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In-Silico Studies of Some Novel Pyrazoline Derivatives Focusing on Melanoma, Antimicrobial and Anti-Inflammatory Activity

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Abstract
Microbial infections often produce pain and chronic inflammation, leading cause of cancer. The compound possessing anti-cancer potency with wide spectrum anti-microbial and anti-inflammatory activity is not common. Study focuses on designing a series of novel pyrazoline derivatives active towards anti-neoplastic, anti-microbial and anti-inflammatory response. The pyrazoline derivatives were investigated against the structure of vanin-1: defining the link between metabolic disease, oxidative stress and inflammation and Crystal structure of antigen 43 from uropathogenic Escherichia coli UTI89. Furthermore, the antitumor activity of pyrazoline compounds was evaluated against the crystal structure of human melanoma-associated antigen B1 (MAGEB1). The reported data highlight the impact of chemical structure variations on biological activity. Specific structural modifications consistently altered activity across all tests. Introducing p-nitro and p-hydroxy groups into the aryl moiety of the pyrazoline analogs resulted in compounds with significant anti-inflammatory, antimicrobial, and anticancer properties. The enhanced activities are attributed to the presence of 4-NO_2, 4-OH, and 4-Cl groups in the phenyl ring at the 5-position of the pyrazoline ring. In certain cases, these compounds demonstrated activities equal to or exceeding those of standard drugs.

Keywords: Pyrazoline, In-silico, Anti-inflammatory, Antibacterial activity, Melanoma.

1. Introduction

Cancer ranks as the second-leading cause of death globally, just behind cardiovascular diseases. Among the various types, skin cancer (SC) is one of the most prevalent, with incidence and mortality rates expected to rise alarmingly. Melanoma, a highly aggressive form of skin cancer, originates from the melanocytes, the pigment-producing cells in the epidermis. Major risk factors for melanoma include genetic predisposition, exposure to UV radiation, and a previous history of skin cancer. While the 5-year survival rate for localized melanoma is 98.3%, it drastically drops to 62.4% for regional-stage disease and plummets to 16.0% for distant-stage melanoma. The increasing incidence of melanoma and the emerging resistance to targeted therapies underscore the urgent need for novel treatment options.1-3

Studies have demonstrated the potential of the pyrazole pharmacophore in targeted treatment. The pyrazole nucleus, present in various molecular structures, has diversified applications in treating several diseases, including melanoma. Inflammatory factors, such as cytokines like IL-16, TNF-β, and IL-8, have been linked to an increased melanoma risk. These markers promote tumor growth and progression by

creating a pro-inflammatory microenvironment. Inflammation, the body's general response to disease or damage, can occur due to infections, tumors, physical trauma, or other conditions. Chronic inflammation leads to continuous tissue damage and repair, increasing the risk of mutations and potentially transforming normal cells into cancerous ones.[4-7]

Identifying novel compounds that effectively treat infectious and inflammatory states, without the side effects of current therapies, is a significant challenge in biomedical research. Managing inflammatory conditions related to infections with multiple drugs poses problems, especially for patients with impaired liver or kidney functions or those at risk of drug-drug interactions. Consequently, there is a growing interest in developing new anticancer agents with antibacterial properties and enhanced broad-spectrum and anti-inflammatory potency.

Electron-rich nitrogen heterocycles, particularly 2-pyrazoline derivatives, play a crucial role in diverse biological activities. These derivatives are frequently studied for their antimicrobial, anti-inflammatory, antihypertensive, antiviral, and anticancer properties. Encouraged by these findings, we focused on synthesizing substituted 2-pyrazolines with various phenyl ring substitutions to explore their potential therapeutic applications.[8-13]

2. Methodology

Molecular docking studies:

Docking is a computational technique widely used in drug discovery and molecular biology to predict how small molecules (ligands) bind to target proteins. This methodology forecasts the native position, conformation (native pose or binding mode), and orientation of a ligand within the protein's binding site. Docking software like AutoDock Vina employs algorithms such as the Lamarckian genetic algorithm, Monte Carlo simulated annealing, and other genetic and evolutionary methods to account for ligand flexibility while keeping the target protein receptor rigid. The scoring functions for ligands are based on the AMBER force field, which includes factors like hydrogen bonding, electrostatic interactions, Van der Waals forces, desolvation terms, and conformational entropy. In contrast, AutoDock 4.0 allows for receptor flexibility by enabling the movement of side-chains, providing a more dynamic prediction of receptor-ligand interactions.[14-18]

Physicochemical properties and Toxicity studies

A. SwissADME and Molinspiration

In-silico methods of determination of the physicochemical descriptors and properties is a key role in drug development and target identification. The web tools such as SwissADME gives the different properties of drug based on pharmacokinetic properties, druglike nature and medicinal chemistry friendliness of one or multiple small molecules.

Molinspiration is also a web tool provides the calculation of important molecular properties (logP, polar surface area, number of hydrogen bond donors and acceptors and others), as well as prediction of bioactivity score for the most important drug targets.[18-22]

B. ProTOX-II

ProTOX-II is a web-based platform designed to predict various levels of toxicity, including oral toxicity, organ toxicity (such as hepatotoxicity), and toxicological endpoints (such as mutagenicity, carcinogenicity, cytotoxicity, and immunotoxicity). It also provides insights into toxicological pathways (AOPs) and specific toxicity targets, thereby elucidating the potential molecular mechanisms behind toxic responses.

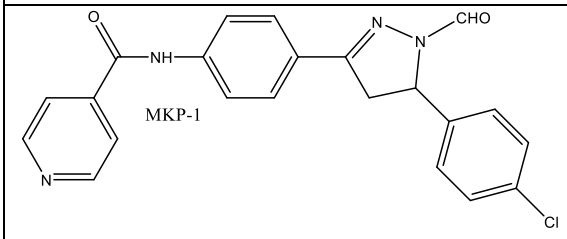
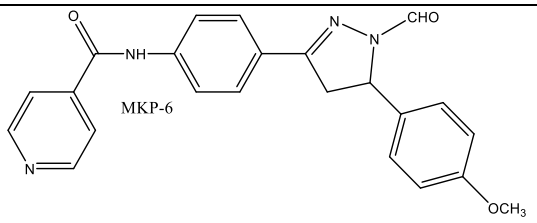
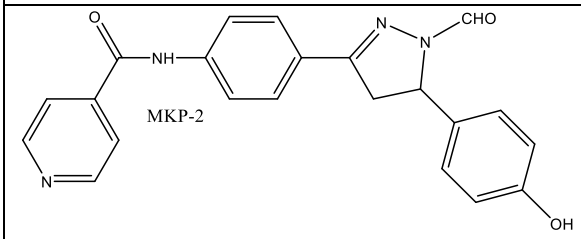
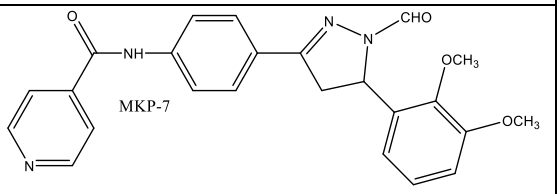
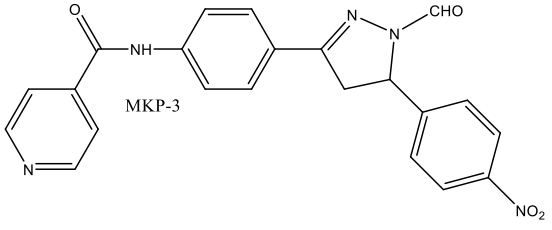
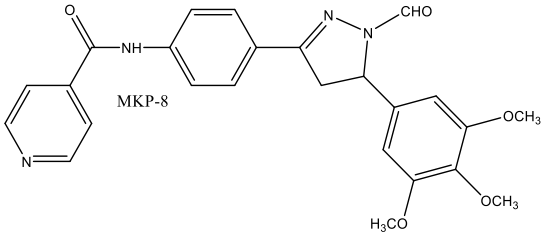
In-silico toxicity models, like ProTOX-II, have the potential to significantly reduce the time and cost associated with drug discovery and development. These models enable quicker validation of the toxic potential of chemicals and their combinations.

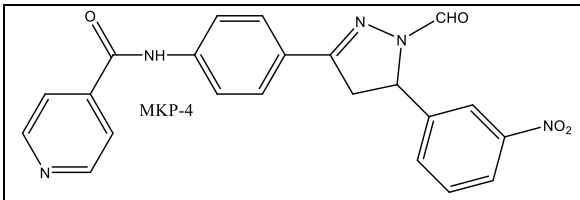
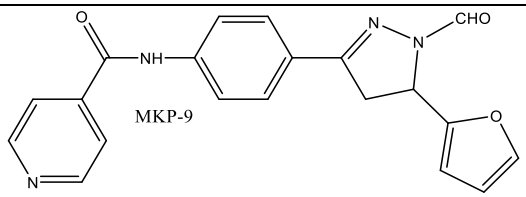
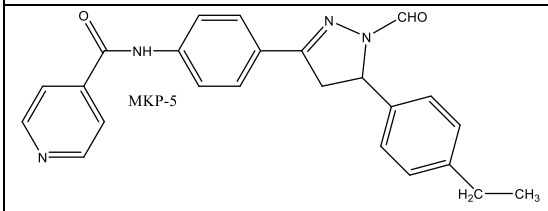
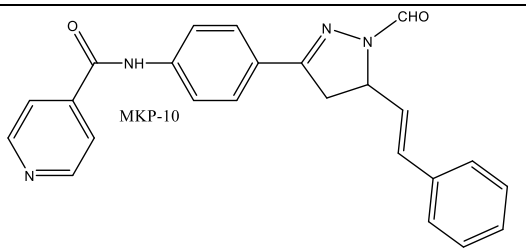
ProTOX-II serves as a virtual laboratory for predicting the toxicities of small molecules. Predicting compound toxicities is a critical component of the drug design and development process. Computational toxicity estimations are not only faster than traditional methods of determining toxic doses in animals but also help to minimize the number of animal experiments required.[22-25]

3. Results and discussion

Molecular docking was carried out to evaluate the interaction potency of the synthesized pyrazoline derivatives (MKP-1-10) by docking them into the catalytic site of receptor protein. The binding affinity scores were used to determine the efficacy of the interactions, with lower scores indicating better interactions.

Table-1. List of the N-(4-(5-(Substituted phenyl)-1-formyl-4,5-dihydro-1H-pyrazol-3-yl) phenyl) isonicotinamide (MKP-1-10).

Compound	
 MKP-1 N-(4-(5-(4-chlorophenyl)-1-formyl-4,5-dihydro-1H-pyrazol-3-yl) phenyl) isonicotinamide	 MKP-6 N-(4-(1-formyl-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl) phenyl) isonicotinamide
 MKP-2 N-(4-(1-formyl-5-(4-hydroxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl) phenyl) isonicotinamide	 MKP-7 N-(4-(5-(2,3-dimethoxyphenyl)-1-formyl-4,5-dihydro-1H-pyrazol-3-yl) phenyl) isonicotinamide
 MKP-3 N-(4-(1-formyl-5-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-3-yl) phenyl) isonicotinamide	 MKP-8 N-(4-(1-formyl-5-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl) phenyl) isonicotinamide

 N-(4-(1-formyl-5-(3-nitrophenyl)-4,5-dihydro-1H-pyrazol-3-yl) phenyl) isonicotinamide	 N-(4-(1-formyl-5-(furan-2-yl)-4,5-dihydro-1H-pyrazol-3-yl) phenyl) isonicotinamide
 N-(4-(5-(4-ethylphenyl)-1-formyl-4,5-dihydro-1H-pyrazol-3-yl) phenyl) isonicotinamide	 (E)-N-(4-(1-formyl-5-styryl-4,5-dihydro-1H-pyrazol-3-yl) phenyl) isonicotinamide

A. *In-Silico* Screening for Anti- Microbial activity:

The *in-silico* screening was conducted to evaluate the potential anti-microbial activity of the synthesized pyrazoline derivatives. These compounds were docked with the bacterial protein receptor PDB ID 7KO9, and the experimental docking results are summarized in Table 2. The results reveal that the novel pyrazoline derivatives (MKP-1 to MKP-10) exhibited better binding affinity scores compared to the standard drug ciprofloxacin. Specifically, compounds MKP-2, MKP-4, and MKP-10 demonstrated superior binding affinity scores of -7.1, -7.1, and -7.3, respectively, outperforming the standard drug, which had a score of -6.8. Compound MKP-4 formed conventional hydrogen bonds with LYS A:159, while compound MKP-10 formed conventional hydrogen bonds with GLY A:377 and GLY A:356.

Table 2: Binding energy of synthesized compounds with 7KO9 (Anti-Microbial activity):

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
MKP-1	-7	32.214	29.672
MKP-2	-7.1	9.617	2.659
MKP-3	-6.9	16.561	14.196
MKP-4	-7.1	29.903	24.334
MKP-5	-7	71.722	67.587
MKP-6	-6.8	10.203	2.589
MKP-7	-7	39.649	36.51
MKP-8	-7	50.87	44.705
MKP-9	-6.7	21.392	19.206
MKP-10	-7.3	15.555	11.949
ciprofloxacin	-6.8	32.387	34.21

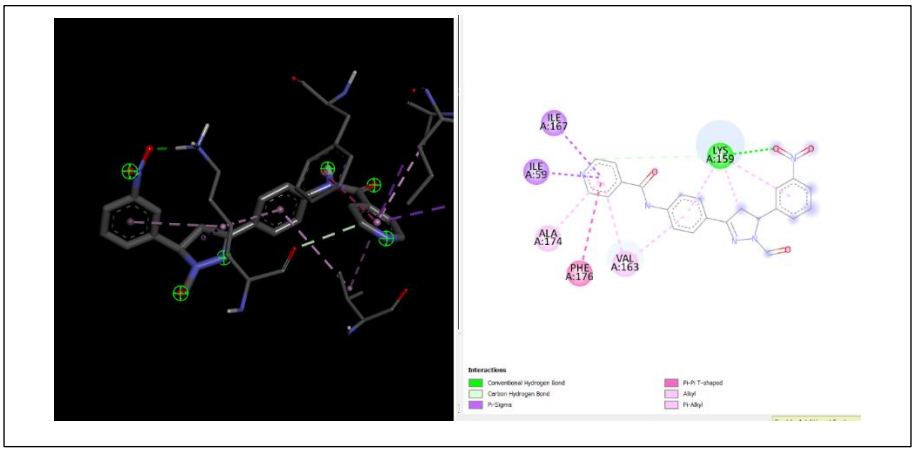


Fig-1: 3-D and 2-D interaction of compound MKP-4 with 7KO9 protein

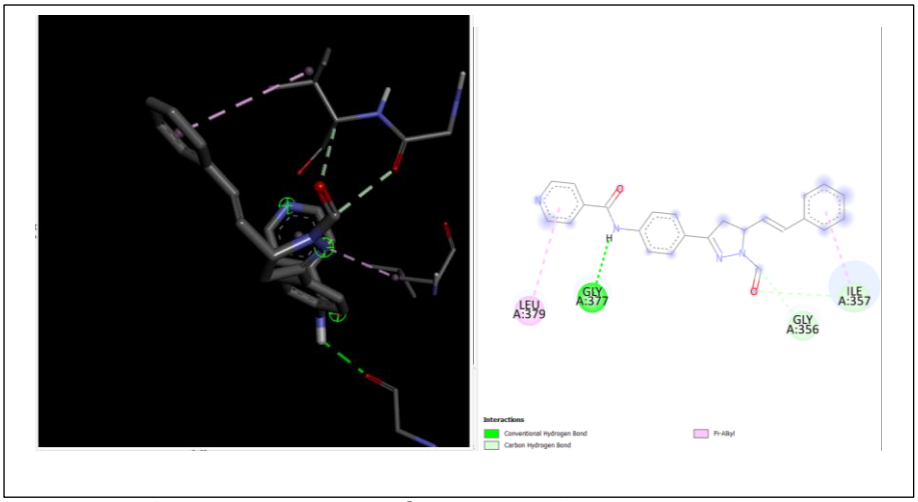


Fig-2: 3-D and 2-D interaction of compound MKP-10 with 7KO9 protein

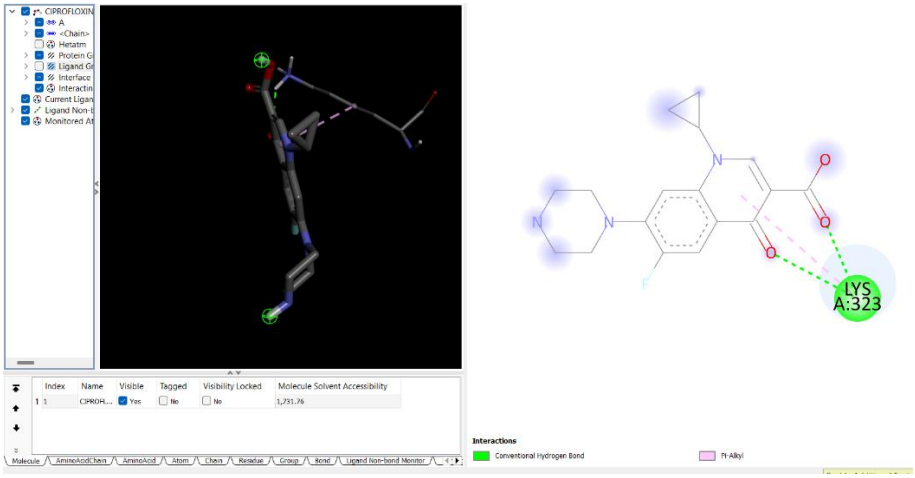


Fig-3: 3-D and 2-D interaction of ciprofloxacin with 7KO9 protein

B. *In-Silico* Screening for Anti-Inflammatory activity:

The *in-silico* screening evaluated the potential anti-inflammatory activity of the synthesized pyrazoline derivatives by docking them with the bacterial protein receptor PDB ID 4CYG. The experimental docking

results, summarized in Table 3, reveal that the novel pyrazoline derivatives (MKP-1 to MKP-10) exhibited better binding affinity scores compared to the standard drug indomethacin. Specifically, compounds MKP-2 and MKP-4 showed superior binding affinity scores of -9.5, outperforming indomethacin, which had a score of -7.2. Compound MKP-2 formed conventional hydrogen bonds with SER B:45, while compound MKP-4 formed conventional hydrogen bonds with GLU B:48.

Table 3: Binding energy of synthesized compounds with 4CYG (Anti-Inflammatory activity):

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
MKP-1	-8.3	75.606	73.41
MKP-2	-9.5	10.002	2.784
MKP-3	-8	34.938	30.114
MKP-4	-9.5	9.475	2.137
MKP-5	-8.1	40.114	37.226
MKP-6	-8.1	48.716	45.448
MKP-7	-8.9	9.723	2.502
MKP-8	-7.7	2.444	0.341
MKP-9	-7.8	49.822	46.308
MKP-10	-8.6	11.502	4.514
Indomethacin	-7.2	49.822	46.308

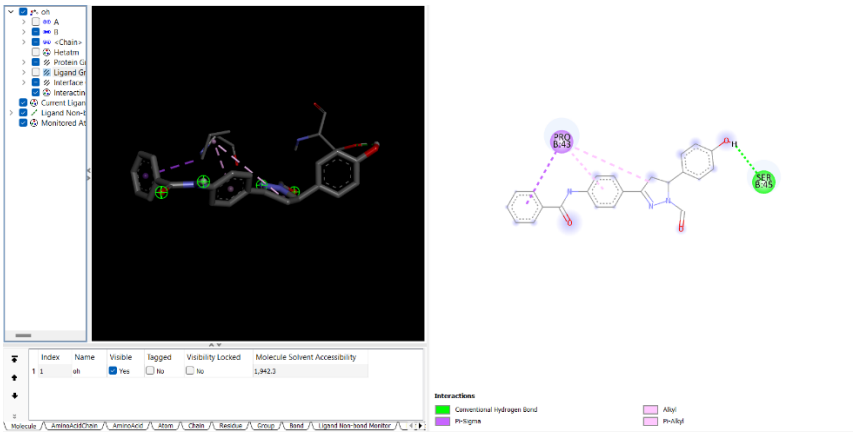


Fig-4:3-D and 2-D interaction of compound MKP-2 with 4CYG protein

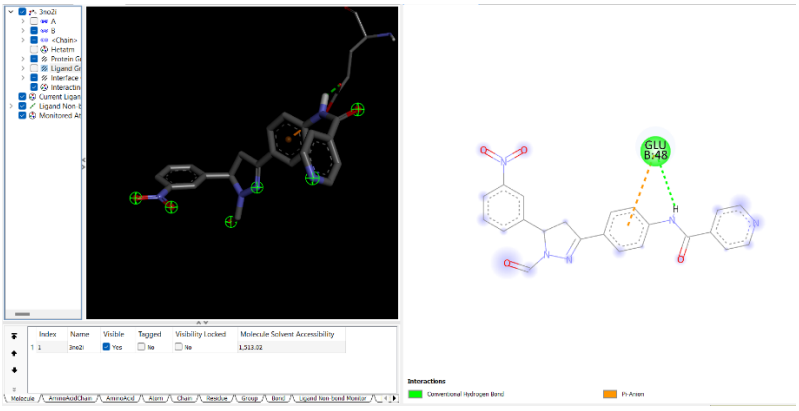


Fig-5:3-D and 2-D interaction of compound MKP-4 with 4CYG protein

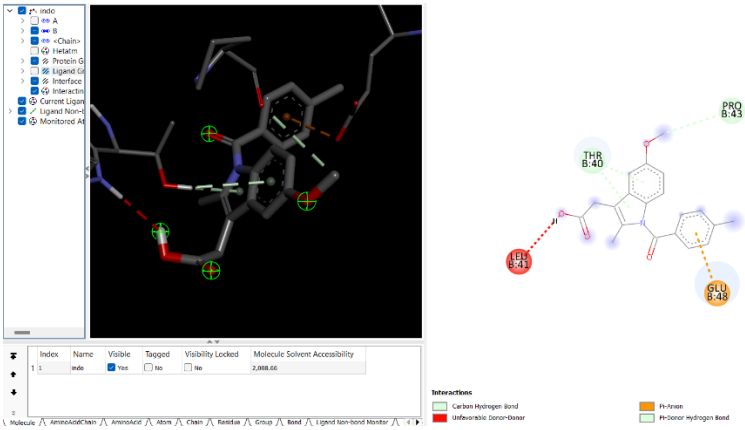


Fig-6:3-D and 2-D interaction of indomethacin with 4CYG protein

C. *In-Silico* Screening for Melanoma:

The *in-silico* screening was conducted to evaluate the anti-cancer potential of the synthesized compounds, these pyrazoline derivatives were docked with bacterial protein PDB ID 6R7T receptor, and the experimental docking results are summarized in Table 4. The table reveals that the novel pyrazoline derivatives (MKP-1-10) exhibited better binding affinity scores. Specifically, compounds MKP-1, MKP-3 and MKP-4 demonstrated superior binding affinity scores of -8.3, -8.4 and -9.1. Compound MKP-4 formed conventional hydrogen bonds with ILE B:131, TYR B:177, ARG B:128.

Table 4: Binding energy of synthesized compounds with 6R7T (Anti-cancer activity):

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
MKP-1	-8.3	5.442	3.132
MKP-2	-7.7	36.418	32.964
MKP-3	-8.4	36.541	33.414
MKP-4	-9.1	30.548	28.546
MKP-5	-7.6	40.787	35.287
MKP-6	-7.6	36.475	32.727
MKP-7	-8.2	10.048	2.735
MKP-8	-7.8	24.891	21.885
MKP-9	-7.7	26.529	22.403
MKP-10	-8.1	9.498	4.048

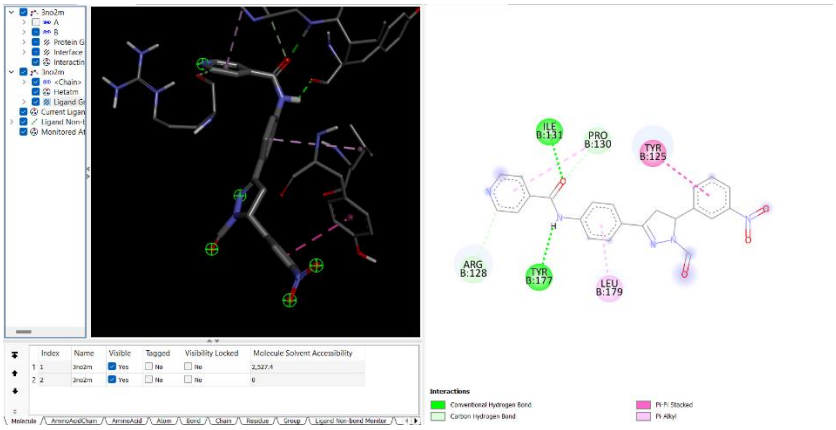


Fig-7:3-D and 2-D interaction of MKP-4 with 6R7T protein

D. *In-silico* Toxicity Studies

Toxic doses are often expressed as LD50 values in mg/kg body weight. The LD50 (median lethal dose) is the dose at which 50% of test subjects die upon exposure to a compound. Toxicity classes are defined according to the globally harmonized system of classification and labelling of chemicals.

LD50 Values (mg/kg):

- Class I: Fatal if swallowed (LD50 ≤ 5)
- Class II: Fatal if swallowed (5 < LD50 ≤ 50)
- Class III: Toxic if swallowed (50 < LD50 ≤ 300)
- Class IV: Harmful if swallowed (300 < LD50 ≤ 2000)
- Class V: May be harmful if swallowed (2000 < LD50 ≤ 5000)
- Class VI: Non-toxic (LD50 > 5000)

All the synthesized compounds were subjected to online toxicity prediction using ProTox-II. Most of the synthesized compounds fell into Class IV, as the high LD50 values indicate their safety. All derivatives were found to be non-hepatotoxic, non-mutagenic, and non-cytotoxic, except for some carcinogenicity concerns.

Table 5: *In-silico* Toxicity studies of synthesized compounds

Compound code	*Predicted LD50 (mg/kg)*	*Predicted Toxicity Class*	*Hepatotoxicity*	*Carcinogenicity*	*Immunotoxicity*	*Mutagenicity*	*Cytotoxicity*
MKP-1	1000	4	Active	Inactive	Inactive	Inactive	Inactive
MKP-2	1000	4	Inactive	Inactive	Inactive	Inactive	Inactive
MKP-3	1000	4					

			Inactive	Inactive	Inactive	Inactive	Active
MKP-4	1000	4	Inactive	Inactive	Inactive	Inactive	Inac-tive
MKP-5	1000	4	Inactive	Active	Inactive	Inactive	Inac-tive
MKP-6	1000	4	Active	Inactive	Inactive	Active	Inac-tive
MKP-7	1000	4	Active	Inactive	Active	Active	Inac-tive
MKP-8	1000	4	Inactive	Active	Active	Inactive	Inac-tive
MKP-9	1000	4	Aactive	Active	Inactive	Inactive	Inac-tive
MKP-10	1000	4	Active	Inactive	Inactive	Inactive	Inac-tive

E. *In-silico* Physicochemical Studies.

All the compounds showed a good lipophilic profile with low miLogP and all the compound followed Lipinski rule of five with no violation of rule.

Table 6: *In-Silico* Physicochemical studies obtained from Molinspiration

Compound Code	*mi-LogP*	*TPSA*	*N at-oms*	*MW (g/mol)*	*nON*	*nOHNH*	*n viola-tion*	*n rotb*	*Vol-ume*
MKP-1	3.23	74.66	29	404.86	6	2	0	4	345.44
MKP-2	2.07	94.89	29	386.41	7	2	0	4	339.41
MKP-3	2.51	120.49	31	415.41	9	1	0	5	355.24
MKP-4	2.48	120.49	31	415.41	9	1	0	5	355.24
MKP-5	3.46	74.66	30	398.47	6	1	0	5	365.27

MKP-6	2.60	83.90	30	400.44	7	1	0	5	357.45
MKP-7	2.37	93.13	32	430.46	8	1	0	6	383.00
MKP-8	2.18	102.36	34	460.49	9	1	0	7	408.54
MKP-9	1.80	87.80	27	360.37	7	1	0	4	313.47
MKP-10	3.30	74.66	30	396.45	6	1	0	5	359.32

F. Bioactivity score.

The results indicated that some of the synthesized compounds possess physicochemical properties within the acceptable range. Using the Molinspiration software online test, the bioactivity of all compounds was predicted and is summarized in Table 7. The bioactivity scores of the synthesized compounds suggest they have a likelihood of displaying good to moderate activity towards GPCR ligands, ion channel modulators, kinase inhibitors, nuclear receptor ligands, protease inhibitors, and other enzyme inhibitors. These scores can be interpreted as follows: active (bioactivity > 0), moderately active (bioactivity score between -5.0 and 0.0), and inactive (bioactivity score < -5.0).

Table 7: *In-Silico* bio-activity scores of synthesized compounds.

Compound code	***GPCR ligand***	***Ion channel modulator***	***Kinase inhibitor***	***Nuclear receptor ligand***	***Protease inhibitor***	***Enzyme inhibitor***
MKP-1	-0.22	-0.56	-0.23	-0.51	-0.28	-0.21
MKP-2	-0.18	-0.52	-0.18	-0.37	-0.23	-0.14
MKP-3	-0.33	-0.56	-0.32	-0.53	-0.34	-0.25
MKP-4	-0.33	-0.57	-0.32	-0.53	-0.35	-0.26
MKP-5	-0.21	-0.54	-0.26	-0.44	-0.23	-0.17
MKP-6	-0.25	-0.61	-0.24	-0.48	-0.29	-0.22
MKP-7	-0.27	-0.87	-0.28	-0.51	-0.33	-0.23
MKP-8	-0.24	-0.56	-0.21	-0.50	-0.30	-0.20
MKP-9	-0.38	-0.84	-0.53	-0.64	-0.53	-0.30
MKP-10	-0.09	-0.42	-0.21	-0.18	-0.11	-0.13

G. *In-silico* ADME properties:

The novel pyrazoline compounds (MKP-1 to MKP-10) were subjected to *in-silico* ADME property prediction using the Swiss-ADME online software. The adsorption (% ABS) of the compounds from the intestinal tract was calculated using the formula: % ABS = 109 - (0.345 x Topological Polar Surface Area (TPSA)). Swiss-ADME provides physicochemical properties of potential oral drug candidates based on

five different rules: Lipinski's, Ghose, Veber, Egan, and Muegge. The novel compounds exhibit an acceptable pharmacokinetic profile.

The solubility of these compounds in water is classified quantitatively as follows: insoluble (< -10), poorly soluble (-10 to -6), moderately soluble (-6 to -4), soluble (-4 to -2), very soluble (-2 to 0), and highly soluble (> 0). According to the results, all the compounds are moderately soluble in water.

Table 9: *In-silico* ADME properties obtained from SwissADME

Compound code	***MKP-1***	***MKP-2***	***MKP-3***	***MKP-4***	***MKP-5***	***MKP-6***	***MKP-7***	***MKP-8***	***MKP-9***	***MKP-10***
Num. heavy atoms	27	29	30	27	27	24	24	30	26	30
Num. Arom. Heavy atoms	12	6	12	12	12	11	6	12	12	18
Num. Rotatable bonds	9	10	11	9	9	8	8	9	8	7
Num. H-bond acceptors	6	7	7	6	4	4	4	4	5	4
Num. of H-bond donars	2	1	1	2	1	1	1	1	2	1
Molar refractivity	102.48	110.64	113.45	102.48	108.18	96.81	95.42	123.42	101.00	124.55
Total Polar Surface Area(Å)	93.06	63.63	91.29	93.06	66.84	91.84	63.60	66.84	83.83	74.66 A^2
Log Po/w (ilogp)	2.87	0.00	3.59	3.02	3.38	3.23	2.89	3.79	2.74	2.52
Water solubility	Soluble	Moderately soluble	Moderately soluble	Soluble	Moderately soluble	Soluble	Moderately soluble	Moderately soluble	Moderately soluble	Moderately soluable
GI absorption	High	High	high	High	high	High	High	High	High	High
BBB permeant	No	Yes	yes	No	yes	yes	Yes	Yes	yes	yes

Drug likeness (violation)	Yes; (0)	Yes; (0)	Yes; (0)	Yes; (0)	Yes; (0)	Yes; (0)	Yes; (0)	Yes; (0)	Yes; (0)	Yes; (0)
Lead likeness (violation)	No; (1), MW> 350	No; (1), MW> 350	No; (1), MW> 350	No; (1), MW> 350	No; (1), MW> 350	No; (1) MW> 350	No; (1) MW> 350	No; (3), MW> 350	No; (3), MW> 350	No; (1) MW> 350

DISCUSSION

Novel pyrazoline derivatives MKP-1 to MKP-10 were subjected to molecular docking studies using bacterial protein 7KO9, inflammatory protein 4CYG, and melanoma protein 6R7T. The docking results revealed that pyrazoline derivatives MKP-1 to MKP-10 exhibit moderate to better binding affinity scores compared to the standard drug. Notably, compounds MKP-2 and MKP-4 demonstrated higher binding affinity scores among the ten pyrazoline compounds and the standard drugs. Specifically, compound MKP-4 displayed the best binding affinity scores across all activities among the ten pyrazoline compounds. *In-silico* ADME property predictions were also conducted for these pyrazoline compounds (MKP-1 to MKP-10). The results established that our synthesized pyrazoline compounds have good drug-likeness scores.

CONCLUSIONS

In summary, the novel pyrazoline derivatives (MKP-1-10) were successfully synthesized and evaluated for their potential anti-microbial, anti-inflammatory, and anti-cancer activities through *in-silico* studies. Molecular docking studies revealed that certain derivatives, particularly MKP-2 and MKP-4, exhibited superior binding affinity scores when compared to standard drugs. These derivatives showed promising interactions with key proteins involved in microbial, inflammatory, and cancer pathways, highlighting their potential as multi-target therapeutic agents.

The introduction of specific functional groups, such as 4-NO2, 4-OH, and 4-Cl, in the phenyl ring at the 5-position of the pyrazoline ring significantly enhanced their bioactivity. The *in-silico* ADME and toxicity predictions indicated that these compounds possess favourable pharmacokinetic profiles and are generally non-toxic, further supporting their potential as drug candidates.

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