Discovery Studio software. These studies are solely based on the chemical structure of the molecule. The following structures are drawn in 3D using DS Viewer Pro Suite 5.0 and the drawn structures were appended into Accord for Excel and the parameters which we have to calculate, had been selected. Substitutions for the derivatives are given in Table 1.

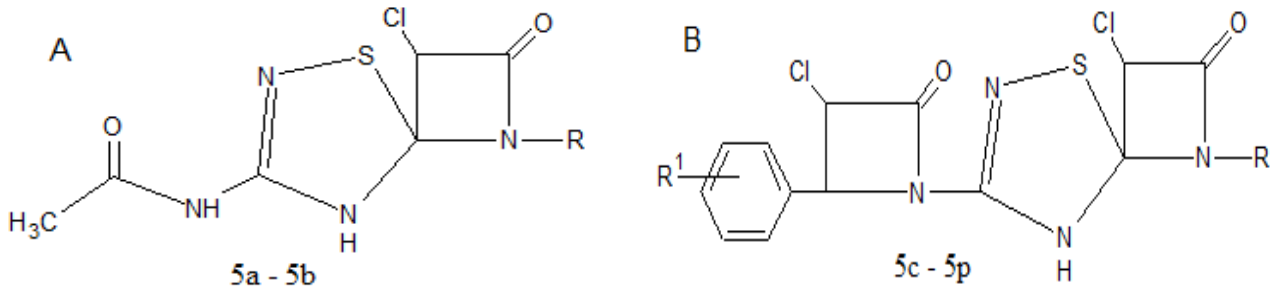

Figure 1
Structure of (A) 5a - 5b (B) 5c – 5p

Table 1
Set of compounds for screening

Compound	R	R^1
5a	C_6H_5	-
5b	CH_2=CH-CH_2-	-
5c	C_6H_5	4-OH
5d	C_6H_5	4-Cl
5e	C_6H_5	2,6-diCl
5f	C_6H_5	2,4-diCl
5g	C_6H_5	3,4,5-triOCH_3
5h	C_6H_5	4-NO_2
5i	C_6H_5	H
5j	CH_2=CH-CH_2-	H
5k	CH_2=CH-CH_2-	4-OH
5l	CH_2=CH-CH_2-	4-Cl
5m	CH_2=CH-CH_2-	2,6-diCl
5n	CH_2=CH-CH_2-	2,4-diCl
5o	CH_2=CH-CH_2-	3,4,5-triOCH_3
5p	CH_2=CH-CH_2-	4-NO_2

RESULTS

Totally 16 derivatives of 5a-5p were extensively subjected to screening, to study their Lipinski parameters. The results are as listed in table 2 & table 3. The molar refractivity, molecular weight, No. of hydrogen bond donors, acceptors & rotatable bonds and total no. of atoms are within the range

Table 2
Calculated Lipinski parameters

Compound	Log P	Molar Refractivity	Polar Surfacearea	Molecular Weight
5a	2.402	75.776	198.856	310.765
5b	1.41	65.161	240.953	274.732
5c	4.397	109.18	264.884	449.318
5d	5.297	112.29	234.584	467.764
5e	5.885	117.09	211.261	502.209
5f	5.924	117.09	213.304	502.209
5g	4.146	126.87	324.624	523.397
5h	4.64	114.81	319.465	478.316
5i	4.705	107.49	227.54	433.319
5j	3.713	96.87	280.086	397.286
5k	3.405	98.564	319.690	413.285
5l	4.305	101.67	260.203	431.731
5m	4.893	106.48	256.628	466.176
5n	4.932	106.48	276.091	466.176
5o	3.154	116.26	363.525	487.364
5p	3.648	104.19	365.768	442.283

Table 3
Calculated Lipinski parameters

Compound	Hydrogen bond donor	Hydrogen bond acceptor	No. of rotatable bonds	Total No. of atoms
5a	2	6	3	31
5b	2	6	4	28
5c	2	7	3	43
5d	1	6	3	42
5e	1	6	3	42
5f	1	6	3	42
5g	1	9	6	54
5h	1	9	4	44
5i	1	6	3	42
5j	1	6	4	39
5k	2	7	4	40
5l	1	6	4	39
5m	1	6	4	39
5n	1	6	4	39
5o	1	9	7	51
5p	1	9	5	41

DISCUSSION

Log P values of all 16 derivatives are well below 5.6 except 5e and 5f, due to the presence of electron withdrawing groups such as dichloro. So Log P parameter of all the derivatives except 5e and 5f obey Lipinski's rule and fall well within the range of -0.4 to +5.6.[13] Molar refractivity of all 16 derivatives was in the range of 40 to 130.[13] So Molar refractivity parameter of all the derivatives obey Lipinski's rule and fall well within the range of 40 to 130. Polar surface area of all sixteen compounds was not present below 140 $Å^2$ and does not obey Lipinski's stated limit. And molecular weights of all 16 derivatives except 5e, 5f and 5g are in between 180 to 500 daltons,[13] as the molecular weights are more due to the presence of bulkier groups such as 2,6-dichloro, 2,4-dichloro and 3,4,5-trimethoxy. So molecular weight of all the remaining derivatives except 5e, 5f and 5g obey Lipinski's rule and fall well within the range. Results are listed in table 2. All the sixteen derivatives have hydrogen bond donors less than 5[11], hydrogen bond acceptors less than 10[11], rotatable bonds less than 10[14] and total number of atoms ranges from 20 to 70[13], there by obeying Lipinski rule. Results are listed in table 3. All the derivatives except 5e, 5f and 5g obey all the limits and thus meet the criteria for Lipinski's rule of five and are likely to be orally active. 5e, 5f and 5g 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 5a-5p was 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, all the derivatives except 5e, 5f and 5g obey all the parameters of Lipinski's rule of five. So it can be concluded from the results that all derivatives except 5e, 5f and 5g 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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CONFLICT OF INTEREST

Conflict of interest declared none.

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