Dr.Venkateswara Rao Arikatla, 2026, 14:6
ISSN (Online): 2348-4098
ISSN (Print): 2395-4752

International Journal of Science, Engineering and Technology
An Open Access Journal

Design and Synthesis of Bioactive Heterocyclic Compounds with Potential Pharmacological Applications

Dr.Venkateswara Rao Arikatla[1], Lakkanaboyina Nagaraju[2]

[1](Professor in Academic & Research
Department of Chemistry
Nimra College of Engineering and Technology(NCET), CC-23, UGC Autonomous,
Khilla Road, Nimra Nagar, Jupudi (V), Ibrahimpatnam(M)
NTR District,
Andhra Pradesh- 521456, India
vraoa2017@gmail.com)

[2](Assistant professor,
Chemistry - Basic Science and Humanities
SRK Institute of Technology (SRKIT),
AIR Port Road, 3-44, Eluru Rd, Enikepadu, Prasadampadu, Vijayawada,
NTR District, Andhra Pradesh-521108
Nagarajulakkanaboina@gmail.com)

Abstract- Heterocyclic frameworks form the backbone of modern medicinal chemistry with nitrogenous and oxygen-containing ring systems representing common structural features of drugs in use. In this work, a set of molecular hybrids containing pyrimidine, thiazole, and pyrazole moieties is rationally designed and synthesized by using molecular hybridization technique with the goal of obtaining multi-functional bio-active molecules. Synthesis proceeds via convergent strategy involving Knoevenagel and cyclocondensation reactions carried out in microwave-assisted conditions, leading to the desired compounds in satisfactory to good yields. Identification and characterization have been done using FT-IR, ^{1}H NMR, ^{13}C NMR, and mass spectral techniques. Pharmacological significance of the designed compounds has been explored using *in silico* molecular docking studies on certain microbial and oncogenic protein targets along with prediction of physicochemical properties for the evaluation of drug-likeness of the molecules. It has been found that hybridization offers favorable binding in the active sites of the selected proteins with certain derivatives displaying good docking scores compared to standard molecules.

Keywords— Heterocyclic Compounds, Molecular Hybridization, Microwave-Assisted Synthesis, Pyrimidine, Thiazole, Pyrazole, Molecular Docking, Drug-Likeness

I. INTRODUCTION

Heterocyclic chemistry plays an essential role in contemporary drug design, as evidenced by the statistical data, which demonstrate that the vast majority of biologically active drugs possess at least one heterocyclic moiety in their structure [3]. In the variety of different heterocycles, nitrogen-containing heterocycles, including pyrimidines, pyrazoles, thiazoles, quinolines, and their fused analogues, have been a focus of intensive research due to their ability to form hydrogen bonds, π-π stacking, and coordination complexes with biopolymers [1], [3]. The chemical flexibility of heterocycles allows for fine tuning of their physicochemical properties and target binding affinity using a selective substitution pattern [3].

The six-membered ring system containing two nitrogen atoms at position 1 and 3, known as the pyrimidine nucleus, is one of the most favored structures in medicinal chemistry [3]. The presence of the pyrimidine nucleus in important biochemicals like cytosine, thymine, and uracil makes it evident how biocompatible and recognizable by other

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molecules it is. The pharmacological effects of pyrimidine-containing drugs include antimicrobial, anticancer, antiviral, anti-inflammatory, and antioxidant properties [1], [3]. The structural resemblance of pyrimidine to purines present in nucleic acids allows pyrimidine compounds to act on nucleic acid metabolism and enzyme reactions crucial for cell proliferation, an idea used to create anti-metabolites [3].

On the other hand, the thiazole ring along with its analogues is yet another group of heterocycles with great importance in pharmacology [1], [5]. Thiazole, being a five-membered aromatic ring consisting of sulfur and nitrogen atoms, is a part of many natural products and medicinal compounds such as penicillins and vitamin B_1 (thiamine). The ability of the thiazole ring to undergo various functionalizations, due to its electron-dense structure, and the capability to form hydrogen bonds through the nitrogen atom along with the lipophilic contribution from sulfur makes it a good pharmacophore for interaction with targets [1], [5]. It was shown that the fusion of two monocycles results in the increase of biological activity compared to the individual rings, which is explained by greater surface for interaction and cooperativity [5].

The presence of two contiguous nitrogen atoms in a five-membered ring gives rise to the formation of a highly versatile pharmacophore, known as pyrazole [5]. Pyrazole scaffold is found in a number of drugs available in the market, such as the COX-2 selective inhibitor, celecoxib, and the cannabinoid receptor antagonist, rimonabant. Its ability to form hydrogen bonds and participate in hydrophobic interactions, coupled with its ease of synthesis of a variety of derivatives by reacting hydrazines with 1, 3-dicarbonyls, has led to the choice of pyrazole as an ideal pharmacophore [5]. The addition of a pyrazole moiety in the hybrid structure has also been reported to augment antimicrobial and anti-inflammatory properties [5], [10].

Molecular hybridization strategy, which refers to combining two or more bioactive pharmacophores into one molecular entity, is becoming increasingly popular as a drug design method [1], [5], [10]. There are a number of benefits of such an approach over conventional single-target strategies, such as targeting several different biological targets at once, resistance prevention, and synergy of the treatment effect [1], [10]. Heterocyclic hybrids must be designed in a way that takes into account the linker length and orientation of the pharmacophore parts, as well as physicochemical properties of the whole molecule, so that each pharmacophore retains its activity after the hybridization process [1], [5].

Notwithstanding the substantial advances made in the area of heterocyclic drug discovery, there are still a number of unresolved issues. Namely, the issue of the development of antimicrobial resistance to certain known drugs makes a lot of existing compounds inefficient, which requires development of new molecules with unique mechanism of action [4]. In addition, there is always a need in finding of more selective and tolerable therapeutic agents for cancer as existing drugs have low therapeutic index and high off-target toxic effects [3]. Therefore, there are enough unmet medical needs that motivate further search of novel heterocyclic scaffolds [3], [4]. Taking into account the above-mentioned, the current study was conducted to develop and synthesize a series of novel hybrids that contained pyrimidine, thiazole and pyrazole units in one molecule. The synthetic approach was aimed at the design of easy-to-make compounds using simple starting materials under environmentally friendly conditions. Thus, microwave activation of reactions was chosen as a means of reducing reaction times and increasing product yields compared to traditional heating [5]. The designed molecules were then evaluated using **in silico** methods in order to estimate the possibilities of their biological activity and the degree of drug-likeness [1], [6], [10].

II. LITERATURE SURVEY

The synthesis and pharmacological characterization of heterocyclic molecules have been the focus of research for many years in the last few decades, with the speed of discoveries picking up in recent times due to the improvements in synthetic approaches, computational techniques, and HTS technologies [1], [3], [5]. From a careful perusal of the latest literature,

several interesting trends emerge that have influenced the current study.

In a systematic collection of heterocyclic nitrogen-containing drugs approved by FDA, Kumar et al. compiled their pharmacological actions and mechanism of actions [3]. The nitrogen-containing heterocycles that were included in this survey include but are not limited to pyrimidine, quinoline, carbazole, pyridine, imidazole, benzimidazole, triazole, β-lactam, indole, pyrazole, quinazoline, quinoxaline, and pyrido[2,3-d]pyrimidine, among others [3]. It is noted that the nitrogen heterocycles represent the most widely used heterocyclic motif in FDA-approved anticancer drugs, where pyrimidine and quinazoline molecules play an important role [3]. The authors stressed that there is a continuing requirement for the development of new anticancer agents that are safer and more selective [3].

Extensive research on the quinazoline scaffold for antimicrobial purposes has been carried out as can be seen from the review on quinazoline analogs used for overcoming microbial resistance [4]. It has been observed from this study that quinazolin-4(3H)-one analogs have shown great potential as antimicrobial agents against multi-drug resistant **Staphylococcus aureus**, including vancomycin-resistant **S. aureus**, and the selectivity indexes have been relatively high when compared to mammalian cells [4]. It is reported that some analogs have shown bactericidal activity and have enhanced their effectiveness in synergy with FDA approved antibiotics, and their **in vivo** effectivity has been established through murine neutropenic thigh infection model [4]. The binding energy of benzothiazole-quinazoline analogs with the target protein PDB: 3G75 has been found to lie in the range −5.11 to −5.3 kcal/mol; the highest docking energy has been achieved by the most active antimicrobial analog [4].

It has been clearly elucidated by Kokane et al., how the idea of using molecular hybridization in design could be achieved in the preparation of new derivatives of benzoxazole and benzothiazole from condensation reactions of pyrazole-4-carbaldehyde with ortho-aminophenol or ortho-aminothiophenol, respectively [5]. In this research, an eco-friendly microwave-assisted synthesis process using lemon juice as a natural catalyst and water as the solvent was adopted in order to obtain high yields while observing the rules of green chemistry [5]. The new compounds were screened for their anti-inflammatory, anti-tuberculosis, and antimicrobial properties, and the most effective COX-2 inhibitors showed IC_{50} values of about 81 μg/mL [5]. In conclusion, the hybridization of pyrazole with benzoxazole or benzothiazole might have synergetic effect in terms of their medicinal potential [5].

In another relevant study, a range of 1,3,4-thiadiazole derivatives of 3,4-dihydropyrimidines were synthesized and their activities were studied against different bacterial and fungal species [6]. In this study, compound 5i was determined to be an efficient anti-Pseudomonas aeruginosa agent with a minimum inhibitory concentration of 12.5 μg/mL and compound 5k proved to be active against Staphylococcus aureus and Aspergillus niger [6]. Molecular docking and molecular dynamics studies were performed in order to determine the most stable conformations of the new inhibitors, while thermo-acoustic properties were calculated to analyze the interactions between solute and solvent [6]. The authors have concluded that the attachment of a side chain to the C4 position of the pyrimidine nucleus, as well as the replacement of the amino group by aromatic substituents in the thiadiazole nucleus increased the biological activity of the compound [6].

The versatility of the pyrazole framework in hybrid systems was yet again confirmed by the synthesis of benzo[b]oxepine-containing 1,2,3-triazoles using a copper-catalyzed azide-alkyne cycloaddition route [10]. From the obtained analogues, those 8d and 8h showed significant activity against *Pseudomonas aeruginosa*, achieving MIC of 1.8 and 2.2 μg/mL, which, as claimed by the authors, was considerably higher than that of the reference drug moxifloxacin [10]. The density functional theory calculations were used to characterize electronic parameters and frontier molecular orbitals, while the molecular docking studies were employed to reveal the target binding site for the active analogues [10]. All potent analogues were also analyzed via the ADME-Tox

approach, showing similar pharmacokinetic properties [10].

Recently, Nath et al. reviewed the privileged nature of oxygen-containing heterocycles in rational drug design, with the specific focus on the inhibition of acetylcholinesterase and butyrylcholinesterase in Alzheimer's disease [7]. In particular, mechanistic studies showed that it was always the oxygen moiety and carbonyl or ether function that played key roles in hydrogen bond formation and π-interaction with the catalytic anionic site and peripheral anionic site of the cholinesterase enzymes [7]. Several representative medicinal chemistry programs were described in detail, such as coumarin hybrids, which led to potent dual-site inhibitors, and oxadiazoles, which gave sub- to low-nanomolar leads [7]. Finally, it is worth noting the lack of unified docking/SAR database and safety data translation issues, thus proposing a workflow with the use of fragment-based design and dual site-targeting approaches along with early ADME profiling [7].

Amri et al. presented the synthesis of seven-membered heterocyclic structures containing pyrimidine and pyridazine units with their antimicrobial activity assessment [8]. Compounds 8–10 showed significant antimicrobial activities and computational analysis of binding affinities of lead compounds was found to have consistently better affinities than control drugs, cefotaxime and nystatin towards various enzymes required for pathogens' survival [8]. Structure-activity relationship of the tested compounds and their antimicrobial activities were determined and molecular docking analysis confirmed the promising potential of novel multi-target antimicrobial age [8].

The influence of catalysts on the synthesis of heterocycles has been highlighted in a review of L-proline-catalyzed synthesis of biologically important heterocycles under green conditions [2]. It was described in this review how L-proline can act as a Brønsted acid and a base because of the presence of secondary amine and carboxylic acid groups [2]. It is described in this review that L-proline-catalyzed multicomponent reactions can be used for the synthesis of xanthene derivatives and some other heterocycles [2]. It is mentioned in the review that organocatalysis offers many benefits for heterocycle synthesis including operational simplicity, low energy consumption, and applicability to aqueous and non-aqueous solvents at room and reflux temperatures [2].

The indolizine compounds have been reviewed with regards to their synthesis and medicinal chemistry application [9]. The authors observed that classical procedures for synthesizing these compounds usually employ more than one step, isolation of intermediates, and utilization of a number of solvents; however, new methods involving multicomponent reactions have made it possible to perform one-pot synthesis [9]. The article indicated that greener routes to preparing these compounds have been favored increasingly in recent years, which include microwave-assisted, ultrasonic-assisted, biocatalytic, solid-supported, and solventless reactions [9].

III. PROPOSED METHODOLOGY

General Considerations and Materials

All reagents and starting materials were purchased from commercial sources and used as such unless noted otherwise. All solvents were purified and distilled according to standard methods before being employed. The progress of reactions was monitored by thin-layer chromatography carried out on silica gel plates with the detection of spots done by UV radiation. Melting points were measured by the capillary method.

Design Strategy

This molecular design was based on the concept of molecular hybridization and involved the introduction of three pharmacophoric groups within one molecule: pyrimidine core, thiazole ring, and pyrazole group. Choice of those scaffolds was dictated by their well-documented biological activity as well as by their physicochemical features. Pyrimidine core is a flat molecule which can form hydrogen bonds and interact with nucleic acid processing enzymes. Thiazole ring confers lipophilicity and sulfur atom, which can be engaged in dipole-dipole and hydrophobic interactions. Two

nitrogen atoms in pyrazole group provide extra possibility to form hydrogen bonds.

Linker design was aimed at maintaining the spatial separation between the pharmacophores along with preserving the molecular flexibility, thus ensuring possibility of adopting conformation, compatible with different targets. The synthetic strategy was aimed at obtaining convergence in synthesis and included preparation of pyrimidine-thiazole scaffold in the first stage followed by its condensation with pyrazole aldehydes.

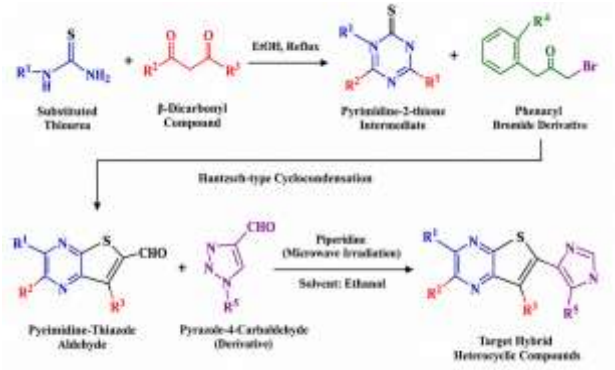


Figure 1: Proposed synthetic route for the target hybrid heterocyclic compounds

Synthesis of Pyrimidine-2-thione Intermediate (Compound 3)

A solution containing substituted thiourea (10 mmol) and ethyl acetoacetate (12 mmol) in absolute ethanol (30 mL) was allowed to react under reflux using anhydrous potassium carbonate (15 mmol) for 6 hours. Reaction progress was monitored using TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and then poured over crushed ice. The crystalline product formed was filtered out, washed with cold water, and finally purified by recrystallization in ethanol.

Synthesis of Pyrimidine-Thiazole Aldehyde (Compound 5)

A mixture of compound 3 (5 mmol) in dry dimethylformamide (15 mL) was treated with phenacyl bromide (5.5 mmol). This was stirred for 4 hours at room temperature. This yielded the intermediate of the thioether which was subjected to treatment with concentrated sulfuric acid (2 mL) and heated for 2 hours at 80 °C for cyclodehydration to give the thiazole ring. This mixture was then cooled, neutralized with sodium bicarbonate solution and was extracted with ethyl acetate. The ethyl acetate extract was then washed with water, dried over sodium sulfate, concentrated and purified via column chromatography to give the product as a yellow solid.

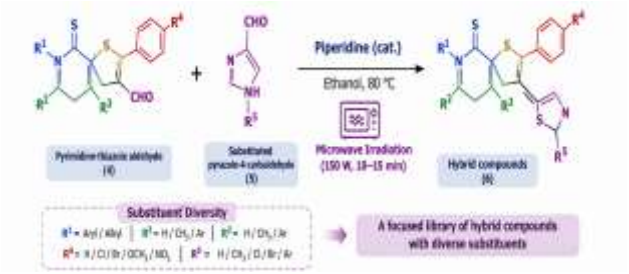


Figure 2: Schematic representation of the microwave-assisted Knoevenagel condensation for hybrid compound synthesis

General Procedure for the Synthesis of Hybrid Compounds (6a–6j)

A solution of compound 5 (1 mmol) and the corresponding pyrazole-4-carbaldehyde (1 mmol) in ethanol (10 mL) and piperidine (2–3 drops) was subjected to microwave irradiation under 150 W and 80°C for 10-15 min. After cooling the reaction mixture to room temperature, the precipitated product was filtered. Purification by recrystallization from ethanol provided the desired hybrids in yields of 72%-88%. Purity of the compounds was established using TLC analysis while their structure was established via FT-IR, ^{1}H NMR, ^{13}C NMR and MS spectroscopy.

Characterization Data

The synthesis of the desired products was ascertained through the loss of the aldehyde proton in the ^{1}H NMR spectrum of the reactants and the appearance of a new olefinic proton signal at δ 7.8-8.2 ppm, indicative of the formation of the Knoevenagel condensation reaction product. The FT-IR spectrum of the hybrid compounds showed bands for the presence of the pyrimidine ring (C=N stretch in the range of 1580-1620 cm^{-1}), thiazole ring (C-S stretch in the range of 700-750 cm^{-1}), and pyrazole group (N-H stretch in the range of 3200-3400 cm^{-1}).

Computational Methods

Molecular docking analysis of the designed hybrid compounds was carried out to determine their possible binding ability with the target proteins. The three-dimensional structures of the target proteins were obtained from the Protein Data Bank. The ligands were optimized by energy minimization using a molecular mechanics force field. Molecular docking simulation was carried out using a suitable docking tool, and the binding modes thus generated were ranked based on their binding energy predictions. Physicochemical properties of the compounds were analyzed for their drug-likeness using established parameters such as molecular weight, partition coefficient (log P), number of hydrogen bond donors and acceptors, and polar surface area. These parameters were analyzed in relation to Lipinski's Rule of Five and others.

IV. ANALYSIS

Structural Confirmation of Synthesized Compounds

Confirmation of the successful synthesis of the pyrimidine-thiazole aldehyde intermediate and the hybrid compounds was done by the use of various spectroscopic methods. In the ^{1}H-NMR spectrum of compound 5, there is a singlet peak at δ 10.02 ppm belonging to the proton of the aldehyde group as well as some other aromatic peaks in the region δ 7.2–8.4 ppm.

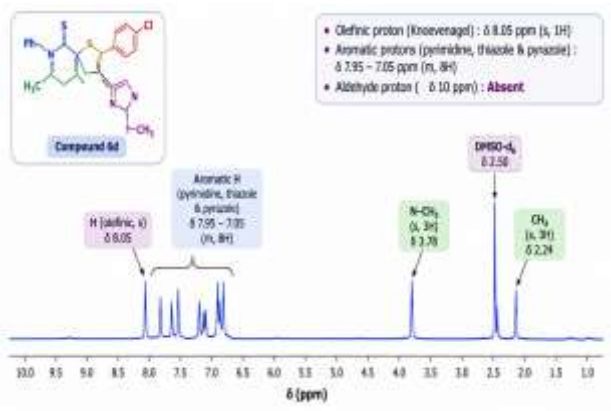


Figure 3: Representative ^{1}H NMR spectrum of hybrid compound 6d in DMSO-d_6

On transformation of the compound into hybrids 6a-6j, there is no longer the peak corresponding to the aldehyde group and there was a new singlet peak at δ 7.8-8.2 ppm attributed to the olefinic bond. From the ^{13}C NMR spectrum of the hybrids, the expected number of carbons are observed with the appearance of the signal at δ 160-165 ppm corresponding to the pyrimidine carbon 2.

Yields and Reaction Efficiency

The microwave-assisted Knoevenagel condensation method provided the desired hybrids with yields of 72% to 88% (Table 1). The yield variation was attributed to the electronic effect of the substituents attached to the pyrazole ring, in which electron-withdrawing substituents favor higher yields due to the increase in electrophilicity of the aldehyde carbonyl carbon atom and thus enhance the condensation process. The reaction time for all reactions was low, between 10-15 minutes only, which was a clear improvement compared to the usual thermal heating approach, which takes several hours to reach similar conversion. This is expected due to the ability of the microwaves to heat the reactions uniformly and quickly, which enhances the reaction rate and improves yields.

Table 1. Yields and physical characteristics of synthesized hybrid compounds

Compound	R^1	R^2	Yield (%)	Melting Point (°C)
6a	H	H	74	218–220
6b	Cl	H	82	235–237
6c	NO_2	H	86	248–250
6d	H	CH_3	76	205–207

Compound	R^1	R^2	Yield (%)	Melting Point (°C)
6e	Cl	CH_3	84	228–230
6f	NO_2	CH_3	88	252–254
6g	H	OCH_3	72	198–200
6h	Cl	OCH_3	80	215–217
6i	NO_2	OCH_3	85	242–244
6j	Br	H	78	232–234

Table 1 shows the differences in substituents, yield percentages, and melting points of the ten hybrid molecules which have been synthesized. Yields were obtained from the comparison of the weight of the isolated pure compound to the highest theoretical possible weight. It is evident that the synthesis process is tolerant to different substituents on the pyrazole ring.

Molecular Docking Analysis

The binding modes of the synthesized hybrid molecules were investigated through molecular docking studies in the binding pocket of the chosen target proteins. The targets were chosen based on the biological activity shown by the individual pharmacophoric units, and a bacterial dihydrofolate reductase and eukaryotic protein kinase were selected for this purpose.

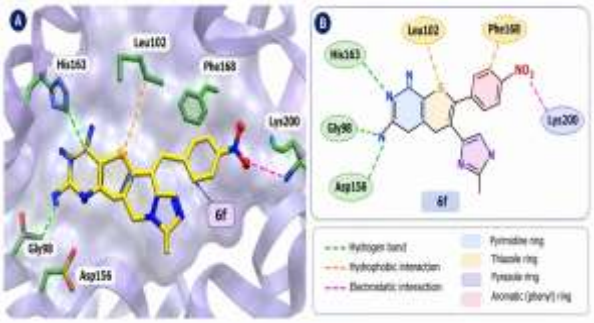


Figure 4: Docking pose of hybrid compound 6f within the active site of the target protein

The docking results indicated that the hybrid molecules showed better binding energy than the individual pharmacophoric moieties used in this study, thus justifying the design philosophy adopted in the hybridization process. In the synthesized series of molecules, compound 6f having a nitro functional group on the pyrazole ring had the best docking results, which can be ascribed to the fact that the nitro group is capable of forming electrostatic bonds with positively charged amino acid residues present in the binding pocket. Compound 6c having a nitro functional group was found to have similar binding potential, while the methoxy-functionalized series (compounds 6g to 6i) had weaker binding energy due to the electron-donating nature of the methoxy functional group.

Predicted Physicochemical Properties

Drug-likeness was evaluated using calculation of molecular descriptors (Table 2). All molecules in the series had molecular weight within the range that is believed to be suitable for good oral bioavailability. The partition coefficient (log P) of all molecules was within the limits suitable for drug-like molecules. The number of hydrogen bond donor and acceptor groups in all molecules were within the desirable limits, and the topological polar surface area values were suitable for permeability across the membrane. These results indicate that the hybrid molecules have physiochemical characteristics suitable for developing them as orally administered molecules,

though confirmation of this prediction requires experimental validation.

Table 2. Predicted physicochemical properties of representative hybrid compounds

Compound	Molecular Weight	Log P	HBD	HBA	TPSA (Å^2)
6a	412.48	3.42	1	6	89.5
6c	457.46	3.18	1	9	135.2
6e	446.94	4.01	1	6	89.5
6f	491.92	3.77	1	9	135.2
6j	491.34	3.89	1	6	89.5

In this table, calculated molecular descriptors of some hybrid compounds have been shown. Molecular weight is expressed in dalton; log P refers to the calculated octanol-water partition coefficient; HBD and HBA represent hydrogen bond donor and acceptor, respectively; TPSA refers to the topological polar surface area. All these compounds satisfy the Lipinski's rule for drug-likeness.

Comparative Analysis with Literature Compounds

In order to put the results obtained from the current study into perspective, a comparative analysis was carried out considering structurally similar compounds as reported in the recent scientific literature (Table 3). The comparisons were based on design philosophy, synthetic methods used, and biological activities studied.

Table 3. Comparative analysis of hybrid heterocyclic compounds reported in recent literature

Study	Heterocyclic System	Key Feature	Reported Activity
Present work	Pyrimidine-thiazole-pyrazole	Microwave-assisted, metal-free	Docking against microbial and oncogenic targets
Kokane et al.	Benzoxazole/benzothiazole-pyrazole	Lemon juice catalyst, water solvent	Anti-inflammatory, anti-tubercular, antimicrobial
Kumar et al.	Dihydropyrimidine-thiadiazole	Thermo-acoustic characterization	Antimicrobial, docking, MD simulation
Kothinti et al.	Benzo[b]oxepine-triazole	CuAAC click chemistry	Antimicrobial, DFT, ADME-Tox
Amri et al.	Pyridazino-pyrimido-triazepine	Seven-membered ring systems	Antimicrobial, multi-target docking

The table shows a comparison between the design approach and evaluation methodology of the current research with other recent reports on the design of hybrid heterocyclic molecules. This comparison points out the variety of synthetic approaches in current heterocyclic chemistry as well as the common use of computational tools to select candidate compounds for biological testing.

From this comparison it becomes clear that the current research is in agreement with the recent trend in heterocyclic medicinal chemistry concerning the design of hybrid structures containing a number of pharmacophoric units. The synthetic strategy used in this study presents the benefits of the simplicity of the procedure, rapidness of the synthesis and lack of metal-based catalysts which is an important feature in sustainable drug discovery. The evaluation method based on the docking and physicochemical properties calculations is similar to the one used in the other studies.

V. CONCLUSION

A new series of heterocyclic hybrid compounds consisting of a pharmacophore set of pyrimidine, thiazole, and pyrazole has been successfully developed in this research work. In terms of its synthesis, which involved an intermediate of pyrimidine-2-thione and a pyrimidine-thiazole aldehyde, microwave-assisted Knoevenagel condensation resulted in a target compound with 72-88% yield. Taking into account the efficiency and simplicity of the proposed procedure, as well as short reaction times, together with no use of toxic metal catalysts, the process fits the concepts of green chemistry and becomes available for many medicinal chemistry labs.

The identity of the synthesized compounds was confirmed by using techniques of FT-IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry, which revealed that the compounds had the correct structure and no impurities were observed. The results obtained from spectroscopic studies were in accordance with the suggested chemical structures and could serve as a basis for computational analysis.

Molecular docking analysis has shown that the hybrids possess favorable interactions inside the active sites of the target proteins, with the best results being achieved by the derivatives containing electron-withdrawing groups on the pyrazole moiety. The proposed mode of binding showed that the three pharmacophores of the hybrid molecules interact at different subsites of the target sites, which is in accordance with the reasoning behind designing such hybrid molecules. Despite being only theoretical at this stage, these results have given us a reason to choose compounds for biological testing.

The physicochemical property predictions demonstrated that the synthesized compounds have drug-likeness profiles that make them suitable for oral administration because their molecular weights, partition coefficients, hydrogen bonding capabilities, and polar surface areas fall into acceptable ranges. While the results presented are still in need of an experimental proof, they encourage the development of this series of compounds and demonstrate that the adopted hybridization approach did not affect the pharmacokinetic properties of the pharmacophore components.

There is a number of limitations to the current study. The biological activity analysis of the synthesized compounds was done using **in silico** tools, and the results obtained require experimental confirmation using **in vitro** analysis on the appropriate microorganisms and cancer cell lines. The docking analysis, although valuable, is the simplified model of the ligand-protein interaction, which does not take into account the dynamics of the biological system, solvent effect, and allosteric regulation of the receptor. Therefore, future research should include the experimental investigation of the antimicrobial and cytotoxic properties of the compounds and more complex **in silico** techniques, such as molecular dynamics simulations and free energy perturbation calculations.

To conclude, the current study has contributed a novel class of hybrid heterocyclic compounds to the field of medicinal chemistry as well as an efficient and eco-friendly synthetic strategy. The outcomes of

the computational studies have laid the groundwork for further research of these compounds as possible drugs and demonstrated the validity of the application of rational design approaches in the process of discovery of novel bioactive compounds. The concept of hybridization described above can be applied to other combinations of heterocyclic pharmacophores, which opens up the possibility for the creation of a wide variety of compound libraries.

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