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Swissadme Analysis Of Some Selected Analogues Of Pyrrole

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ABSTRACT

As pyrrole has significant medicinal properties analogues of pyrrole (**I-VI**) were selected and modelled by SwissADME database and physicochemical, pharmacokinetics, drug-likeness and medicinal properties were analysed. The results show that all studied molecules obey Lipinski rule and possess high gastrointestinal (GI) absorption with blood brain barrier (BBB) permeation. **I-VI** exhibit good bioavailability score, positive leadlikeness and progressive synthetic accessibility.

KEYWORDS: Heterocycles, Pyrrole, Theoretical study, SwissADME database and ADME properties

I. INTRODUCTION

Heterocycles are common fragments of the vast majority of marketed drugs. This is a reflection of the central role that heterocycles play in modern drug design. They can serve as useful tools to manipulate lipophilicity, polarity, and hydrogen bonding capacity of molecules, which may lead to improved pharmacological, pharmacokinetic, toxicological, and physicochemical properties of drug candidates and ultimately drugs [1].

Multi-target drugs against selective multiple targets improve therapeutic efficacy, safety and resistance profiles by collective regulations of a primary therapeutic target together with compensatory elements and resistance activities. Efforts have been made to employ *in-silico* methods for facilitating the search and design of selective multi-target agents. These methods have shown promising potential in facilitating drug discovery directed at selective multiple targets [2].

The discovery of novel synthetic compounds with drug-like properties is an ongoing challenge in medicinal chemistry. Natural products have inspired the synthesis of compounds for pharmaceutical application, most of which are based on *N*-heterocyclic motifs. Among these, the pyrrole ring is one of the most explored heterocycles in drug discovery programs for several therapeutic areas, confirmed by the high number of pyrrole-based drugs reaching the market. Pyrrole and its hetero-fused derivatives with anticancer, antimicrobial, and antiviral activities were reported, for which a specific target was identified, being responsible for their biological activity. It emerges that the powerful pharmaceutical and pharmacological features provided by the pyrrole nucleus as pharmacophore unit of many drugs are still recognized by medicinal chemists [3].

Survey of pyrrole derivatives with potential for biomedical application is presented. Structures are organised by their origin – biosynthesis or artificial chemical synthesis. Assortment of references outline the state of the art and point to in-depth reports. Current trends in the design and development of pyrrole-based drugs are highlighted [4].

Attempts have been made to disclose various tactical approaches to synthesize pyrrole and pyrrole containing analogs. The structure–activity relationship studies have been discussed along with their therapeutic applications which have been reported during last decade. Some molecules as the main components of the market and clinical trials have also been discussed [5].

Cancer remains one of the most significant health issues worldwide. By designing compounds with anticancer activity characterized by high selectivity towards cancer cells, medicinal chemistry focuses on the protection of healthy cells and tissues. The hybrid pharmacophore approach, which afforded a series of new pyrrole flavones has been reported [6].

A catalyst-free, green protocol has been developed for the preparation of polysubstituted nitropyrrole derivatives by the reaction of malononitrile and phenylglyoxal monohydrates, with nitroketene acetals. The ADME studies of the synthesized compounds were performed and key physiochemical properties were calculated by using SwissADME web tool. The distinguished features of the presented method are mild reaction condition, eco-friendly medium, good yields and without column chromatographic purification. All the synthesized compounds obey well with Lipinski's rule of 5 with zero violation having good pharmacokinetics properties [7].

An eco-friendly protocol has been developed for the synthesis of pyrroles in aqueous media, employing tetrahydrofuran and aniline derivatives as reactants and betacyclodextrin-SO_3H as a catalyst [8].

Many articles documented several bioactive cores accommodating indolequinone and its analogue. Noteworthy, mitomycin A acts as excellent medicine for variety of cancer treatment and its analogue EO-9 is under clinical trial. It has been registered that indolequinone fused with ursolic acid (a triterpenoid rich in many Chinese medicines), which is a vital scaffold for the preparation of novel anticancer agent [9].

Even though many documents are reported about the role of *N*-containing heterocyclic compounds in the medicinal field, no theoretical research has been reported on the selected compounds (**I-VI**) so far. Therefore, this work concentrates on the pharmacological properties using SwissADME server [10].

II. METHODOLOGY

The Swiss ADME web tool has been utilized to explore the physicochemical properties, pharmacokinetics, drug-likeness and to study the medicinal chemistry of the selected pyrrole analogues (**I-VI**) for this present work. The 2D structure of the studied compounds were first modelled (Figure 1.) and converted into corresponding SMILES (Simplified Molecular Input Line Entry System) which is shown in Table 1 and the program was further performed to study the ADME properties of the molecules.

III. RESULTS AND DISCUSSION

Physicochemical properties

The physicochemical properties of **I-VI** obtained using SwissADME web tool have been listed in Table 1. From the result it is inferred that all have one rotatable bond (RB) except **V** which has two RB. No studied compound has either hydrogen bond donor or acceptor. Molar refractivity (MR) and topological polar surface area (TPSA) of all the compounds are good and more solubility nature of the compounds offer the positive point towards the drug development.

Pharmacokinetics study

The pharmacokinetics and drug-likeness of the selected compounds are shown in Table 2. It is indicating that the gastrointestinal (GI) absorption is high with blood brain barrier (BBB) permeation for all the selected molecules. This result shows the positive indication for the interaction between studied molecules and the central nervous system. All (I-VI) have good skin permeation also.

Table 1. Physicochemical descriptors of I-VI by SwissADME web tool

Descriptor	I	II	III	IV	V	VI
SMILES	c1ccc(cc1)n1ccccc1	Cc1ccc(cc1)n1cccc1	Cc1ccccc1n1cccc1	c1ccc2c(c1)c(ccc2)n1cccc1	c1ccc(cc1)c1ccc(cc1)n1cccc1	c1ccc2c(c1)c1cc(ccc1C2)n1cccc1
MF	$C_{10}H_9N$	$C_{11}H_{11}N$	$C_{11}H_{11}N$	$C_{14}H_{11}N$	$C_{16}H_{13}N$	$C_{17}H_{13}N$
MW	143.19	157.21	157.21	193.24	219.28	231.29
NRB	1	1	1	1	2	1
NHA	0	0	0	0	0	0
NHD	0	0	0	0	0	0
MR	45.77	50.74	50.74	63.28	71.21	74.22
TPSA	4.93	4.93	4.93	4.93	4.93	4.93
Log $P_{o/w}$	2.18	2.44	2.42	2.57	2.84	2.92
Log S (ESOL)	-3.34	-3.59	-3.12	-3.96	-4.77	-4.57

Table 2. ADME descriptors of I-VI by SwissADME web tool

Descriptor	I	II	III	IV	V	VI
GI absorption	High	High	High	High	High	High
BBB permeant	Yes	Yes	Yes	Yes	Yes	Yes
Log K_p (skin permeation)	-4.99	-4.82	-5.35	-4.94	-4.29	-4.71
Lipinski Rule	No violation	No violation	No violation	No violation	No violation	No violation
Bioavailability Score	0.55	0.55	0.55	0.55	0.55	0.55
Leadlikeness	1	1	1	2	2	2
Synthetic accessibility	1	1	1.04	1.23	1.46	2.16

Lipinski rule

Lipinski rule of 5 helps to distinguish between drug-like and non-drug-like molecules [11]. It predicts high probability of success or failure due to drug likeness for molecules complying with 2 or more of the following rules.

- Molecular mass less than 500 Dalton
- High lipophilicity (expressed as LogP less than 5)
- Less than 5 hydrogen bond donors
- Less than 10 hydrogen bond acceptors
- Molar refractivity should be between 40-130

I-VI are obeying Lipinski's rule thereby eligible for being an oral drug at the preliminary stage of drug discovery.

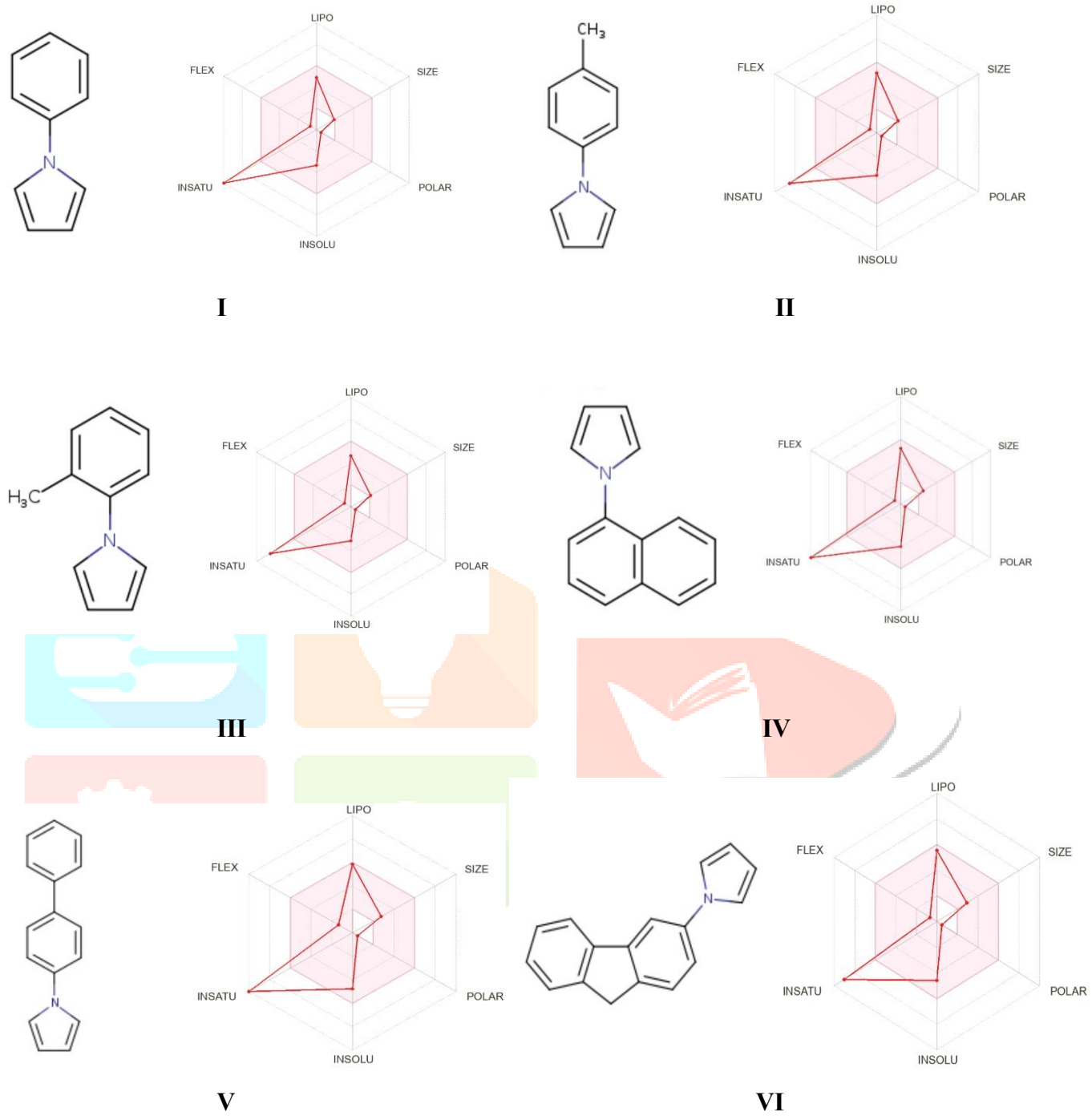

Figure 1. Modelled structure and bioavailability radar of I-VI by SwissADME web tool

Bio-availability Radar

The modelled structure and bioavailability radar of the selected compounds (**I-VI**) have been shown in Figure 1. In bioavailability radar of the compounds Pink / Red area is seen in the plot which reflects the maximum range of lipophilicity, Size, Polarity, insolubility, instauration and flexibility. By analysing the radar of **I-VI**, it is showing good range for all the characteristics which provide the hopeful pathway.

Medicinal chemistry

Bioavailability score is also good for all the molecules under study. Affirmative result of leadlikeness with notable synthetic accessibility score makes **I-VI** as promising candidates to proceed for further drug development.

IV. CONCLUSION

Pyrrole nucleus is one of the most explored heterocycles in drug discovery. From this set of theoretical predictions, it is inferred that **I-VI** are potential molecules for the experimentalists to step ahead in the drug development.

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