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Computational Design, Metabolism and Toxicity Studies of Some Novel Chalconesemicarbazone Derivatives

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In the present study we have used pharmacophore hybridization technique of drug design and designed a pharmacophore model 'chalconesemicarbazone', which is having hydrogen acceptor site, hydrogen donor site, lipophilic site etc, which may help in binding with receptors and plays an important role in pharmacological activities. On these observations, we have designed a synthetic scheme to synthesize this pharmacophore and also synthesize some lead compounds. The pharmacophore of the synthesized compound was developed by using ligandscout-2.02 software by minimizing energy with MM3 force field. The possible metabolites and the toxicity of some selected synthesized chalconesemicarbazones were predicted by computational method using Pallas version-3.1 ADME-Tox prediction (metabolism prediction by Mexalert/RetroMex and toxicity prediction by Hazardexpert/ToxAlert) software. Compound 15 has high probability of toxicity. The major pathway of metabolism was found to be *p*-hydroxylation and amide hydrolysis.

Key Words: Chalcones, Pharmacophore, Semicarbazones, Ligandscout, Pallas.

INTRODUCTION

Computational chemistry is a branch of chemistry that uses computers to assist in solving chemical problems. It uses the results of theoretical chemistry, incorporated into efficient computer programs, to calculate the structures and properties of molecules and solids. While its results normally complement the information obtained by chemical experiments, it can predict unobserved chemical phenomena. It is widely used in the design of new drugs. Examples of such properties are structure (*i.e.*, the expected positions of the constituent atoms), absolute and relative (interaction) energies, electronic charge distributions, dipoles and higher multipole moments, vibrational frequencies, reactivity or other spectroscopic quantities and cross sections for collision with other particles[1,2].

It is extremely important to consider the ADME characteristics of compounds earlier in the discovery process to wager bets on compounds that have a greater potential to survive the development and clinical trial stages of drug development. Increasing the odds of success to one in five (instead of ten) would reduce the total cost of bringing a new therapeutic to the market by 33 %. Experimental determination of ADME and pharmacokinetic (PK) characteristics is both expensive and time consuming and is not practical for large numbers of compounds, especially when the pharmaceutical industry is under severe pressure to cut costs and improve efficiency. The price tag to support various ongoing discovery projects in a pharmaceutical company for synthesis and high throughput measurement of permeability, solubility, metabolic stability and acute toxicity can run into millions of dollars at the rate of $5,000 - $10,000 per compound[3].

Much attention is being focused on the application of *in silico* screens to reliably predict ADME attributes solely from molecular structure. *In silico* prediction of ADME properties will not only reduce costs and development cycle times by wisely directing resources to essential experimental testing, but also bring forward their consideration earlier at the lead generation stage when compounds are being synthesized and tested almost exclusively to meet pharmacological target potency levels. At the cost of experimental results indicated above, a mere 10-20 % reduction in high throughput experimental measurement of permeability, solubility, metabolic stability and acute toxicity through the use of *in silico* screens can lead to significant savings. Further, application of *in silico* screens offers an ideal 'fail-early-fail-cheaply' strategy for drug discovery because their application requires nothing more than inputting the basic structural information of a compound into a validated model. Attrition during the drug development

process is a serious economic problem for the pharmaceutical industry and it is often due to inappropriate ADME/Tox characteristics[4,5].

It has been estimated that 20-40 % of the drug failures in investigational drug development phases are due to safety issues, not counting multiple incidents of adverse effects of existing drugs. The early drug discovery process needs to address in parallel not only potency but also pharmacokinetics and toxicological properties[6].

EXPERIMENTAL

A series of chalconesemicarbazones was synthesized and characterized[7-9]. Structure and physicochemical properties of the synthesized compounds are given in Fig. 1 and Table-1.

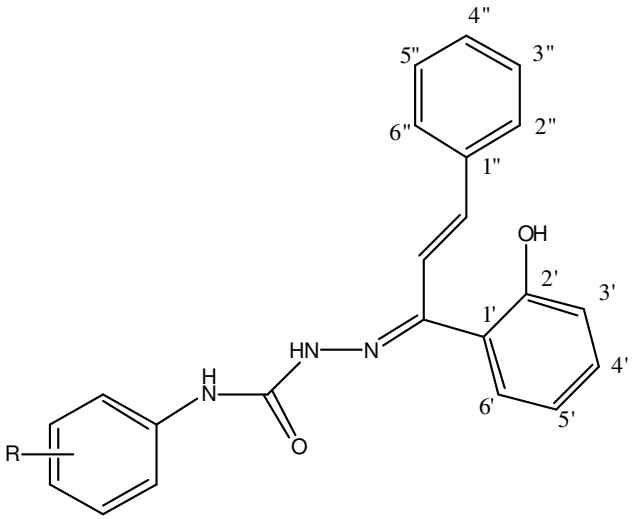

Fig. 1. Structure of chalconesemicarbazone

The pharmacophore of the synthesized compound was developed by using ligandscout 2.02 software by minimizing energy with MM3 force field. The possible metabolites and the toxicity of some selected synthesized chalconesemicarbazones were predicted by computational method using Pallas version-3.1 ADME-Tox prediction (metabolism prediction by Mexalert/RetroMex and toxicity prediction by Hazardexpert/ToxAlert) software.

RESULTS AND DISCUSSION

Pharmacophore designing: We used pharmacophore hybridization technique of drug design and designed a pharmacophore model 'chalconesemicarbazone', which is having hydrogen acceptor site, hydrogen donor site, lipophilic site *etc*. (Fig. 2).

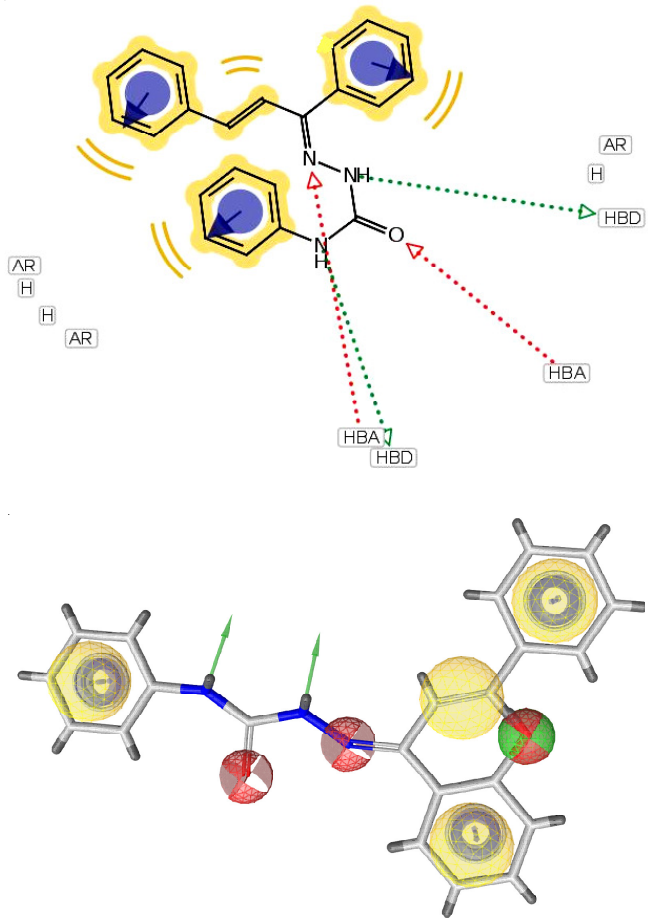

Fig. 2. Pharmacophoric design of compound by ligandscout 2.02

The pharmacophore of the synthesized compound was developed by using ligandscout 2.02 software by minimizing energy with MM3 force field. Various symbols showing

TABLE-1
PHYSICOCHEMICAL DATA OF CHALCONESEMICARBAZONES DERIVATIVES

Compound No.	R	R_1	R_2	Yield (%)	m.w.	m.f.	m.p. (ºC)	R_f Value
4	2-CH_3	H	H	57	371	$C_{23}H_{21}N_3O_2$	150	0.78
5	2-CH_3	H	4”-OH	66	387	$C_{23}H_{21}N_3O_3$	145	0.71
7	2-CH_3	H	4”-$N(CH_3)_2$	58	414	$C_{25}H_{26}N_4O_2$	148	0.57
8	2-CH_3	4-OH	6”-OH	57	403	$C_{23}H_{21}N_3O_4$	142	0.60
10	2-CH_3	H	6”-OH	63	387	$C_{23}H_{21}N_3O_3$	140	0.55
11	2-CH_3	5-OH	6”-OH	61	403	$C_{23}H_{21}N_3O_4$	135	0.63
12	2-CH_3	5-OH	4”-OH	56	403	$C_{23}H_{21}N_3O_4$	120	0.69
13	2-CH_3	5-OH	4”-OCH_3	57	417	$C_{24}H_{23}N_3O_4$	126	0.51
14	4-CH_3	H	H	52	371	$C_{23}H_{21}N_3O_2$	206	0.53
15	4-CH_3	H	4”-OH	65	387	$C_{23}H_{21}N_3O_3$	188	0.63
17	4-CH_3	H	4”-$N(CH_3)_2$	64	414	$C_{25}H_{26}N_4O_2$	195	0.62
18	4-CH_3	4-OH	6”-OH	55	403	$C_{23}H_{21}N_3O_4$	178	0.58
20	4-CH_3	H	6”-OH	54	387	$C_{23}H_{21}N_3O_3$	180	0.69
21	4-CH_3	5-OH	6”-OH	67	403	$C_{23}H_{21}N_3O_4$	183	0.54
22	4-CH_3	5-OH	4”-OH	50	403	$C_{23}H_{21}N_3O_4$	165	0.59

pharmacophoric features in ligandscout 2.02 software are given in Table-2.

The ligandscout application was initialized/started by double click on the icon. In the file menu (appeared at main window of ligandscout), the molecule to be analyzed was imported/opened whose structure was already saved in .mol file format, then with the help of molecule menu (appeared at main window of ligand scout) molecule was subjected for energy minimization. From the pharmacophore menu, the desire pharmacophore (Fig. 2) was created and saved.

***In silico* toxicity prediction/metabolism prediction:** The possible metabolites and the toxicity of some selected synthesized compounds were predicted by computational method using Pallas version 3.1 ADME-Tox prediction software and pentium IV processor.

The application was initialized/started by double click on the icon. In the New menu (appeared at main window of Pallas), the molecule to be analyzed was drawn by work sheet of Pallas, then with the help of select menu, molecule was subjected for prediction (option) of metabolism by Mexalert/RetroMex and toxicity by Hazardexpert/ ToxAlert respectively and noted.

TABLE-2
SYMBOLS SHOWING PHARMACOPHORIC FEATURES IN LIGANDSCOUT

Depiction in Ligand Scout	Pharmacophore feature
	Hydrogen bond donor
	Hydrogen bond acceptor
	Positive ionizable area
	Negative ionizable area
	Hydrophobic onteractions
	Aromatic ring
	Metal binding feature
	Excluded volume

TABLE-3
IN SILICO TOXICITY PREDICTION OF THE COMPOUNDS BY PALLAS 3.1 SOFTWARE

Compound	Toxicity	Overall toxicity	Oncogenicity	Mutagenicity	Teratogenicity	Irritability	Sensitivity	Immunotoxicity	Neurotoxicity
4	Not probable	17	0	0	17	0	0	0	0
5	Probable	53	0	29	17	53	0	0	29
7	Not probable	17	0	0	17	0	0	0	0
8	Not probable	15	0	0	15	0	0	0	0
10	Probable	53	0	29	17	53	0	0	29
11	Not probable	15	0	0	15	0	0	0	0
12	Not probable	14	0	0	14	8	0	0	0
14	Not probable	17	0	0	17	0	0	0	0
15	High probable	53	0	29	17	53	0	0	29
17	Not probable	17	0	0	17	0	0	0	0
18	Not probable	15	0	0	15	0	0	0	0
20	Probable	53	0	29	17	53	0	0	29
21	Not probable	15	0	0	15	0	0	0	0
22	Not probable	14	0	0	14	8	0	0	0

TABLE-4
IN SILICO METABOLISM PREDICTION OF THE COMPOUNDS BY PALLAS 3.1 SOFTWARE

Compound	Alert	Count	Reactions				
			P-hydroxilation	Amide hydrolysis	Phenol-sulphate conjugation	Formation of O-glucuronide	Formation of N-glucuronide
4	Probable	5	3	2	–	–	–
5	Probable	8	4	2	1	1	–
7	Probable	4	2	2	–	–	–
11	Probable	5	3	2	–	–	–
13	Probable	8	4	2	1	1	–
15	Probable	7	3	2	1	1	–
20	Probable	8	4	2	1	1	–
21	Probable	5	3	2	–	–	–

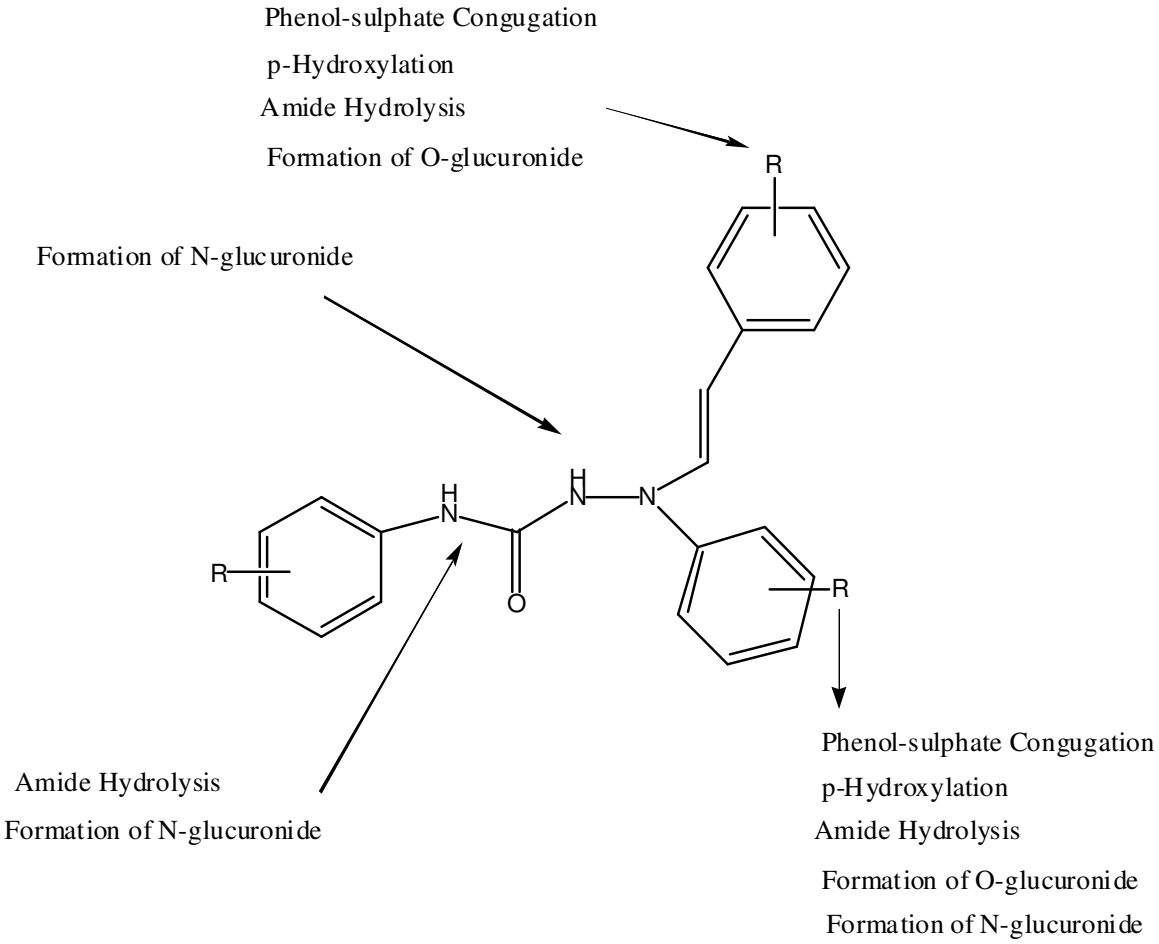

Fig. 3. *In silico* metabolism of chalconesemicarbazone derivatives

In silico toxicity prediction of the synthesized compounds is given in Table-3 which shows that compound **5**, **10**, **15** and **20** have high probability of toxicity while compounds **4**, **7**, **8**, **11**, **12**, **14**, **17**, **18**, **21** and **22** have minimal probability of toxicity.

In silico metabolism prediction of the synthesized compounds is given in Table-4 and Fig. 3. The major pathway of metabolism was found to be *p*-hydroxylation and amide hydrolysis however in some compounds glucuronide and sulfate conjugation may also occur.

Conclusion

A pharmacophore model 'chalconesemi-carbazone' is designed, which may have an important role in various pharmacological activities and synthesized some lead compounds. The possible metabolites and the toxicity of some selected synthesized chalconesemicarbazones were predicted by computational method. Compounds **4**, **7** and **11** were found to be least toxic while compound **15** was found to be highly toxic. The results have shown that most of the compounds may be metabolized through *p*-hydroxylation and amide hydrolysis or may be through phenol-sulphate conjugation, formation of O-glucuronide, formation of N-glucuronide.

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