IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

STUDY OF DRUG LIKELINESS PROPERTIES OF 1(2'-HYDROXY-3'-NITRO-5'-METHYLPHENYL)-3- ARYL/HETERYL-2-PROPEN-1-ONES

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ABSTRACT

Chalcones are reported to possess varied physiological and biological activities. The activities exhibited are antibacterial, insecticidal, antirhinovirus, antipicornivirus, pesticidal, herbicidal, fungicidal, germicidal, carcinogenic, antitubercular, antiparasitic and anti-inflammatory activity.

The complex balance of various molecular properties and structure features which determine whether particular molecule is similar to known drug is known as Druglikeness property. The drug likeliness properties of synthesized compounds were determined using various tools like ADMET Predictor, QikProp, Molinspiration and Osiris drug like property calculators. These properties, mainly hydrophobicity, electronic distribution, hydrogen bonding characteristics, molecule size and flexibility and of course presence of various pharmacophoric features influence the behavior of molecule in a living organism, including bioavailability, transport properties, affinity to proteins, reactivity, toxicity, metabolic stability and many others.

In the present work attempts were made to study the druglikeness properties synthesized compounds druglikeness properties of 1(2'-hydroxy-3'-nitro-5'-methylphenyl)-3- aryl/heteryl-2-propen-1-ones using Osiris drug like property calculators and Toxicity Prediction Tools. The comparative study of the various physico-chemical properties like clogP, solubility, drug-likeness and drug score and also toxicity related risks as tumorogenicity, mutagenicity, irritation, and reproduction effectively were calculated of synthesized compounds by the methodology developed by Osiris. The results of this study of drug-likeness properties of synthesized compounds were found to be encouraging.

KEY WORDS

Chalcones, Prediction, Comparison, Drug-likeness, OSIRIS property calculator.

INTRODUCTION

The chalcones are the most important raw materials for the preparation of heterocyclic compounds. Heterocyclic compounds are well known for their various biological physiological activities. The versatile applications of oxygen, nitrogen and sulphur heterocyclic compounds have made this area of extensive for research. The acetyl group has immense importance as it can be used in various syntheses.

Drug-likeness may be defined as a model of various molecular properties and structure features which determine whether particular molecule can be a potential drug or not. Drug-likeness is a broad term used to define absorption, distribution, metabolism, excretion and toxic (ADMET) properties of a drug molecule. Chris Lipinski of Pfizer in 1997, derived an easy rule 'known as rule of thumb' for drug-likeness in molecules after surveying the world's marketed drugs. In drug-likeness, a quantitative or qualitative characterization feature of the chemicals known may help pharmaceutical and computational chemists to select higher quality drug effects of this from huge pool of compounds and to improve the efficiency of drug design technique. The drug likeliness properties of synthesized compounds were determined using various tools like ADMET Predictor, QikProp, Molinspiration and Osiris drug like property calculators. These properties, mainly hydrophobicity, electronic distribution, hydrogen bonding characteristics, molecule size and flexibility and of course presence of various pharmacophoric features influence the behavior of molecule in a living organism, including bioavailability, transport properties, affinity to proteins, reactivity, toxicity, metabolic stability and many others.

The discrimination between drug-like and nondrug-like is based on the molecular physicochemical properties and structural fingerprints by using a wide variety of chemical descriptor method and statistical tools. The tools which estimate drug-likeness are valuable in the early steps of the lead discovery and which can be used to separates compounds with undesirable properties from screening and to beneficial hits from first screens. Lipinski's Rule of Five was used to evaluate drug-likeness availability of the compounds by using important parameters like molecular weight, predicted lipophilicity, number of hydrogen bond donors or acceptors and number of rotatable bonds. OSIRIS property calculator is used mainly in drug discovery for knowing the mutagenic and tumorognic potentials of new chemical compounds. Toxicity related risks as tumorogenicity, mutagenicity, irritation, and reproduction effectively and various physico-chemical properties like clogP, solubility, drug-likeness and drug score can be calculated by the methodology developed by Data warrior software of Osiris property explorer.

In the present work, the predication and comparison of druglikeness properties of 1(2'- hydroxyl -3'- nitro -5'-methyl phenyl)-3- aryl/heteryl-2-propen-1-ones and their derivatives were studies.

MATERIAL AND METHODS

A mixture of equimolar quantities of 2'-hydroxy-3'-nitro-5'-methyl acetophenone and aryl/heteryl aldehyde dissolved in ethanol and 40 % KOH was added in portions at 10^0C. The reaction flask was corked and kept at room temperature for 8-10 hours. The contents of the flask were then acidified by dilute hydrochloric acid and poured over ice-cold water. Solid obtained was filtered, washed with water and crystallized from proper solvents. The melting points, yield, molecular formula and elemental analysis are recorded in table-1. These compounds gave red colouration with concentrated sulphuric acid, indicating

the presence of α, β unsaturated carbonyl system. The purity of the compounds was checked by TLC. The general reaction can be represented in Fig.-1. The formation of compounds was confirmed by IR, NMR and elemental analysis. The compounds formed can, therefore, be named as 1(2'-hydroxy-3'-nitro-5'-methylphenyl)-3-aryl/heteryl-2-propen-1-ones.

OSIRIS Property Explorer- Toxicity related risks (tumorogenicity, mutagenicity, irritation, and reproduction effectivity) and various physico-chemical properties (clogP, solubility, drug-likeness and drug score) can be calculated by the methodology developed by Osiris. The toxicity risk predictor locates fragments within a molecule, which indicate a potential toxicity risk. Properties calculated by OSIRIS Property Explorer are summarized in Table 2. The drug score combines druglikeness, cLogP, logS, molecular weight and toxicity risks in one handy value than may be used to judge the compound's overall potential to qualify for a drug.

Molinspiration calculations – Molinspiration calculations tool was used to calculate logP, molecular polar surface area, molecular weight, molecular volume, and number of rotatable bonds etc. Octanol/water partition coefficient (logP) is calculated as a sum of fragment based contributions and correction factors (Table 2). Total Molecular Polar Surface Area (TPSA) is calculated based on the methodology a sum of fragment contributions. Other drug likeliness properties calculated like Number of non-hydrogen atoms (Natoms), molecular weight (MW), number of hydrogen-bond acceptors (nON), number of hydrogen-bond donors (nOHNH groups), number of rule of 5 violations (nviolations), number of rotatable bonds (nrotb) and molecular volume.

RESULTS AND DISCUSSION

All the 1(2'-hydroxy-3'-nitro-5'-methylphenyl)-3-aryl/heteryl-2-propen-1-ones compounds synthesized from tri-substituted acetophenone and various aromatic aldehydes in alkaline medium. The yields of synthesized compounds were ranging from 65 to 82%. All synthesized compounds were characterized on the basis of melting point, elemental analysis, IR spectra, ^{1}HNMR, and mass spectral analysis.

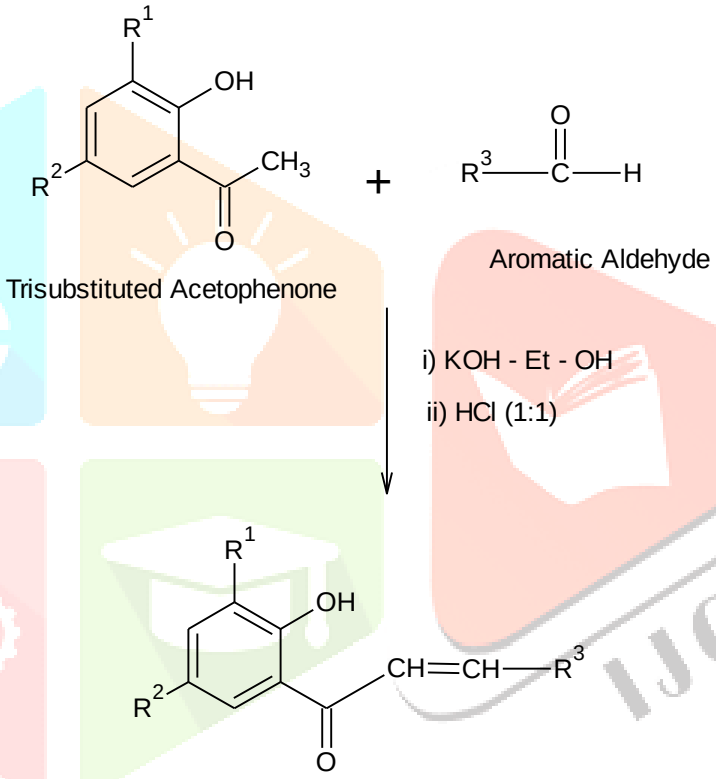
The molecular properties of the selected compounds were calculated using Data warrior (OSIRIS) of organic portal and Molinspiration calculations tool and the values were given in Table-3**.** The values of clogP (partition coefficient between n-octanol and water), molecular weight, drug likeness and the drug score were compared.

Molecular weight of synthesized compounds ranges from 283 to 328 and the value of clogp less than 3. The magnitude of drug-likeness and drug score of compounds ranges from -5.73 to -9.87 and drug score ranges from 0.11 to 0.32. Toxicity risk of synthesized molecules based on Data warrior software of Osiris property explorer were studied and found that as all synthesized molecules have high risk in case of irritation. The compound number Ig and Ih have shown high risk reproduction effectively and the compound number Ib and Ii have shown high risk Tumorogenicity and compound Ii have shown high risk Mutagenic while other synthesized compounds are have not shown risk.

CONCLUSION

In the present study nine newly synthesized compounds were tested for their molecular properties as molecular weight, clogp, Topological polar surface area (TPSA), solubility, drug-likeness and drug score. Another important aspect of this study was consideration of reliability of the synthesized compounds were tested for their toxicity risk like tumorogenicity, mutagenicity, irritation, and reproduction effectively using data warrior software of Osiris property explorer. Compounds Ia, Ib have high risk irritation and tumorogenicity. Compounds Ic, Id, Ie have median risk in case of irritation and no risk in all other tests. Compounds If, Ig, Ih and Ii have high risk in tumorogenicity, mutagenicity, irritation, and reproduction effectively.

Reaction Scheme-

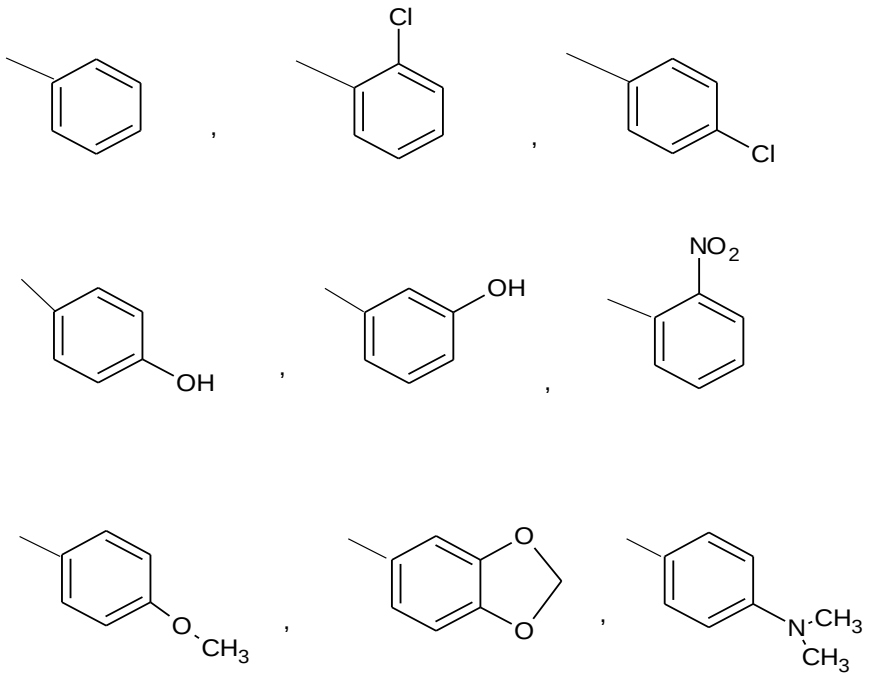


phenyl-2-propen-1-ones

$R^1 = -NO_2$, $R^2 = CH_3$

Fig.1:- Synthesis of 1(2'-hydroxy-3'-nitro-5'-methylphenyl)-3-aryl/heteryl-2-propen-1-ones (Ia-Ii)

$R^3 =$



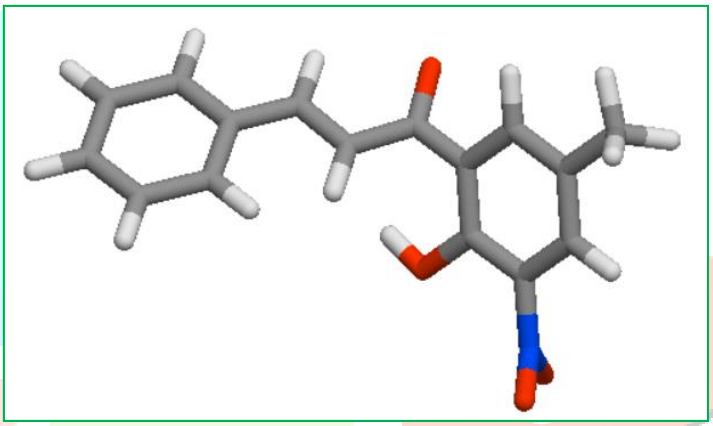


Fig:-1(2'-hydroxy-3'-nitro-5'-methylphenyl)-3-phenyl-2-propen-1-ones

Table-1:- Characteristics data for synthesized 1(2'-hydroxy-3'-nitro-5'-methylphenyl)-3-aryl/heteryl-2-propen-1-ones

Sr. No.	Entries	M. P. ^{0}C	Yield %	Molecular formula	Mol. Wt.
1.	Ia	125	75	$C_{16}H_{13}O_4N$	283
2.	Ib	108	70	$C_{16}H_{12}O_4NCl$	317.5
3.	Ic	102	75	$C_{16}H_{12}O_4NCl$	317.5
4.	Id	98	65	$C_{16}H_{13}O_5N$	299
5.	Ie	145	60	$C_{16}H_{13}O_5N$	299
6.	If	131	80	$C_{16}H_{12}O_6N_2$	328
7.	Ig	92	82	$C_{17}H_{15}O_5N$	313
8.	Ih	90	72	$C_{17}H_{13}O_6N$	327
9.	Ii	116	70	$C_{18}H_{18}O_4N_2$	326

Table-2:-Drug-likeness properties and Toxicity related and physico-chemical properties calculations for synthesized compounds (Ia-Ii) using molinspiration web based tool and OSIRIS Property calculator

Sr.	Entries	clogp	Solubility	Mol.	TPSA	Drug-	Drug-	Colour

No.				Wt.		likeness	likeness Score	
1	**Ia**	2.38	-4.35	283	83.12	-9.5	0.31	Red
2	**Ib**	2.99	-5.08	317	83.12	-5.37	0.16	Red
3	**Ic**	2.99	-5.0	317	83.12	-5.17	0.27	orange
4	**Id**	2.03	-4.05	299	103.3	-5.92	0.32	orange
5	**Ie**	2.03	-4.05	299	103.3	-6.01	0.32	orange
6	**If**	1.46	-4.81	328	128.9	-8.12	0.29	orange
7	**Ig**	2.31	-4.37	313	92.35	-5.75	0.18	Red
8	**Ih**	2.49	-5.06	327	101.15	-5.48	0.16	Red
9	**Ii**	2.28	-4.38	326	86.36	-9.87	0.11	Red

Table-3:- Toxicity risk of synthesized molecules based on Data warrior software of Osiris property explorer.

Entries	Mutagenic	Tumorogenicity	Irritant	Reproductive effect
Ia	None	None	High	None
Ib	None	High	High	None
Ic	None	None	Medium	None
Id	None	None	Medium	None
Ie	None	None	Medium	None
If	None	None	High	None
Ig	None	None	High	High
Ih	None	None	High	High
Ii	High	High	High	None

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