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STUDY OF DRUG LIKENESS PROPERTIES SUBSTITUTED INDAZOLES

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ABSTRACT

In heterocyclic compounds Indazole-containing derivatives represent one of the influential heterocycles in drug molecules. Diversely substituted indazole derivatives bear a variety of functional groups and display versatile biological activities such as antibacterial, analgesic, antipyretic, antiinflammatory, antitumor, antifungal, and anti-HIV. Hence, they have gained considerable attention in the field of medicinal chemistry. The various molecular properties and structure features which determine whether particular molecule is similar to known drug is known as Druglikeness property. In the present work attempts were made to study the druglikeness properties of synthesized indazole derivatives using Molsoft database prediction tools.

KEY WORDS:- Indazole derivatives, Drug-likeness, Molsoft database prediction tools.

INTRODUCTION

The heterocyclic aromatic organic compound Indazole, is also called isoindazole. This is fusion bicyclic compounds as benzene and pyrazole. The nitrogen-containing heterocycles are important building blocks of many biologically active natural products and available known drugs. Indazoles are one of the most important classes of nitrogen-containing heterocyclic compounds. Indazoles and its derivatives are rare in nature but synthetic indazoles and its derivatives possesses a wide range of pharmacological activities, such as anti-inflammatory, antiarrhythmic, antitumor, antifungal, antibacterial, analgesic, antipyretic, and anti-HIV activities. Both natural and synthetic heterocyclic molecules have been

immensely explored for their deep applicability in the field of medicinal, industrial and agricultural chemistry. These compounds have the ability to resemble drugs. Drug properties comprise the structural, physicochemical, biochemical, pharmacokinetic, and toxicity characteristics of a compound. Certain values of drug properties are more advantageous for discovering new drugs. Drug likeness is a qualitative criterion used for drug like property of the compounds.

Drug-likeness was established from structural or physicochemical inspections of development compounds advanced enough to be considered drug-candidates. The drug likeliness properties of synthesized compounds were determined using various tools like Molsoft, 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.

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 properties of a drug molecule. 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 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.

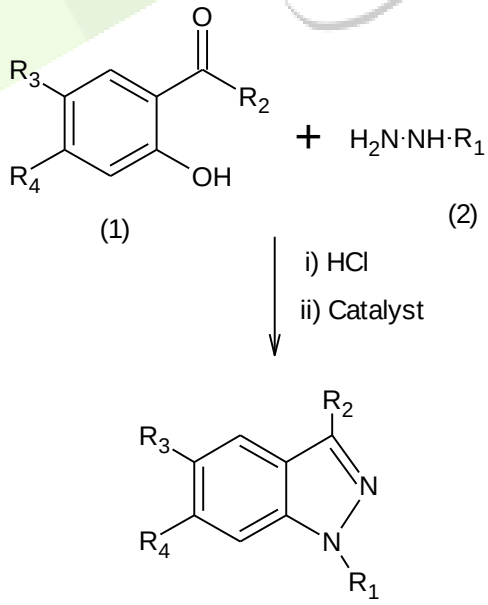
In the present work attempts were made to study of druglikeness properties synthesized indazoles and its derivatives by using Molsoft database tool. The comparative study of the various physico-chemical properties like clogP, solubility, drug-likeness and drug score. The results of this study of drug-likeness properties of synthesized compounds were found to be encouraging.

MATERIAL AND METHODS

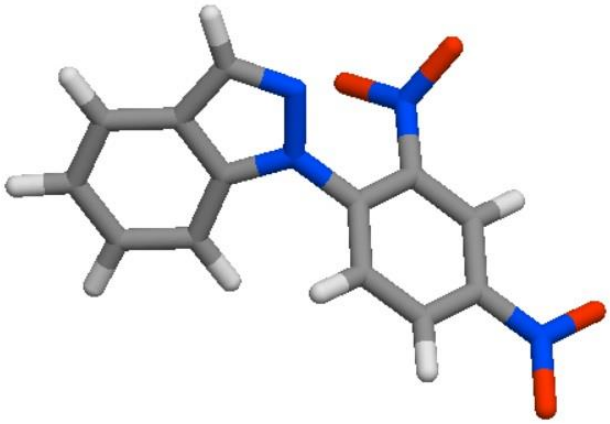
The reaction of substituted salicyaldehydes with hydrazine hydrate hydrochloride and silica sulphuric acid catalyst under different conditions gave the corresponding 1-*H* indazoles. The progress of the reaction was monitored by TLC using n-hexane:ethyl acetate (8:2) solvent. After completion of the reaction, the reaction mixture was cooled to room temperature and the catalyst was filtered off. The catalyst was washed with the solvent and reused for other reactions. The collected filtrate was poured onto crushed ice to obtain crude product. The product is filtered and purified by recrystallization using methanol. The melting points; yield, molecular formula and elemental analysis are recorded in table-2.

Molsoft L.L.C- Molsoft is a foremost provider of tools, databases and consulting services in the field of structure prediction, structural proteomics, bioinformatics, cheminformatics, molecular visualization and animation, and rational drug design. MolSoft is building unique technologies for structure prediction that improves our understanding of the spatial organization of biological molecules and their interactions with each other, their biological substrates and drug-like molecules at the atomic level.

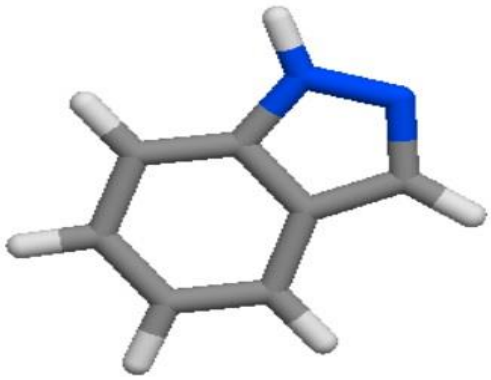
Scheme-



Substituted Indazole (3a - h)



1-(2,4-dinitrophenyl)-1*H*-indazole



1*H*-indazole

RESULTS AND DISCUSSION

All the compounds synthesized from Salicylcladehyde and hydrazine hydrates by using catalyst silica sulphuric acid. The yields of synthesized compounds were ranging from 52 to 68%. 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 Molsoft database tool and the values were given in Table-3**.** The values of mollogP, molecular weight, drug likeness score were compared. Molecular weight of synthesized compounds ranges from 118 to 298 and the value of mollogp ranges from 0.74 to 3.28. The magnitude of drug-likeness score of compounds ranges from -0.80to -2.04 of synthesized molecules based on molsoft database tool.

CONCLUSION

In the present study synthesized compounds were tested for their molecular properties as molecular weight, mollogp, Topological polar surface area (TPSA), solubility, drug-likeness score. Molecular weight of synthesized compounds ranges from 118 to 298 and the value of mollogp ranges from 0.74 to 3.28. The magnitude of drug-likeness score of compounds ranges from -0.80to -2.04.

Another important aspect of this study was consideration of reliability of the synthesized compounds was tested for their drug activity. The compounds 3d, 3g, and 3h shows strong drug properties. Compounds 3b, 3c and 3f show medium drug properties and compounds 3a and 3e shows less drug

property. Compounds with the Phenyl substituted as 3g and 3h druglikeness score values showed as the most potent drug candidate in predictive studies.

Table-1:- Substitution in Substituted Indazoles derivatives (3a-3h)

Entries	R1	R2	R3	R4
3a	H	H	H	H
3b	H	H	H	H
3c	2,4-dinitro phenyl	H	H	H
3d	2,4-dinitro phenyl	Me	H	H
3e	H	H	H	$-NO_2$
3f	H	H	$-NO_2$	H
3g	Phenyl	H	H	H
3h	Phenyl	Me	H	H

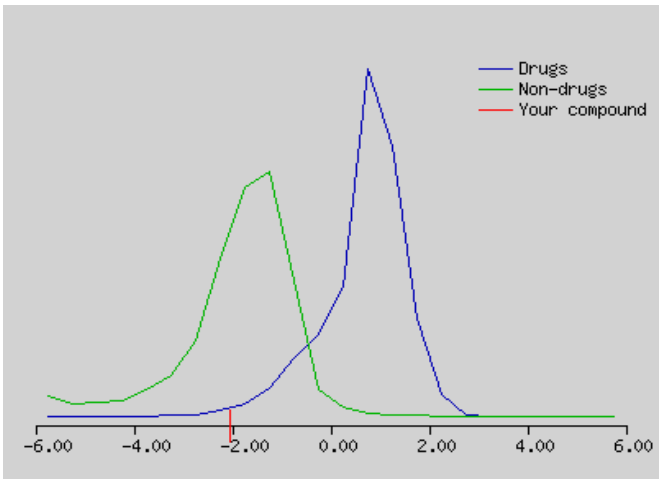
Table-2:- Characterization of Substituted Indazoles derivatives (3a-3h)

Entries	M.F.	Mole Wt.	M.P in ^0C	%Yield
3a	$C_7H_6N_2$	118	147	68
3b	$C_8H_8N_2$	132	114	62
3c	$C_{13}H_8N_4O_4$	284	238	54
3d	$C_{14}H_{10}N_4O_4$	298	195	58
3e	$C_7H_5N_3O_2$	163	180	52
3f	$C_7H_5N_3O_2$	163	209	62
3g	$C_{13}H_{10}N_2$	194	78	64
3h	$C_{14}H_{12}N_2$	208	86	52

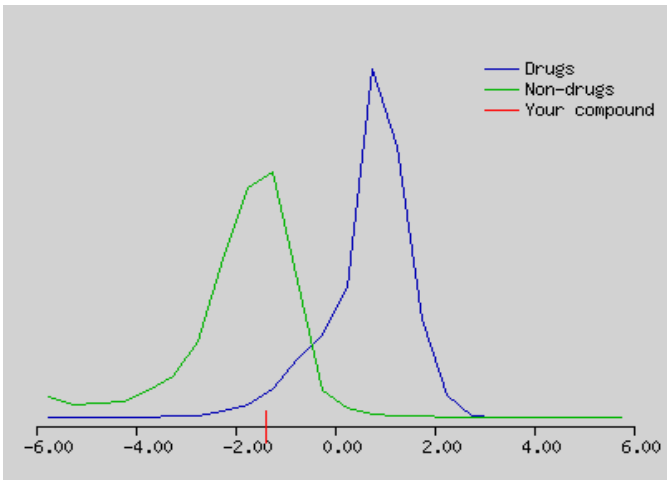
Table-3:-Drug-likeness properties and physico-chemical properties calculations for synthesized compounds (3a-h) using Molsoft database tool.

Sr. No.	Entries	Mol. Wt.	MolLogp	MolLogs	MolPSA	MolVol.	Drug-likeness Score
1	**3a**	118	1.79	1.94	23.64	108.22	-2.04
2	**3b**	132	1.89	-1.61	23.29	129.78	-1.37
3	**3c**	284	1.32	-2.04	89.73	237.79	-1.31
4	**3d**	298	1.12	-1.78	90.08	259.10	-1.23
5	**3e**	163	0.84	-2.00	61.91	133.93	-1.67
6	**3f**	163	0.74	-1.83	61.91	133.93	-1.59
7	**3g**	194	3.28	-3.38	13.81	186.38	-1.15
8	**3h**	208	3.08	-3.07	14.16	207.68	-0.80

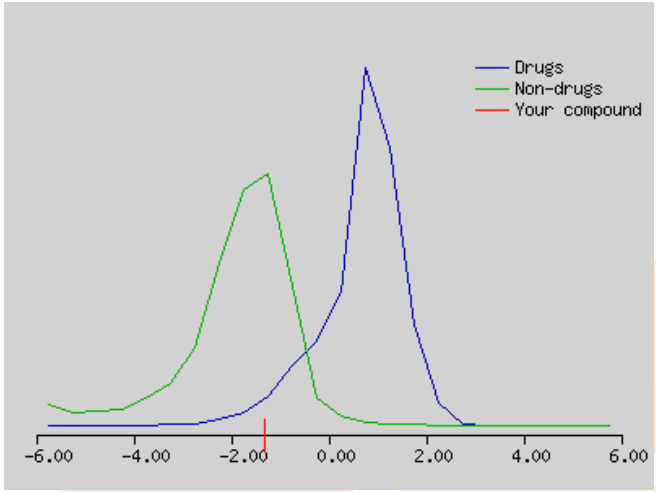
Drug-likeness score represented graphically-



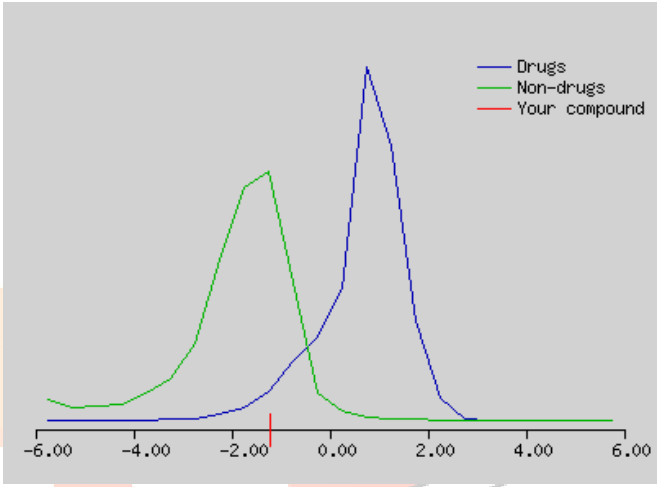
3a



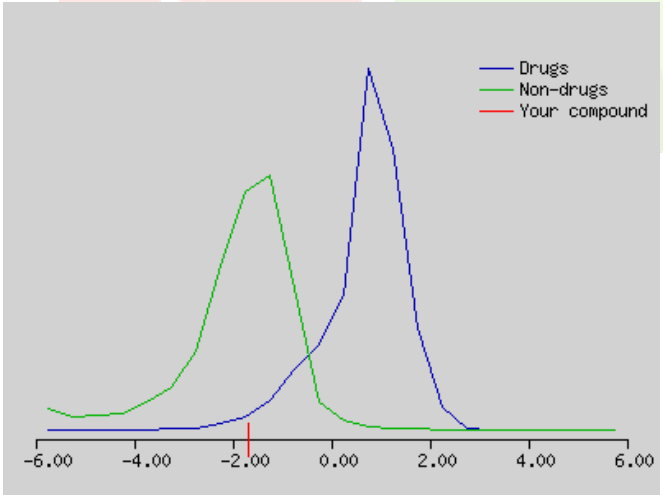
3b



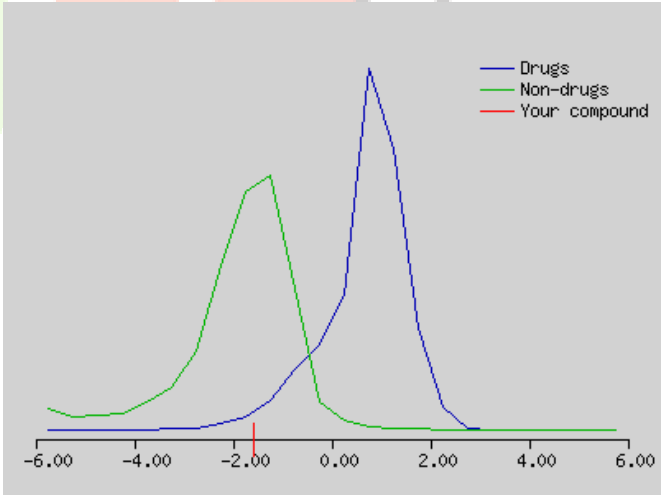
3c



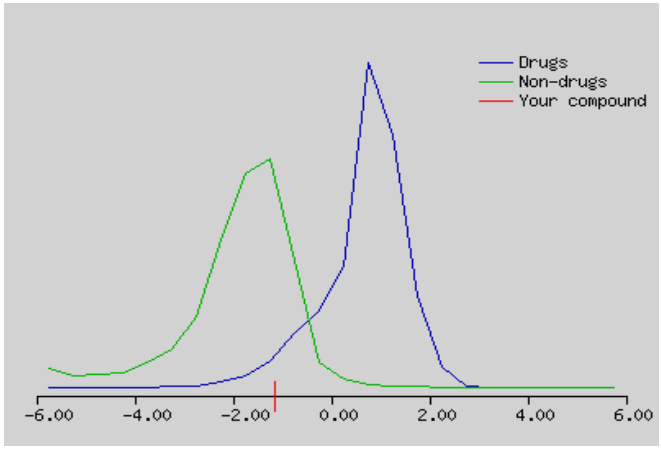
3d



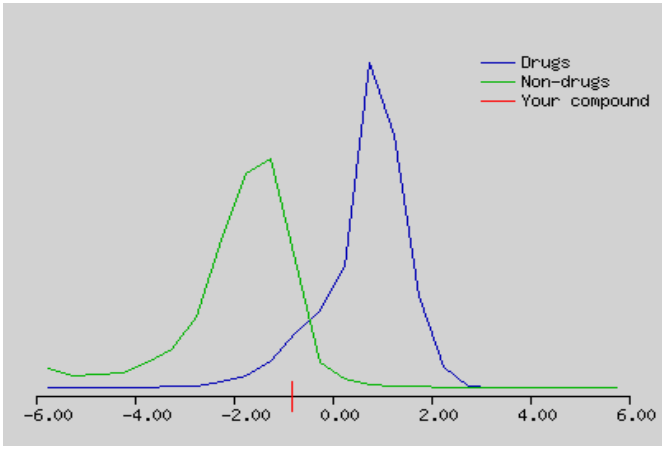
3e



3f



3g



3h

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