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ADME studies of pyrazole containing 1,2,3-triazoles

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KEYWORDS

1,2,3-Triazoles, Pyrazole derivatives, SwissADME, Bioavailability radar, Drug-likeness, Lipinski rule of five, Gastrointestinal absorption.

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Abstract

A series of novel 4-(aryl)-1-(1-methyl-1H-pyrazol-4-yl)-1H-1,2,3-triazole derivatives (IVa–IVl) were evaluated for their physicochemical, bioavailability, and drug-likeness properties using the SwissADME platform. The synthesized compounds exhibited molecular weights ranging from 225.25 to 304.15 g/mol and moderate lipophilicity (MLogP = 1.12–2.54), indicating favorable membrane permeability. The topological polar surface area (TPSA) values were within the acceptable range for oral drug candidates, and all compounds demonstrated high gastrointestinal absorption. Bioavailability radar analysis revealed that most derivatives occupied the optimal physicochemical space required for oral bioavailability. Furthermore, all compounds complied with Lipinski, Ghose, Veber, Egan, and Muegge drug-likeness criteria without any violations. The bioavailability score of 0.55 observed for all derivatives further supports their potential as orally active molecules. Comparative analysis with Erlotinib suggested that the synthesized triazole–pyrazole hybrids possess promising drug-like characteristics and may serve as attractive scaffolds for future therapeutic development.

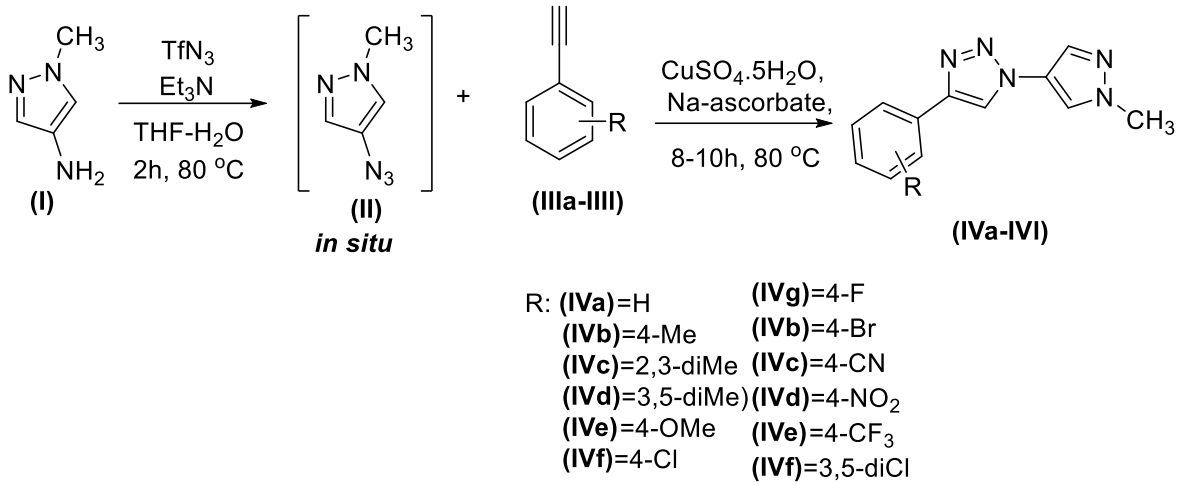
Introduction

Pyrazole and 1,2,3-triazole derivatives represent two of the most important classes of nitrogen-containing heterocycles in contemporary medicinal chemistry owing to their remarkable pharmacological profiles and synthetic versatility [1–3]. Pyrazole-containing compounds have been reported to exhibit a wide spectrum of biological activities, including anticancer, anti-inflammatory, antimicrobial, antiviral, antioxidant, and antitubercular properties [4,5]. Likewise, the 1,2,3-triazole ring system has gained considerable attention because of its excellent metabolic stability, favorable pharmacokinetic characteristics, and ability to participate in hydrogen-bonding interactions with biological targets [6]. The advent of click chemistry, particularly the copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC), has provided a highly efficient and regioselective approach for the synthesis of 1,4-disubstituted 1,2,3-triazoles under mild reaction conditions [1–3].

The molecular hybridization approach, which combines two or more bioactive pharmacophores into a single molecular framework, has emerged as an effective strategy for the development of novel therapeutic agents [7]. In this regard, pyrazole-containing 1,2,3-triazole hybrids have attracted significant interest due to their enhanced biological efficacy and improved drug-like properties [8]. Several studies have demonstrated that these hybrid

molecules possess potent anticancer, antimicrobial, antioxidant, and enzyme inhibitory activities, highlighting their potential as lead candidates for drug discovery programs [8–10]. The presence of multiple nitrogen atoms within the pyrazole and triazole rings facilitates strong interactions with biomacromolecular targets through hydrogen bonding, dipole–dipole interactions, and π–π stacking interactions [5,8].

Recent investigations have further revealed that pyrazole–triazole conjugates exhibit promising inhibitory activity against various cancer-related targets, including epidermal growth factor receptor (EGFR), kinases, and other enzymes involved in tumour progression [9,10]. Consequently, the design and synthesis of novel pyrazole-containing 1,2,3-triazole derivatives continue to be an active area of research aimed at discovering new biologically active molecules with enhanced therapeutic potential. Therefore, the present study focuses on the ADME of a new series of pyrazole-containing 1,2,3-triazole derivatives as potential pharmacologically active agents of synthesized by Jagadeesh Kumar research group [11].



Scheme 1. Synthesis of 4-(aryl)-1-(1-methyl-1H-pyrazol-4-yl)-1H-1,2,3-triazoles and their isolated yields.

Experimental:

https://www.swissadme.ch/index.php is used for the ADME studies and Bioavailability radar, Drug-likeness, Lipinski rule of five, Gastrointestinal absorption.

Results and Discussion (SwissADME Analysis)

The physicochemical properties of compounds IVa–IVl were analyzed using the SwissADME tool and compared with the reference drug Erlotinib. The molecular weights of the synthesized compounds ranged from 225.25 to 304.15 g/mol, which are considerably lower than that of Erlotinib (393.44 g/mol), suggesting favorable oral drug-like characteristics. The lipophilicity values (MLogP = 1.12–2.54) indicate balanced hydrophilic–lipophilic properties, which are essential for membrane permeation and systemic absorption. All compounds possessed only 2–3 rotatable bonds, reflecting structural rigidity and favorable conformational stability. The hydrogen bond acceptor count varied between 3 and 6, while no hydrogen bond donor groups were present, which may enhance passive diffusion across biological membranes.

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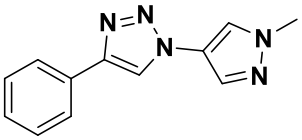
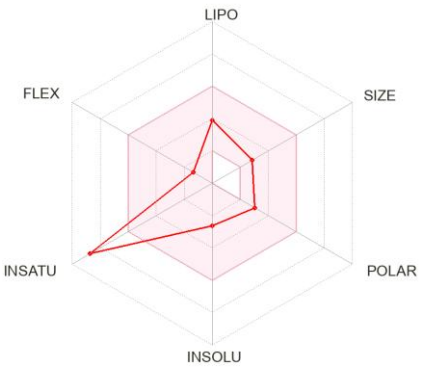
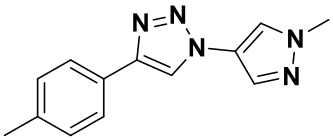
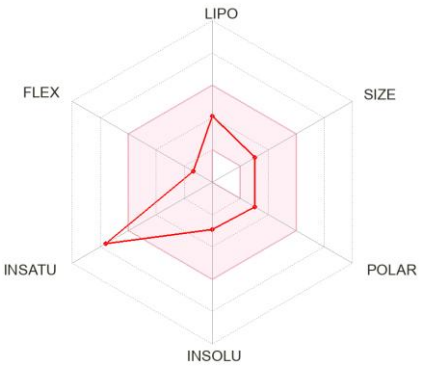
The TPSA values ranged from 48.53 to 94.35 Å², remaining well below the threshold of 140 Å² for good intestinal absorption. Consequently, all compounds exhibited high gastrointestinal absorption, indicating excellent oral bioavailability potential. Bioavailability radar plots further demonstrated that most derivatives fall within the optimal physicochemical space defined by lipophilicity, size, polarity, flexibility, solubility, and saturation. Among the series, compound IVj displayed the highest TPSA (94.35 Å²) due to the presence of a nitro substituent, whereas compounds IVk and IVl exhibited increased lipophilicity owing to trifluoromethyl and dichloro substitutions, respectively. Drug-likeness evaluation revealed that all compounds satisfied Lipinski, Ghose, Veber, Egan, and Muegge criteria without any violations. The uniform bioavailability score of 0.55 observed for all derivatives suggests a high probability of oral bioactivity. Overall, the results indicate that the incorporation of aryl substituents on the pyrazole–triazole framework does not adversely affect drug-likeness and supports the potential of these compounds as promising lead molecules for further biological investigations.

Table 1: Physico-Chemical Space for Bio-availability of compounds IVa – IVl

Entry	Structure	Physico-Chemical Space for Bio-availability
IVa		
IVb		

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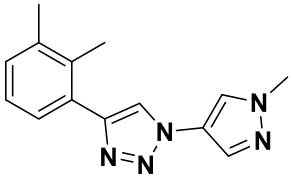
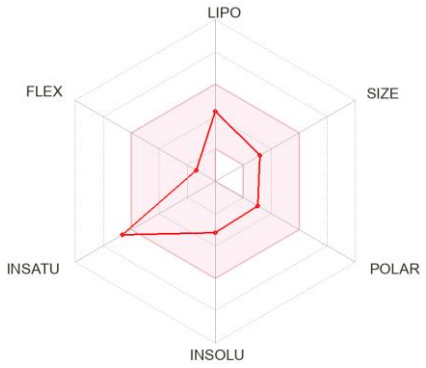
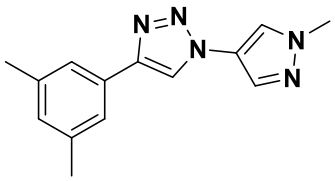
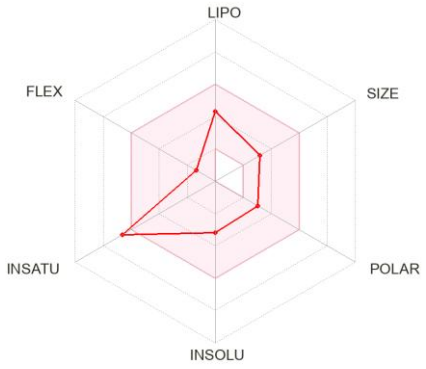
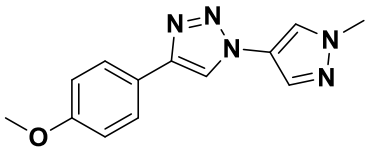
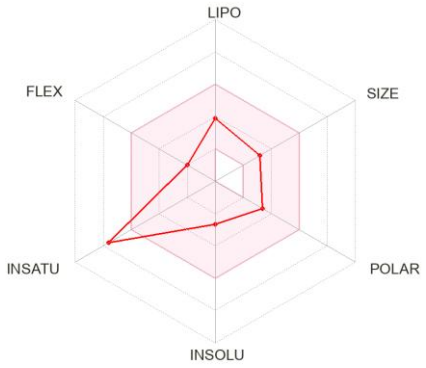
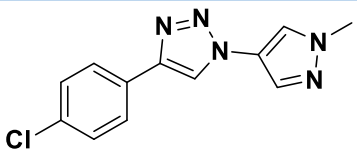
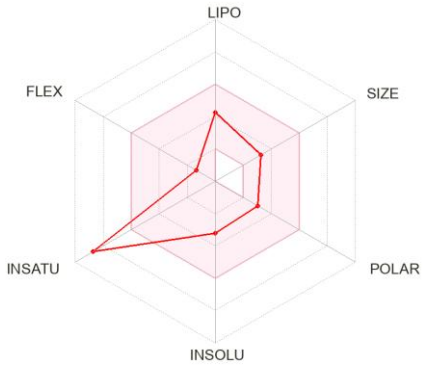
IVc		
IVd		
IVe		
IVf		

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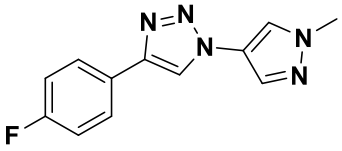
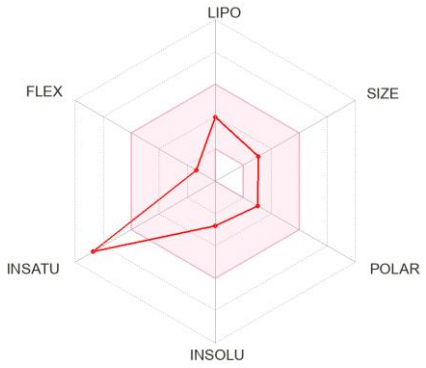
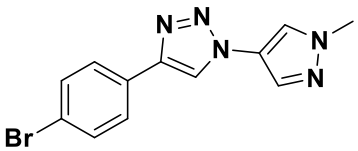
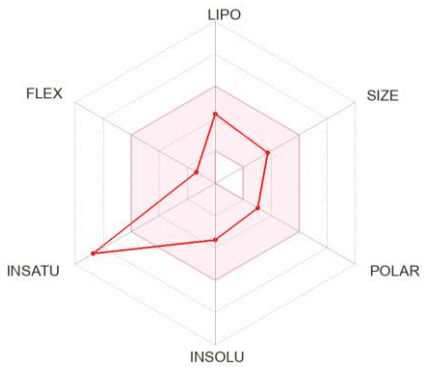
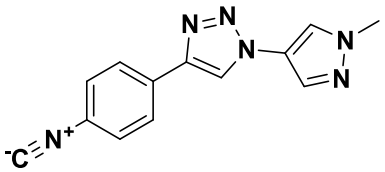
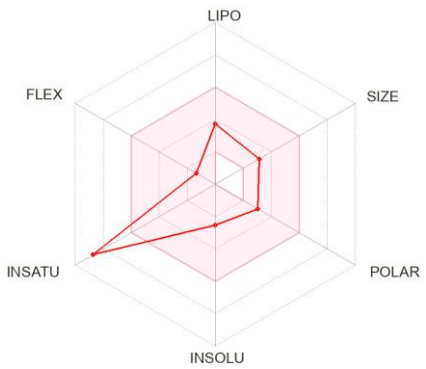
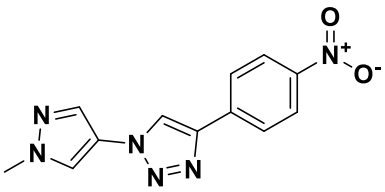
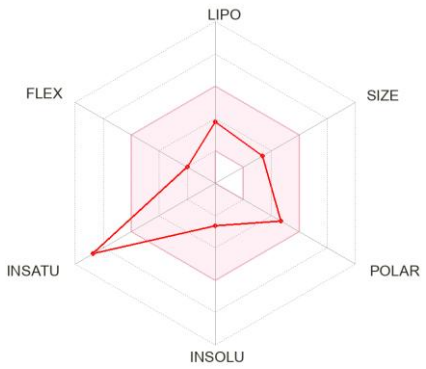
IVg		
IVh		
IVi		
IVj		

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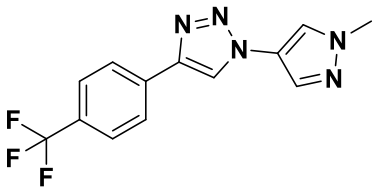
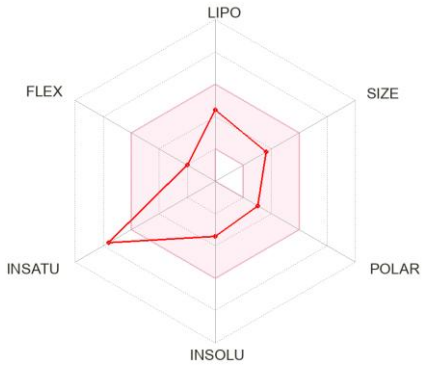
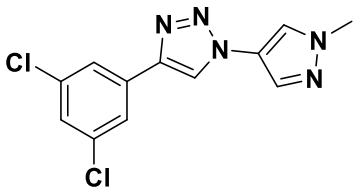
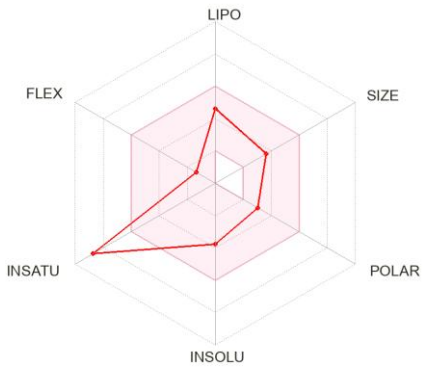
IVk		
IVl		

Table 2: Physicochemical properties of compounds IVa – IVl and Erlotinib using SwissADME tool

Entry	M. wt (g/mol)	MLogP Lipophilicity	No. of rotatable bonds	No. of HBA	No. of HBD	TPSA (Å²)	GI absorption
IVa	225.25	1.47	2	3	0	48.53	High
IVb	239.28	1.74	2	3	0	48.53	High
IVc	253.30	2.01	2	3	0	48.53	High
IVd	253.30	2.01	2	3	0	48.53	High
IVe	255.28	1.20	3	4	0	57.76	High
IVf	259.69	2.01	2	3	0	48.53	High
IVg	243.24	1.88	2	4	0	48.53	High
IVh	304.15	2.14	2	3	0	48.53	High
IVi	250.26	1.12	2	4	0	48.53	High
IVj	270.25	1.36	3	5	0	94.35	High

IVk	293.25	2.40	3	6	0	48.53	High
IVl	294.14	2.54	2	3	0	48.53	High
Erlotinib	393.44	1.62	10	6	1	74.73	High

Table 3: Drug likeness Properties of compounds IVa – IVl using SwissADME tool

Entry	Drug likeness Properties					
	Lipinski (0 violation: MLOGP<4.15)	Ghose (0 violation: WLOGP<5.6)	Veber	Egan (0 violation: WLOGP<5.88)	Muegge (0 violation: XLOGP<5)	Bioavailability Score
IVa	Yes	Yes	Yes	Yes	Yes	0.55
IVb	Yes	Yes	Yes	Yes	Yes	0.55
IVc	Yes	Yes	Yes	Yes	Yes	0.55
IVd	Yes	Yes	Yes	Yes	Yes	0.55
IVe	Yes	Yes	Yes	Yes	Yes	0.55
IVf	Yes	Yes	Yes	Yes	Yes	0.55
IVg	Yes	Yes	Yes	Yes	Yes	0.55
IVh	Yes	Yes	Yes	Yes	Yes	0.55
IVi	Yes	Yes	Yes	Yes	Yes	0.55
IVj	Yes	Yes	Yes	Yes	Yes	0.55
IVk	Yes	Yes	Yes	Yes	Yes	0.55
IVl	Yes	Yes	Yes	Yes	Yes	0.55

Conclusion

SwissADME analysis demonstrated that all synthesized 4-(aryl)-1-(1-methyl-1H-pyrazol-4-yl)-1H-1,2,3-triazoles (IVa–IVl) possess favorable physicochemical and drug-likeness properties. The compounds exhibited moderate lipophilicity, low molecular flexibility, acceptable polarity, and high gastrointestinal absorption. All derivatives complied with Lipinski, Ghose, Veber, Egan, and Muegge rules without any violations, indicating excellent oral drug-like characteristics. Bioavailability radar studies further confirmed that most compounds lie within the optimal physicochemical space required for oral bioavailability. Comparative assessment with Erlotinib revealed that the synthesized compounds possess comparable or superior drug-likeness features while maintaining lower molecular weights. These findings suggest that the pyrazole–triazole hybrids represent promising scaffolds for future pharmacological and anticancer investigations.

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