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Review

Development in the Synthesis of Bioactive Thiazole-Based Heterocyclic Hybrids Utilizing Phenacyl Bromide

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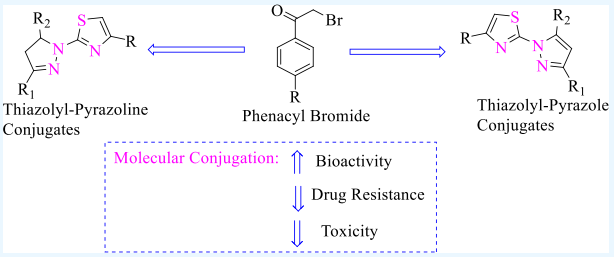
ABSTRACT: Heterocyclic hybrid frameworks represent a burgeoning domain within the realms of drug discovery and medicinal chemistry, attracting considerable attention in recent years. Thiazole pharmacophore fragments, inherent in natural products such as peptide alkaloids, metabolites, and cyclopeptides, have demonstrated a broad spectrum of pharmacological potentials. Given their profound biological significance, a plethora of thiazole-based hybrids have been synthesized through the conjugation of thiazole moieties with bioactive pyrazole and pyrazoline fragments. This review systematically presents a compendium of robust methodologies for the synthesis of thiazole-linked hybrids, employing the (3 + 2) heterocyclization reaction, specifically the Hantzsch-thiazole synthesis, utilizing phenacyl bromide as the substrate. The strategic approach of molecular hybridization has markedly enhanced drug efficacy, mitigated resistance to multiple drugs, and minimized toxicity concerns. The resultant thiazole-linked hybrids exhibit a myriad of medicinal properties *viz*. anticancer, antibacterial, anticonvulsant, antifungal, antiviral, and antioxidant activities. This compilation of methodologies and insights serves as a valuable resource for medicinal chemists and researchers engaged in the design of novel thiazole-linked hybrids endowed with therapeutic attribute.



1. INTRODUCTION

α-Haloketones have captivated global attention as versatile organic synthons since the late 18th century, attributable to their inherent reactivity and capacity to undergo discerning organic transformations when subjected to diverse reagents. The presence of two contiguous electrophilic centers, namely the α-halocarbon and carbonyl carbon, within the molecular framework of phenacyl bromide imparts substantial significance to this carbonyl moiety as a pivotal precursor for the orchestrated synthesis of a versatile spectrum of heterocyclic compounds. These heterocyclic entities are distinguished by their incorporation of nitrogen, sulfur, and oxygen heteroatoms, thereby encompassing a variety of molecular architectures, exemplified by compounds such as[1−3] thiazoles,[4] 2-(thiazol-2-yl)-4,5-dihydropyridazin-3(2*H*)-ones,[5] oxazoles,[6] benzofurans,[7] 3,4-dihydro-2*H*-1,4-benzo[*b*]thiazines,[8] 6-aryl-2-methyl-imidazo[2,1-*b*][1,3,4]thiadiazoles,[9] 7,9-disubstituted-6,7-dihydro-5*H*-benzo[*h*]thiazolo[2,3-*b*]quinazolines,[10] benzo[*f*]pyrido[1,2-*a*]indole-6,11-diones,[11] coumarin-triazolothiadiazine hybrids,[12] and fused 2,3-dihydrofurans[13] (Figure 1).

Among heterocyclic compounds, the chemistry associated with the five-membered thiazole pharmacophore, featuring sulfur and nitrogen heteroatoms, has been extensively pursued. This interest arises from its frequent occurrence in FDA-approved drugs, establishing it as a privileged scaffold within medicinal chemistry.[14] It exhibits versatility and serves as a compelling template for drug design and discovery, manifesting its impact across diverse disciplines such as materials science, dyes, medicines, and agriculture. Notably, this pharmacophore is prevalent in various naturally occurring entities such as vitamin B_1,[15] as well as in pharmaceuticals including sulfathiazole,[16] pramipexole,[17] nitridazole,[18] amiphenazole,[19] abafungin,[20] meloxicam,[21] fentiazac,[22] and febuxostat[23] (Figure 2).

Heterocyclic hybrids are crafted through the fusion of two or more bioactive heterocyclic scaffolds, each with distinct mechanisms, into a novel molecular architecture with multifaceted pharmaceutical activity.[24,25] The structural versatility, diverse biological activities, and potential for optimizing pharmacological properties render these heterocyclic hybrids as potent chemical probes against a spectrum of biological targets.[26] The overarching approach of designing such multifunctional hybrid molecules is broadly acknowledged as

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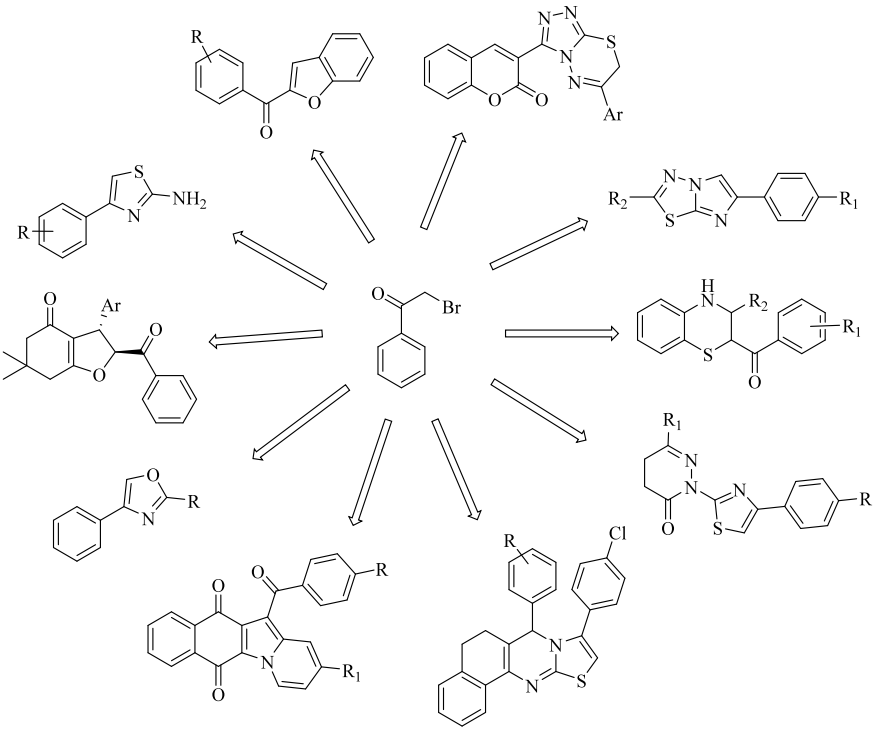

Figure 1. Synthesis of several heterocyclic compounds using phenacyl bromides as a precursor.

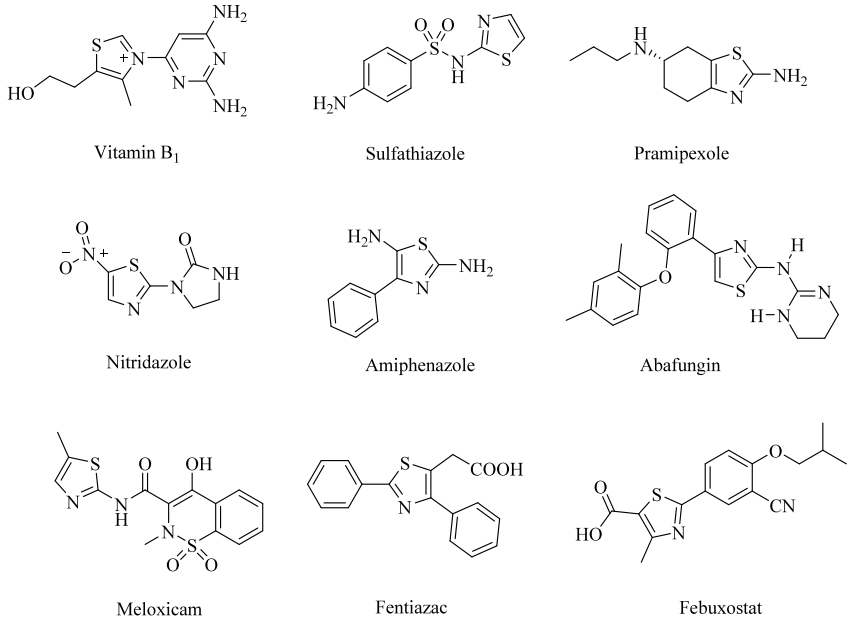

Figure 2. Vitamin B_1 and thiazole-based drugs.

the molecular hybridization strategy in medicinal chemistry. This strategy not only enhances the efficacy of drugs but also serves to circumvent resistance to multiple drugs while mitigating potential toxicity. Medicinal chemists are confronted with considerable hurdles in the endeavor to design efficacious drugs. These challenges pertain to the imperative of devising pharmaceutical agents characterized by robust physiochemical properties, thereby ensuring optimal bioavailability and systemic distribution, proficient metabolic transformation, efficacious elimination, and heightened medicinal efficacy, all while mitigating the risk of potential toxicological effects.[27] In this context, the amalgamation of molecules of medicinal interest through hybridization represents a groundbreaking concept in drug design and discovery, specifically in the context of combatting various infections. In this perspective, a significant number of thiazole-linked hybrids as well as other heterocyclic hybrids with different bioactive moieties have been synthesized in recent years, i.e., thiazole-based imidazo[1,2-*a*]pyridine hybrids,[28] thaizole-based 8,9-dihydro-7*H*-pyrimido[4,5-*b*][1,4]diazepine hybirds,[29] thiazole-based 2,4-diaminotriazine hybrids,[30] thiazole-based coumarin hybrids,[31] thiazole-based aminopyrimidines,[32] coumarin-based hybrids,[33] istain-based hybrids,[34] pyrazoline-based hybrids,[35] thiazolidine-based hybrids,[36] thiazole-based hybrids,[37] and

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anticancer hybrids.[38] In this review, we elucidate contemporary strides in the synthetic methodology for the synthesis of thiazolyl-pyrazoline and thiazolyl-pyrazole hybrids employing phenacyl bromides as an emerging precursor. The resulting hybrids exhibit diverse pharmaceutical applications such as anticancer,[39] antibacterial,[40] antiinflammatory,[41] antifungal,[42] antitubercular,[43] anticonvulsant,[44] antioxidant,[45] antiviral,[46] etc. (Figure 3).

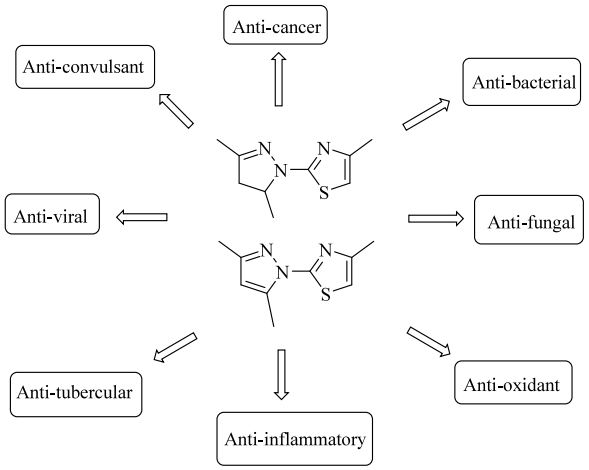

Figure 3. Biological activities of thiazole-linked hybrids.

This review is predominantly structured into two primary classifications, namely thiazolyl-pyrazoline and thiazolyl-pyrazole hybrids. The initial segment is dedicated to thiazolyl-pyrazoline conjugates, further stratified into three subdivisions, *viz*. bioactive five-membered, six-membered and fused heterocyclic hybrids. Hybrid compounds characterized by the presence of both five-membered and six-membered moieties encompass thiophene, furan, triazole, pyrazole, pyrazolone, pyrazine, piperidine, morpholine, pyridine, and other miscellaneous entities. In contrast, fused hybrids incorporate indole, benzofuran, coumarin, benzodioxole, and other miscellaneous entities. The subsequent segment of this review delves into thiazolyl-pyrazole hybrids, further delineated into distinct classifications such as coumarin, benzimidazole, and miscellaneous compounds.

2. THIAZOLYL-PYRAZOLINE HYBRIDS

Thiazolyl-pyrazoline conjugates are synthesized through the coalescence of the thiazole pharmacophore with the pyrazoline derivatives fragment, resulting in the formation of a unified bioactive scaffold exhibiting synergistic biological potentials. This distinctive combination establishes a versatile foundation for the exploration and development of innovative therapeutic agents and bioactive compounds. Therefore, thiazolyl-pyrazole conjugates exemplify an intriguing and dynamic domain of exploration within the field of medicinal chemistry (Figure 4).

2.1. Mechanism for Thiazolyl-Pyrazoline Hybrids. The outlined procedure involves a concise two-step process. In the initial step, a ring closure occurs to form an intermediate pyrazoline **3**. This is achieved through the electron-rich nitrogen of thiosemicarbazide attacking the carbonyl carbon of chalcone **1**. Subsequently, an N−H intramolecular cycloaddition takes place at the double bond **2**. In the next step, nucleophilic substitution of bromine **4** in phenacyl bromide initiates a reaction with the sulfur atom of thioamide, resulting

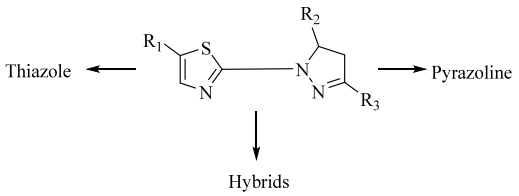

Figure 4. Thiazolyl-pyrazoline hybrids.

in the production of isothiourea **5**. The isothiourea then undergoes cyclocondensation and the elimination of water molecules, ultimately yielding thiazole ring **6** in accordance with the Hantzsch-thiazole synthesis (Scheme 1).

Pyrazoline, alternatively referred to as dihydropyrazole with the molecular formula $C_3H_6N_2$, is characterized by the presence of a single endocyclic bond and has demonstrated noteworthy biological activities (Figure 5).[47]

It serves as a versatile and pervasive scaffold in the design of novel anticancer agents. These include diverse pyrazoline-containing pharmaceuticals, including phenazone utilized as an antiinflammatory agent, muzolimine as a diuretic, methampyrone employed as an analgesic, axitinib an anticancer therapeutic, phenylbutazone prescribed for rheumatoid arthritis and ankylosing spondylitis and aminopyrine, an analgesic (Figure 6).[35]

2.2. Five-Membered-Linked Heterocyclic Hybrids. *2.2.1. Thiophene-Linked Hybrids.* Thiophene, an aromatic sulfur-containing, five-membered heterocycle, represents a privileged scaffold due to its diverse array of biological activities (Figure 7). It has demonstrated efficacy as an antitubercular, antimicrobial, antidiabetic, antioxidant, anticonvulsant, and anticancer agent (Figure 8).[48]

Zhao and his colleagues[49] explored the synthesis of 4-phenyl-2-(3-phenyl-5-(thiophen-2-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole hybrids with the anticancer potentials **9a−9t**. This was achieved via the cyclization of 3-phenyl-5-(thiophen-2-yl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamides **8** with phenacyl bromide **7** in dimethylformamide (DMF) under ambient conditions for a duration of 3 h, resulting in moderate yields. The synthesized conjugates underwent *in vitro* anticancer screening, revealing substantial $BRAF^{V600E}$ inhibitory potential and antiproliferative activity against MCF-7 and WM266.4 cell lines. Notably, 2-(3-(4-chlorophenyl)-5-(thiophen-2-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(4-(trifluoromethyl)phenyl)-thiazole **9t** emerged as the most potent antiproliferative agent with IC_{50} values of 0.16 μM and 0.12 μM against MCF-7 and WM266.4 cell lines, respectively. Additionally, **9t** demonstrated a potent $BRAF^{V600E}$ inhibitory effect, exhibiting an IC_{50} value of 0.05 μM, comparable to the reference drug sorafenib. Furthermore, a three-dimensional quantitative structure−activity relationship (3D-QSAR) modeling and molecular docking analysis conclusively established that derivatives featuring thiophene and thiazole nuclei exhibit considerable promise as therapeutic molecules for further investigation as potential anticancer agents with $BRAF^{V600E}$ inhibitory actions (Scheme 2).

Altıntop and his co-workers[50] synthesized some thiophene coupled **11a−11t** thiazolyl-pyrazoline hybrids with moderate to good yields. The synthesis involved the utilization of phenacyl bromide **7** and 3-(5-chloro/methylthiophen-2-yl)-5-(4-fluorophenyl)-1-thiocarbamoyl-2-pyrazoline **10** as starting materials. The reaction mixture was reflux in ethanol on a water bath for 6 h to afford the desired products. The

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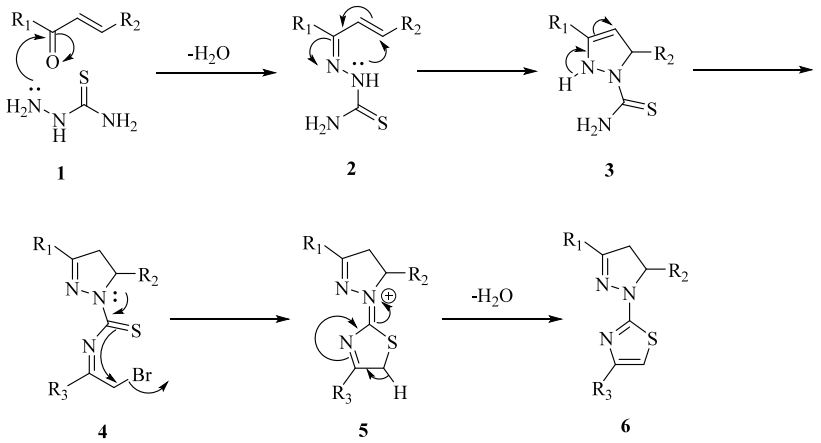
Scheme 1



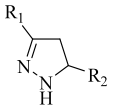


Figure 5. Pyrazoline.

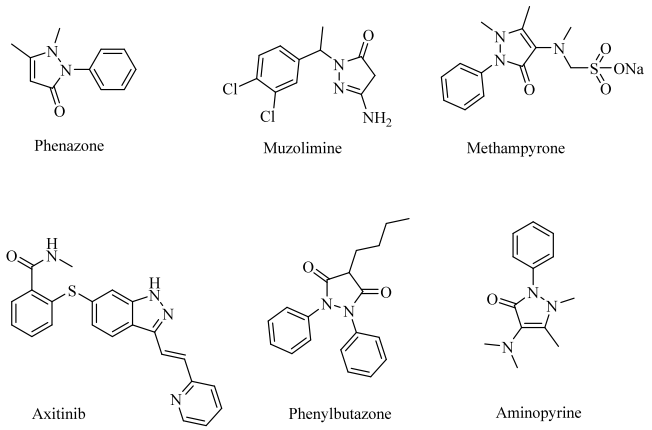


Figure 6. Pyrazoline-based drugs available in the market.

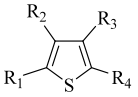


Figure 7. Structure of thiophene.

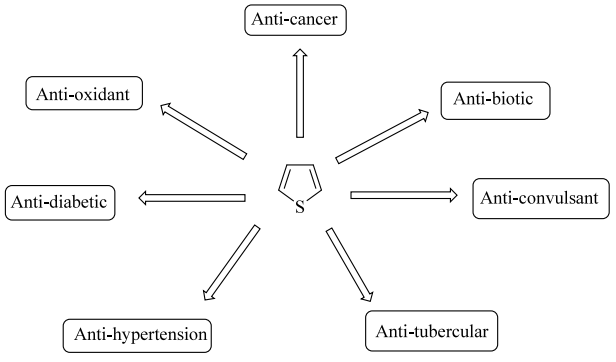


Figure 8. Vast biological profile of thiophene.

antifungal activity of the synthetic compounds was evaluated using the broth microdilution method. Among the screened conjugates, 2-[5-(4-fluorophenyl)-3-(5-methylthiophen-2-yl)-4,5-dihydro-1*H*-pyrazol-1-yl]-4-(4-methylsulfonylphenyl)-thiazole **11q** emerged as most active anticandidal derivative, displaying remarkable inhibitory activity against *Candida zeylanoides* with an IC_{50} value of 250 μg/mL, surpassing the reference drug ketoconazole. Additionally, the cytotoxicity of all compounds was assessed against NIH/3T3 mouse embryonic fibroblast cells and A-549 human lung adenocarcinoma. Among the studied derivatives, 2-[5-(4-fluorophenyl)-3-(5-chlorothiophen-2-yl)-4,5-dihydro-1*H*-pyrazol-1-yl]-4-(4-bromophenyl)thiazole **11d** exhibited the most promising anticancer activity, demonstrating significant inhibitory effects on A549 cancer cells with an IC_{50} of 62.5 μg/mL compared to the standard drug cisplatin (IC_{50} value of 45.88 μg/mL) and displaying low anticancer effects against NIH/3T3 cells (Scheme 3).

Sulthana and his group[51] orchestrated the synthesis of a few thiazole conjugates **14a−14t**, incorporating a thiophene bioactive moiety, under microwave-assisted conditions. The precursors employed in this synthetic endeavor were pyrazoline derivatives **13** and phenacyl bromide **12**, with the reaction unfolding in ethanol over a 5 to 6 min duration, affording products with exceptional yields. Microwave-assisted synthesis conferred distinct advantages, particularly reducing reaction times and augmenting yields compared to conventional heating methods. The bioactivity of the resultant thiazole analogs was systematically analyzed against a spectrum of fungi and bacteria, including *Candida albicans*, *Malassesia pachydermatis*, *Salmonella typhimurium*, *Klebsiella pneumonia*, *Shigella flexneri*, *Proteus vulgaris*, *Micrococcus luteus*, *Staphylococcus aureus*, and *Enterobacter aerogenes*, utilizing the minimum inhibitory concentration (MIC) method. A multitude of these derivatives showcased promising antimicrobial potentials. In the screening of biological activity, compound 3-(2-(5-(6-bromobenzo[*d*]-[1,3]dioxol-5-yl)-3-(thiophen-2-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazol-4-yl) benzonitrile **14o** emerged as a standout, demonstrating remarkable biological efficacy against *Salmonella typhimurium* and *Proteus vulgaris*, with an MIC value of 31.25 μg/mL. Significantly, this effectiveness outperformed that of traditional drugs like fluconazole and gentamicin. Further exploration through SAR analysis and *in silico* molecular docking studies validated the significance of bromo and cyano substituents in conferring substantial antimicrobial properties.

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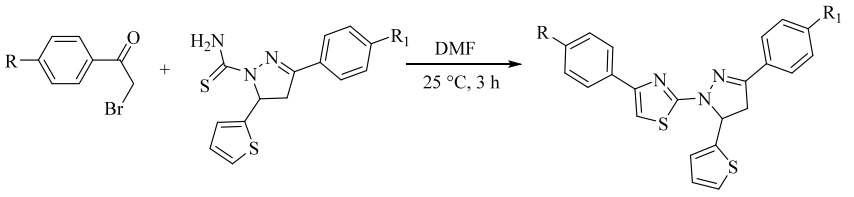
Scheme 2

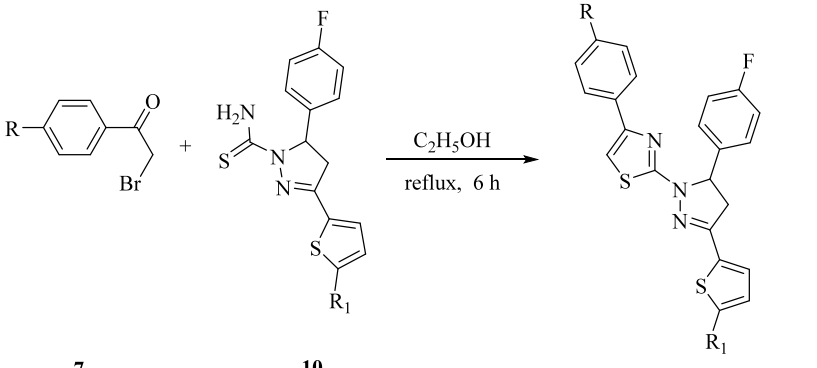


7 **8** **9a-9t**

Yield = 43-76%

9a: R = Br, R_1 = OCH_3
9b: R = H, R_1 = OCH_3
9c: R = OCH_3, R_1 = OCH_3
9d: R = CF_3, R_1 = OCH_3
9e: R = Br, R_1 = F
9f: R = H, R_1 = F
9g: R = OCH_3, R_1 = F
9h: R = CF_3, R_1 = F
9i: R = Br, R_1 = CH_3
9j: R = H, R_1 = CH_3
9k: R = OCH_3, R_1 = CH_3
9l: R = CF_3, R_1 = CH_3
9m: R = Br, R_1 = Br
9n: R = H, R_1 = Br
9o: R = OCH_3, R_1 = Br
9p: R = CF_3, R_1 = Br
9q: R = Br, R_1 = Cl
9r: R = H, R_1 = Cl
9s: R = OCH_3, R_1 = Cl
9t: R = CF_3, R_1 = Cl

Scheme 3



7 **10** **11a-11t**

Yield = 67-95%

11a: R = H, R_1 = Cl
11b: R = F, R_1 = Cl
11c: R = Cl, R_1 = Cl
11d: R = Br, R_1 = Cl
11e: R = NO_2, R_1 = Cl
11f: R = CN, R_1 = Cl
11g: R = SO_2CH_3, R_1 = Cl
11h: R = CH_3, R_1 = Cl
11i: R = OCH_3, R_1 = Cl
11j: R = CF_3, R_1 = Cl
11k: R = H, R_1 = CH_3
11l: R = F, R_1 = CH_3
11m: R = Cl, R_1 = CH_3
11n: R = Br, R_1 = CH_3
11o: R = NO_2, R_1 = CH_3
11p: R = CN, R_1 = CH_3
11q: R = SO_2CH_3, R_1 = CH_3
11r: R = CH_3, R_1 = CH_3
11s: R = OCH_3, R_1 = CH_3
11t: R = CF_3, R_1 = CH_3

This was substantiated by an efficient binding energy of −11.66 *k*cal/mol against the target receptor DNA topoisomerase IV (Scheme 4).

Edrees and coauthors[52] systematically documented the synthesis of numerous hybrids derived from the bioactive thiazole **16a−16h**, intricately linked to a pyrazoline moiety. Further evaluations of these compounds were conducted to assess their potential as anticancer agents, yielding consistently favorable results. The 1,3-dipolar cycloaddition reaction involving *N*-thiocarbamoylpyrazoline **15** and phenacyl bromide **7** was facilitated under ambient conditions for 10−20 min, employing DABCO (1,4-diazabicyclo[2.2.2]octane), an ecofriendly catalyst, resulting in the desired derivatives. The cytotoxicity of the synthesized compounds was meticulously examined against human hepatocellular carcinoma cell lines (HepG2), revealing the compound 2-(5-(2,4-dichlorophenyl)-3-(thiophen-2-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(4-fluorophenyl)thiazole **16b** as displaying superior potency compared to the established anticancer drug cisplatin. Furthermore, an in-depth exploration of the efficacy of these derivatives unveiled a correlation between the electronic nature of substituents at the para position of the phenyl ring and anticancer activity. In this study, it is concluded that the inclusion of halogens significantly enhanced the anticancer activity, while the presence of an electron releasing methyl group diminished the activity against human hepatocellular

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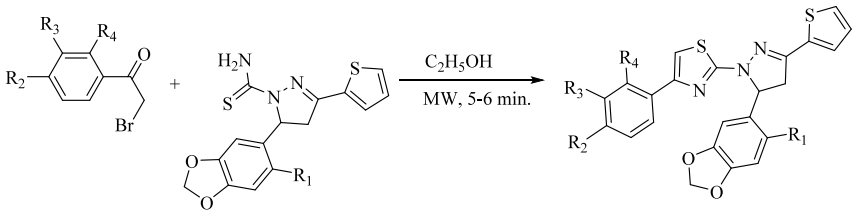
Scheme 4

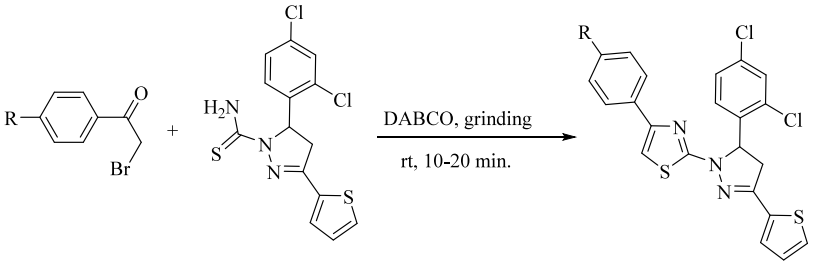


12 **13** **14a-14t**

Yield = 81-92%

14a: R_1 = H, R_2 = H, R_3 = H, R_4 = H
14b: R_1 = H, R_2 = CH_3, R_3 = H, R_4 = H
14c: R_1 = H, R_2 = NO_2, R_3 = H, R_4 = H
14d: R_1 = H, R_2 = CN, R_3 = H, R_4 = H
14e: R_1 = H, R_2 = H, R_3 = CN, R_4 = H
14f: R_1 = H, R_2 = F, R_3 = H, R_4 = H
14g: R_1 = H, R_2 = H, R_3 = H, R_4 = F
14h: R_1 = H, R_2 = Cl, R_3 = H, R_4 = H
14i: R_1 = H, R_2 = Cl, R_3 = F, R_4 = H
14j: R_1 = H, R_2 = Cl, R_3 = H, R_4 = F
14k: R_1 = Br, R_2 = H, R_3 = H, R_4 = H
14l: R_1 = Br, R_2 = CH_3, R_3 = H, R_4 = H
14m: R_1 = Br, R_2 = NO_2, R_3 = H, R_4 = H
14n: R_1 = Br, R_2 = CN, R_3 = H, R_4 = H
14o: R_1 = Br, R_2 = H, R_3 = CN, R_4 = H
14p: R_1 = Br, R_2 = F, R_3 = H, R_4 = H
14q: R_1 = Br, R_2 = H, R_3 = H, R_4 = F
14r: R_1 = Br, R_2 = Cl, R_3 = H, R_4 = H
14s: R_1 = Br, R_2 = Cl, R_3 = F, R_4 = H
14t: R_1 = Br, R_2 = Cl, R_3 = H, R_4 = F

Scheme 5



7 **15** **16a-16h**

Yield = 71-82%

16a: R = H
16b: R = F
16c: R = Cl
16d: R = Br
16e: R = CH_3
16f: R = OCH_3
16g: R = NO_2
16h: R = NH_2

carcinoma cell lines (HepG2). In addition to their anticancer potential, the antimicrobial properties of the synthesized derivatives were assessed. Among the evaluated compounds, 2-(5-(2,4-dichlorophenyl)-3-(thiophen-2-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-phenylthiazole **18a** demonstrated significant potential against *Candida albicans*, *Proteus vulgaris*, and *Staphylococcus aureus*, with respect to standard drugs ketoconazole and gentamycin. These findings underscore the multifaceted pharmacological potential of the synthesized compounds, positioning them as promising candidates for further therapeutic development (Scheme 5).

Mandawad et al.[53] have represented few thiazole-linked pyrazolines **19a−19l**, distinguished by their conjugation with trisubstituted thiophene, displaying pronounced antioxidant efficacy and serving as inhibitors of superoxide species. The synthetic route for these derivatives involves the cyclization of 4,5-dihydropyrazole-1-carbothioamide **18** and phenacyl bromide **17** in polyethylene glycol (PEG-400) under controlled conditions at a temperature range of 40−45 °C, with continuous stirring for a duration of 2 h, resulting in a modest yield. The enumerated pyrazolines underwent comprehensive evaluation as superoxide inhibitors and radical scavengers utilizing the 1,1-diphenyl-2-picrylhydrazyl radical (DPPH) assay. Among the synthesized compounds, 4-(3-(2-(benzylthio)-5-chlorothiophen-3-yl)-1-(4-(4-chlorophenyl)thiazol-2-yl)-4,5-dihydro-1*H*-pyrazol-5-yl)-*N*,*N*-dimethylbenzolamine **19j** with an IC_{50} value of 6.2 μM, demonstrating commendable superoxide inhibitory and radical scavenging activities in comparison to standard references such as allopurinol and ascorbic acid. Furthermore, molecular modeling investigations substantiated the potential of compound **19j**, bearing *N*,*N*-dimethyl aniline, as a superoxide dismutase (XO) inhibitor. This affirmation arises from its adept ability to bind to the XO active site, thereby facilitating suppression at the molecular level (Scheme 6).

2.2.2. Furan/Thiohene-Linked Hybrids. Furans, acknowledged as heterocyclic compounds with a five-membered ring structure, occupy a prominent role in numerous therapeutic medications, exhibiting a spectrum of diverse medicinal properties (Figure 9). These compounds manifest noteworthy

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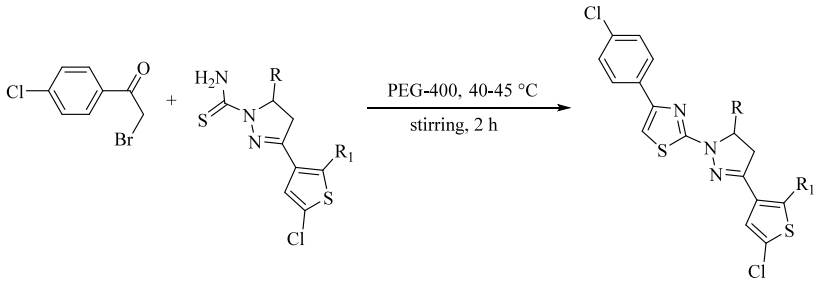
Scheme 6



19a: R = 2-butyl-4-chloro-1*H*-imidazole, R_1 = Cl
19b: R = 2-butyl-4-chloro-1*H*-imidazole, R_1 = $SCH_2C_6H_5$
19c: R = 2-butyl-4-chloro-1*H*-imidazole, R_1 = SO_2NH_2
19d: R = 4-ClC_6H_4, R_1 = Cl
19e: R = 4-ClC_6H_4, R_1 = $SCH_2C_6H_5$
19f: R = 4-ClC_6H_4, R_1 = SO_2NH_2
19g: R = 4-BrC_6H_4, R_1 = Cl
19h: R = 4-BrC_6H_4, R_1 = $SCH_2C_6H_5$
19i: R = 4-BrC_6H_4, R_1 = SO_2NH_2
19j: R = 4-$N(CH_3)_2C_6H_4$, R_1 = Cl
19k: R = 4-$N(CH_3)_2C_6H_4$, R_1 = $SCH_2C_6H_5$
19l: R = 4-$N(CH_3)_2C_6H_4$, R_1 = SO_2NH_2

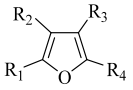


Figure 9. Structure of furan.

attributes such as antiaging, antiulcer, antihistaminic, anticholinergic, antiparkinsonianism, antidiuretic, analgesic, anti-inflammatory, muscle relaxant, antihypertensive, antiarrhythmic, antidepressant, anxiolytic, and the inhibition of sickle cell formation. The diverse range of pharmacological effects displayed by furans underscore their potential significance in the formulation of pharmaceutical agents endowed with multifaceted therapeutic applications (Figure 10).[54]

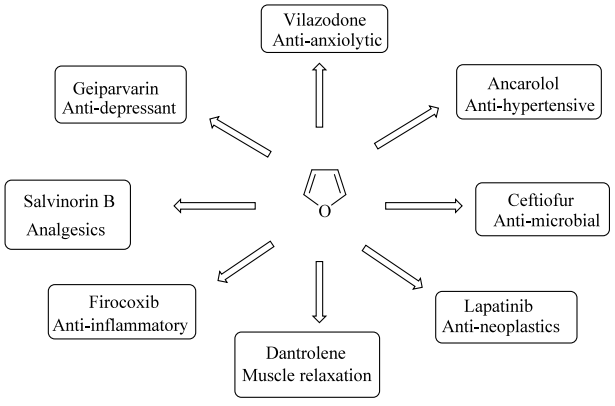


Figure 10. Furan-based drugs available in the market.

Mamidala and his research team[55] developed a microwave-mediated, single-step methodology for the synthesis of several furan hybrids designed as potent anticancer agents, **22a−22l**, with exceptional yields. The multicomponent synthesis involved the cyclization of phenacyl bromide **7** with thiosemicarbazide **20**, followed by the reaction of chalcone **21** with a catalytic amount of sodium hydroxide (NaOH) in ethanol at 70 °C for 5 to 6 min, resulting in the production of the desired compounds. The *in vitro* antiproliferative activity of these synthesized derivatives was evaluated using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) method, with doxorubicin (DOX) serving as a reference drug. The assessment targeted various cancer cell lines, namely (A-549) human adenocarcinoma, (SK-N-SH) human neuroblastoma, (HeLa) cervical cancer, and (DU-145) human prostate cancer cell lines. Biological evaluation results exhibited the striking potency of synthesized hybrids against HeLa cell lines. The SAR studies elucidated that the introduction of a nitro group **22g** on the phenyl ring exhibited significant bioactivity against HeLa cell lines, with an IC_{50} value of (9.97 ± 0.05 μM). Additionally, derivatives featuring a phenyl ring with *p*-chloro **22e** and *p*-methoxy **22c** substituents showed promising activities against these cell lines, with IC_{50} values of (15.61 ± 0.06 μM), (18.47 ± 0.01 μM), and (19.78 ± 0.03 μM), respectively (Scheme 7).

Yang and his co-workers[56] synthesized and assessed some novel furan-based pyrazoline derivatives **24a−24r** as antimicrobial agents. The synthetic approach involved the condensation reaction of 3,5-diaryl-4,5-dihydro-1*H*-pyrazole-1-carbothioamides **23** and phenacyl bromide **7** in ethanol under reflux conditions for 5 h, yielding the target compounds in moderate to excellent yields. The antimicrobial screening was performed on the synthesized compounds using the MTT method (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) to assess their biological effect against *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, and *Staphylococcus aureus*. Among the evaluated furan-linked derivatives, the compound 2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-phenylthiazole **24n** demonstrated significant antimicrobial activity with a MIC value ranging from 1.56 to 3.13 μg/mL against *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Bacillus subtilis*, and *Escherichia coli* as compared to standard antimicrobial agent kanamycin B. Furthermore, compound **24n** displayed potent inhibitory activity against *Escherichia coli* with an IC_{50} value ranging between 4.6 and 4.8 μM. These inhibitory potentials were comparable to those of the reference drug DDCP (Scheme 8).

Fathy Abdel-Wahab and collaborators[57] adeptly synthesized a series of 2-(5-(4-fluorophenyl)-3-(thien-2-yl or furan-2-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methyl-5-(aryldiazenyl-)-thiazoles **27a−27b**, with commendable to moderate yields.

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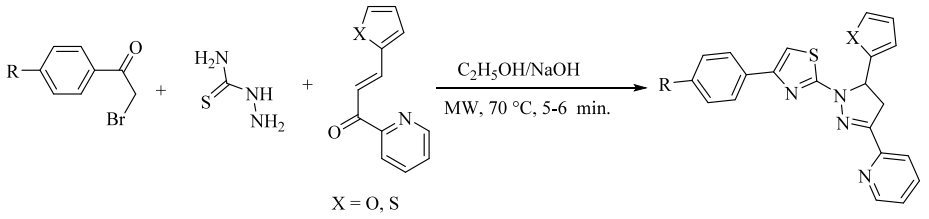
Scheme 7

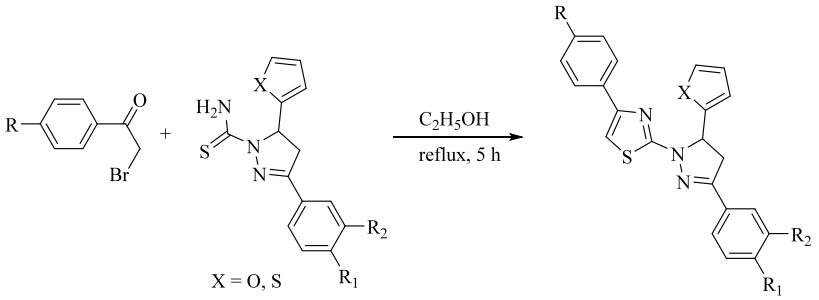


7 **20** **21** **22a-22l**

Yield = 11-95%

22a: R = H, X = O
22b: R = CH_3, X = O
22c: R = OCH_3, X = O
22d: R = F, X = O
22e: R = Cl, X = O
22f: R = Br, X = O
22g: R = NO_2, X = O
22h: R = 2,4-$(Cl)_2$, X = O
22i: R = H, X = S
22j: R = Cl, X = S
22k: R = Br, X = S
22l: R = 2,4-$(Cl)_2$, X = S

Scheme 8

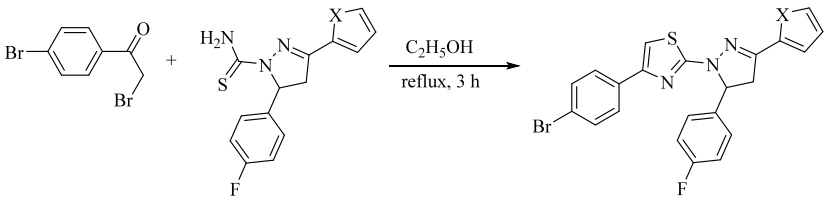


7 **23** **24a-24r**

Yield = 70-80%

24a: R = H, R_1 = F, R_2 = H, X = S
24b: R = H, R_1 = Br, R_2 = H, X = S
24c: R = H, R_1 = Cl, R_2 = Cl, X = S
24d: R = H, R_1 = CH_3, R_2 = H, X = S
24e: R = H, R_1 = OCH_3, R_2 = H, X = S
24f: R = OCH_3, R_1 = F, R_2 = H, X = S
24g: R = OCH_3, R_1 = Br, R_2 = H, X = S
24h: R = OCH_3, R_1 = Cl, R_2 = Cl, X = S
24i: R = OCH_3, R_1 = CH_3, R_2 = H, X = S
24j: R = OCH_3, R_1 = OCH_3, R_2 = H, X = S
24k: R = H, R_1 = F, R_2 = H, X = O
24l: R = H, R_1 = Br, R_2 = H, X = O
24m: R = H, R_1 = Cl, R_2 = Cl, X = O
24n: R = H, R_1 = CH_3, R_2 = H, X = O
24o: R = OCH_3, R_1 = F, R_2 = H, X = O
24p: R = OCH_3, R_1 = Br, R_2 = H, X = O
24q: R = OCH_3, R_1 = Cl, R_2 = Cl, X = O
24r: R = OCH_3, R_1 = CH_3, R_2 = H, X = O

Scheme 9



25 **26** **27a-27b**

27a: X = O, **27b:** X = S

Yield = 66-69%

The synthetic protocol involved the reflux of 5-(4-fluorophenyl)-3-heterocycl-4,5-dihydro-1*H*-pyrazole-1-carbothioamides **26** with phenacyl bromide **25** in ethanol, conducted over a duration of 3 h. Further, the recently formulated hybrid compounds were subjected to antimicrobial evaluation against a spectrum of bacterial strains, including *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Bacillus subtilis*, *Bacillus megaterius*, *Sarcina lutea*, as well as fungal strains such as *Aspergillus niger*, *Saccharomyces cerevisiae*, and *Candida albicans*, employing the agar well diffusion methodology. Remarkably, 4-(4-

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bromophenyl)-2-(5-(4-fluorophenyl)-3-(furan-2-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole **27a** exhibited the highest potency against all examined microorganisms. The observed efficacy was comparable to that of conventional reference compounds, namely ciprofloxacin and ketoconazole (Scheme 9).

2.2.3. Triazole-Linked Hybrids. Triazole is also known as a pyrrodiazole heterocyclic moiety with the chemical formula $C_2H_3N_3$. It has two carbon and three nitrogen atoms and belongs to the five-membered aromatic azoles (Figure 11). Its

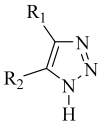


Figure 11. Structure of Triazole.

diverse array of biological activities emanates from its adeptness in binding to various enzymes and receptors within the biological system. Furthermore, it serves as a pivotal structural constituent across numerous therapeutic categories, *viz.* antibacterial, antifungal, anticancer, antioxidant, antiviral, antiinflammatory, analgesic, antiepileptic, antihypertensive, antidepressant, antidiabetic, antianxiety, antitubercular, etc. (Figure 12).[58]

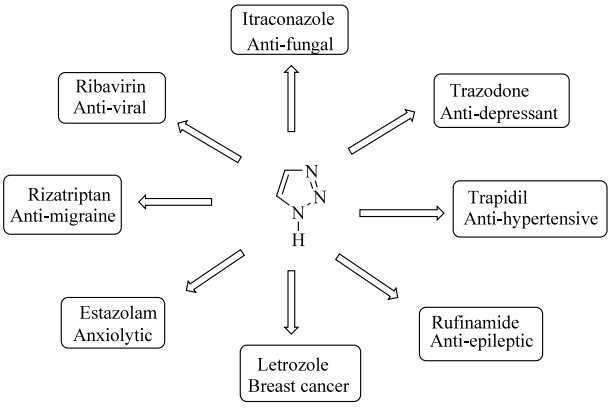


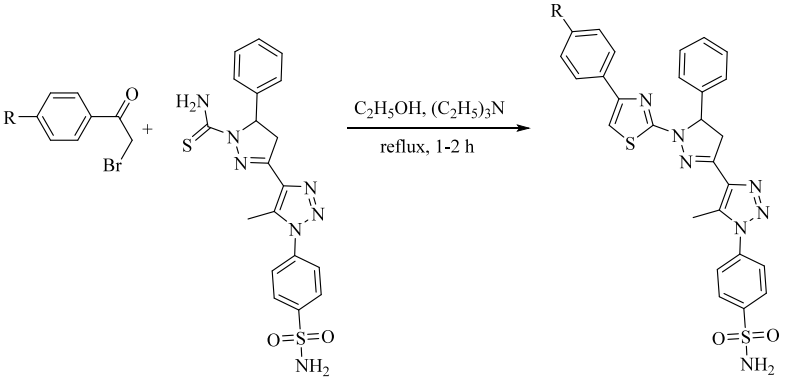
Figure 12. Drugs available in the market with a triazole nucleus.

Bekheit and his group[59] devised an efficacious synthetic pathway for the synthesis of few novel trisubstituted triazoles **29a−29b**, anchored to the benzenesulphonamide moiety. The achievement herein described was acquired through a chemical metamorphosis facilitated by the interaction between 3-(5-methyl-1-(4-sulfamoylphenyl)-1*H*-1,2,3-triazol-4-yl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide **28** and phenacyl bromide **7** within an environment comprising absolute ethanol/triethylamine, under reflux conditions spanning a temporal extent of approximately 1−2 h. The ensuing products were obtained with yields varying from moderate to satisfactory. Subsequent to synthesis, all compounds were investigated for their inhibitory activity against cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) (Scheme 10).

Kariuki and his research team[60] successfully synthesized 4-(4-chlorophenyl)-2-(5-(4-fluorophenyl)-3-(1-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole **31a** and 4-(4-fluorophenyl)-2-(5-(4-fluorophenyl)-3-(1-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole **31b**. The synthetic procedure involved subjecting pyrazoline *N*-thioamide derivatives **30** and phenacyl bromide **7** to reflux in ethanol for a period of 2 h, resulting in the synthesis of the desired conjugates with exceptional yields. The elucidation of the molecular structures of the synthesized compounds was accomplished through single crystal diffraction analysis. Notably, derivatives having the pyrazoline moiety exhibited promising pharmacological activities *viz.* anticancer, antiinflammatory, analgesic, and antimicrobial properties (Scheme 11).

Abdel-Wahab et al.[61] synthesized thiazole-linked triazoles and systematically screened their efficacy as potent antimicrobial agents **33a−33c**. The synthetic approach involved the cyclization of 5-(4-fluorophenyl)-3-(5-methyl-1-*p*-tolyl-1*H*-1,2,3-triazol-4-yl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide **32** with phenacyl bromides **7** under reflux conditions in anhydrous ethanol for 1.5 h. The resultant products were obtained with excellent yields. The synthesized compounds were analyzed for their antimicrobial potential against a spectrum of microbes, including *Saphylococcus aureus*, *Bacillus subtilis*, *Bacillus megaterium*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Escherichia coli*, *Candida albicans*, and *Saccharomyces cerevisiae*, using the agar well diffusion method. Among the compounds studied, 4-(4-bromophenyl)-2-(5-(4-fluoro-

Scheme 10



7 **28** **29a-29b**

29a: R = H **29b:** R = Br

Yield = 52-74 %

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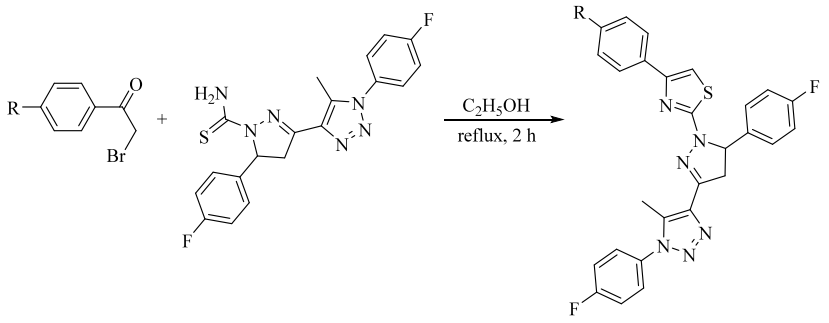
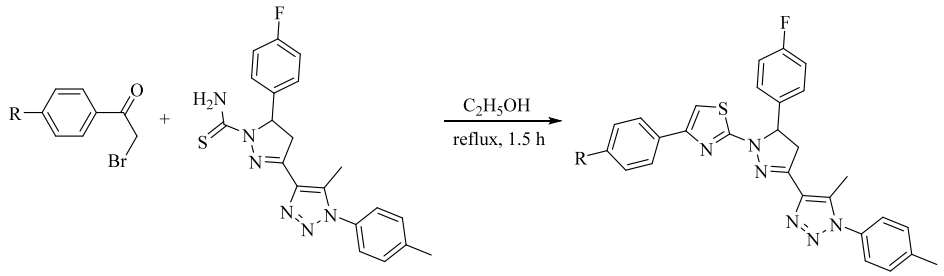
Scheme 11



7 **30** **31a-31b**

31a: R = Cl **31b:** R = Br Yield = 82-85%

Scheme 12

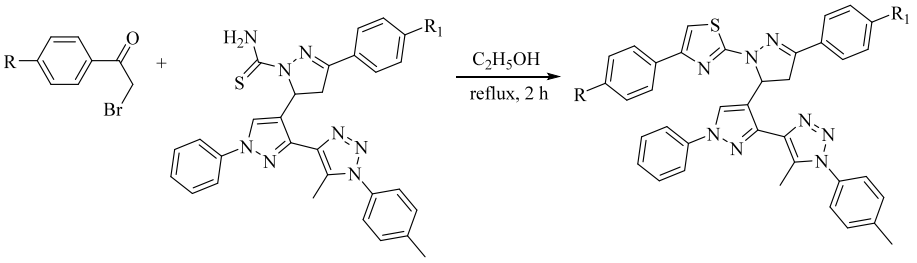


7 **32** **33a-33c**

Yield = 86-88%

33a: R = H **33b:** R = Cl **33c:** R = Br

Scheme 13



7 **34** **35a-35d**

Yield = 82-87%

35a: R = Br R_1 = Br **35c:** R = Cl R_1 = Br

35b: R = Br R_1 = Cl **35d:** R = Cl R_1 = Cl

35e: R = 1-tolyl-5-methyl-1,2,3-triazo-4-yl, R_1 = Br

35e: R = 1-tolyl-5-methyl-1,2,3-triazo-4-yl, R1 = Cl

phenyl)-3-(5-methyl-1-*p*-tolyl-1*H*-1,2,3-triazol-4-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole **33c** exhibited remarkable biological potential, evidenced by an inhibitory zone measuring 30 mm. This noteworthy activity was particularly pronounced against *Staphylococcus aureus*, *Candida albicans*, and *Saccharomyces cerevisiae*. Comparative analysis with reference drugs ciprofloxacin and ketoconazole underscored the superior performance of compound **33c** in these specific microbial contexts (Scheme 12).

Abdel-Wahab and group[62] conducted the synthesis of triazole hybrids incorporating thiazolyl-pyrazolines **35a−35d** through the cyclocondensation reaction of thioamides **34** with phenacyl bromides 7 in ethanol under reflux conditions for 2 h, resulting in favorable yields. The reaction pathway involved the elimination of hydrobromic acid to generate an intermediate, followed by the subsequent elimination of a water molecule, leading to the formation of the desired pyrazoline derivatives. The synthesized pyrazolines underwent analysis to assess their antimicrobial activities against a panel of microorganisms, including *Bacillus subtilis*, *Staphylococcus aureus*, *Bacillus megaterium*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Candida albicans*, and *Saccharomyces cerevisiae*, employing the agar well diffusion method. Among the screened analogs, compound **35c**, identified as 2-(3-(4-bromophenyl)-5-(3-(5-methyl-1-(4-tolyl)-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(4-chlorophenyl)thiazole, exhibited prominent antimicrobial activity. The inhibition zones ranged from 18 to 25 mm, and

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the MIC values varied from 100 to 200 μg/mL. Remarkably, compound **35c** demonstrated superior activity against the tested microorganisms compared to the reference drugs clotrimazole and ciprofloxacin (Scheme 13).

2.2.4. Pyrazole-Linked Hybrids. Pyrazoles, colloquially referred to as 1,2-azoles, represent a class of five-membered aromatic heterocyclic compounds characterized by the presence of two proximate nitrogen atoms (Figure 13). The

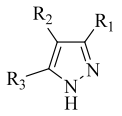


Figure 13. Structure of pyrazole.

conventional synthetic approach for pyrazole production entails the condensation reaction between hydrazines and 1,3-dicarbonyl compounds. A myriad of pharmaceuticals bearing pyrazole moieties has emerged in the market, exemplified by significant examples such as apixaban, fipronil, rimonabant, pyrazofurin, celecoxib, phenylbutazone, novalgine, and ramifenazone as depicted in (Figure 14).[63]

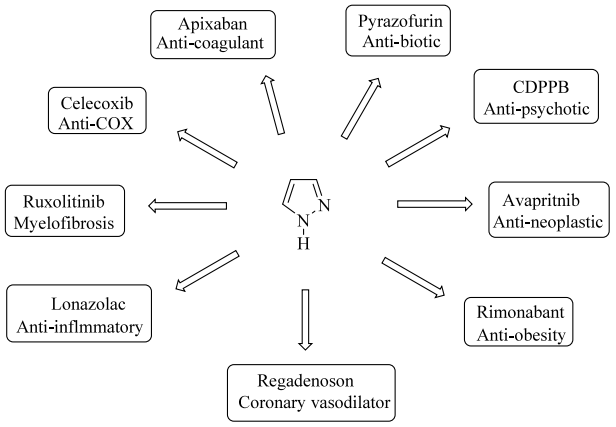


Figure 14. Drugs available in market with a pyrazole nucleus.

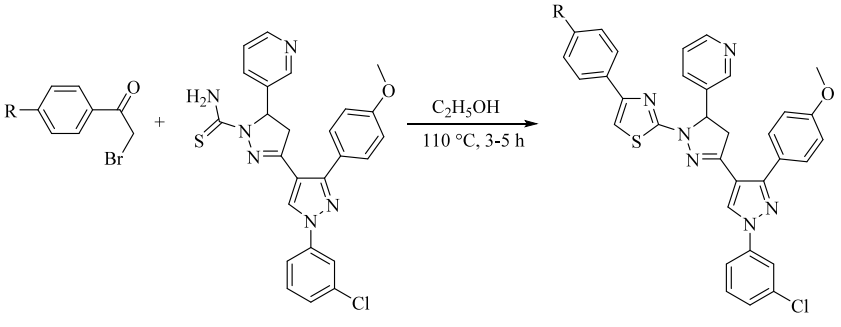
Khalifa et al.[64] elucidated a method for the synthesis of several polysubstituted pyrazoles **37a−37c** through the cyclization process involving a pyrazoline derivative **36** and phenacyl bromide **7** in ethanol, employing heat at 90 °C for 3 to 5 h, resulting in good yields. Further, various synthetic pyrazole derivatives were subjected to evaluation via the sulforhodamine-B (SRB) assay to assess their *in vitro* anticancer efficacy against the MCF-7 cell line. The findings revealed their superior effectiveness compared to the standard reference drug doxorubicin. Particularly, among the synthetic derivatives, 3-{3-[1-(3-chlorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrazol-4-yl]-4,5-dihydro-1-(4-phenylthiazol-2-yl)-1*H*-pyrazol-5-yl}pyridine **37a** exhibited significant concentration-dependent inhibition of cancerous cells, as indicated by its IC_{50} value of 23.01 μM (Scheme 14).

Raut and group[65] demonstrated the synthesis of pyrazoline derivatives **39a−39g** and evaluated their antiinflammatory activity along with antioxidant potential. The synthetic route entailed the reaction between 1-thiocarbamoyl pyrazole derivative **38** and phenacyl bromides **7** in polyethylene glycol (PEG-300) at room temperature, with stirring for 1 to 2 h, resulting in desired compounds in excellent yields. Further, all derivatives underwent *in vitro* assessments to evaluate their antiinflammatory activities. The antiinflammatory activity data displayed that derivatives bearing electron-donating substituents, such as methyl and methoxy, **39g** demonstrated exceptional efficacy. Conversely, compounds with electron-withdrawing substituents, such as nitro **39d**, exhibited a more moderate anti-inflammatory activity profile. Notably, the anti-inflammatory effect of compounds harboring a chloro substitution **39e** was diminished. Additionally, the synthesized compounds were exposed to *in vitro* screening to examine their antioxidative potential against various reactive oxygen species, encompassing assays targeting DPPH, hydrogen peroxide, superoxide scavenging radicals, and nitric oxide. Through an SAR study, it was determined that substitutions on the thiazole ring exhibited minimal impact on antioxidant potentials (Scheme 15).

2.2.5. Pyrazolone-Linked Hybrids. Pyrazolone constitutes a pentameric lactam ring featuring a single ketonic moiety and two nitrogen atoms within its molecular architecture (Figure 15). Compounds containing the pyrazolone nucleus have demonstrated pronounced physiological impacts, *viz.* muscle relaxant, psychoanalgesic, anticonvulsant, antihypertensive, antidepressant, antitumor, antibacterial, antiviral, antifungal, antiinsect, etc. (Figure 16).[66]

Abeed and co-workers[67] elucidated the synthetic procedure for the production of pyrazoline-thiazole hybrids, **42a−42b**, which integrate the 2-pyrazolin-5-one moiety. This synthetic

Scheme 14



7 **36** **37a-37c**

37a: R = H **37b:** R = Cl **37c:** R = Br

Yield = 60-66%

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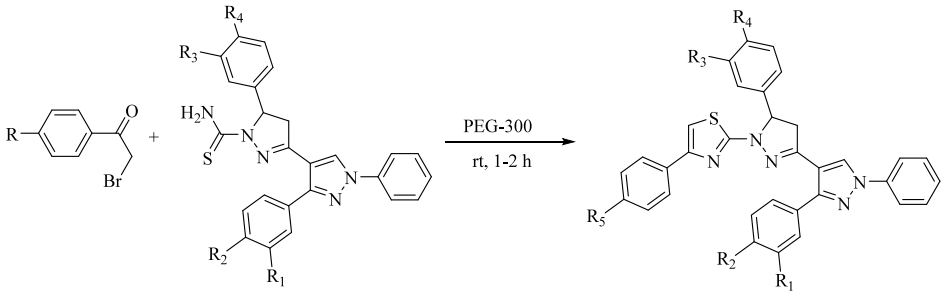
Scheme 15



7 **38** **39a-39g**

Yield = 94-97%

39a: R = H, R_1 = H, R_2 = H, R_3 = H, R_4 = H
39b: R = H, R_1 = H, R_2 = CH_3, R_3 = H, R_4 = H
39c: R = H, R_1 = H, R_2 = CH_3, R_3 = H, R_4 = CH_3
39d: R = H, R_1 = H, R_2 = H, R_3 = NO_2, R_4 = H
39e: R = Cl, R_1 = H, R_2 = H, R_3 = H, R_4 = CH_3
39f: R = CH_3, R_1 = H, R_2 = H, R_3 = H, R_4 = CH_3
39g: R = OCH_3, R_1 = H, R_2 = H, R_3 = H, R_4 = CH_3

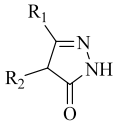


Figure 15. Structure of pyrazolone.

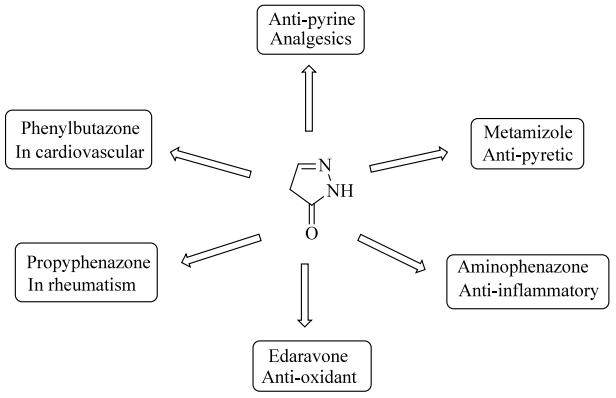


Figure 16. Pyrazolone based drugs available in the market.

pathway involved the reaction of diverse *N*-thiocarbamoyl pyrazolines **41** with phenacyl bromide **40** in ethanol under reflux conditions for 1 h, yielding products with moderate efficiency. The 2-pyrazolin-5-one moiety, serving as proficient precursors, was utilized in the synthesis of innovative heterocyclic frameworks. These newly synthesized compounds demonstrated the anticipated biological efficacy such as antimicrobial, antitubercular, and antiinflammatory properties (Scheme 16).

2.3. Six-Membered-Linked Heterocyclic Hybrids.

2.3.1. Piperidine-Linked Hybrids. Piperidine is a six-membered saturated heterocyclic scaffold including five carbon atoms and one nitrogen atom with molecular formula $(CH_2)_5NH$ (Figure 17).[68−70] This moiety is associated with other bioactive

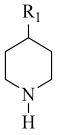
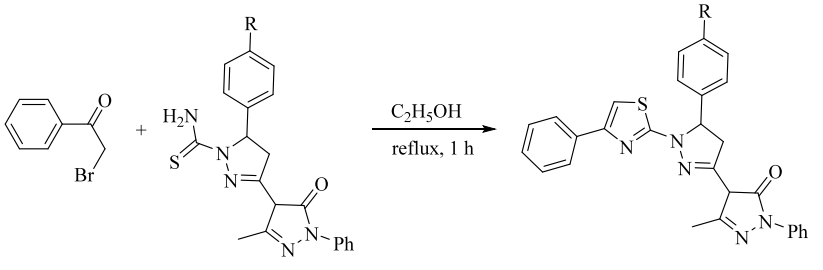


Figure 17. Structure of piperidine.

molecular fragments to ameliorate a number of medical disorders. It has demonstrated notable effects against coagulant, Alzheimer's, cancer, inflammation, hypertension, viruses, etc. (Figure 18).

Acar Çevik et al.[71] have detailed the synthetic route for the preparation of 2-(3-(4-(4-benzylpiperidin-yl)phenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(substitutedphenyl)-thiazole conjugates (**45a−45k**). This involved the utilization of

Scheme 16



40 **41** **42a-42b**

42a: R = H **42b:** R = Cl

Yield = 71-73%

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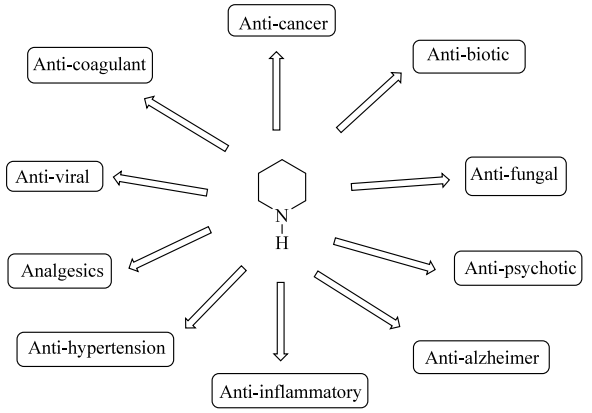


Figure 18. Pharmaceutical attributes of piperidine-based analogs.

phenacyl bromide **43** and 3-(4-(4-benzylpiperidin-1-yl)-phenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazone-1-carbothioamides **44** through a refluxing reaction mixture on a water bath for a duration of 3 h in ethanol, resulting in moderate yields. To assess the *in vitro* inhibitory potential of the synthesized compounds against monoamine oxidase (MAO) enzymes of type A and B, the ampliflu red (10-acetyl-3,7-dihydroxyphenoxazine) assay was employed. Particularly, the hybrid compound **45i** bearing a 2,4-dimethoxy moiety at the phenyl ring demonstrated a remarkable inhibitory activity against MAO A enzymes, with an IC_{50} value of 0.0445 ± 0.0018 μM, outperforming reference drugs moclobemide and selegiline. Furthermore, compounds 2-(3-(4-(4-benzylpiperidin-1-yl)-phenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(*p*-methoxyphenyl)-thiazole **45c** and 2-(3-(-(4-benzylpiperidin-1-yl)-phenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(4-nitrophenyl)-thiazole **45d** exhibited significant suppressive effects against MAO A enzymes, with IC_{50} values of 0.1423 ± 0.0051 μM and 0.2148 ± 0.0067 μM, respectively. The introduction of a methoxy group in these derivatives was observed to enhance inhibitory activity and selectivity for MAO A enzymes, which play a crucial role in the metabolism of neurotransmitters such as serotonin, norepinephrine, and dopamine in the central nervous system (Scheme 17).

2.3.2. Morpholine-Linked Hybrids. Morpholine or 1-oxa-4-azacyclohexane heterocyclic is a six-membered ring comprised of two heteroatoms nitrogen and oxygen, which is used as a heterocyclic secondary amine (Figure 19). It is a versatile lead

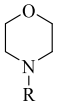


Figure 19. Structure of morpholine.

molecule formed by the chemist for active molecules with strong pharmacological effects. The compounds comprising *N*-substituted morpholine derivatives, including levofloxacin, reboxetine, moclobemide, finafloxacin, phenadoxane, emorfazone, timolol, gefitinib, aprepitant, and linezolid as illustrated in Figure 20, have exhibited pharmacological effectiveness in terms of analgesic, antifungal, antibacterial, antitubercular, antidiabetic, and anticancer properties.[72]

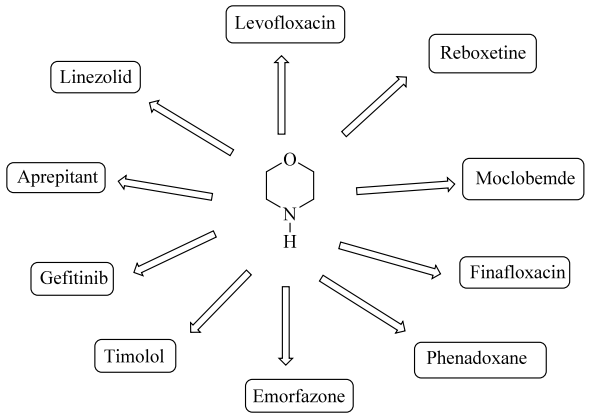
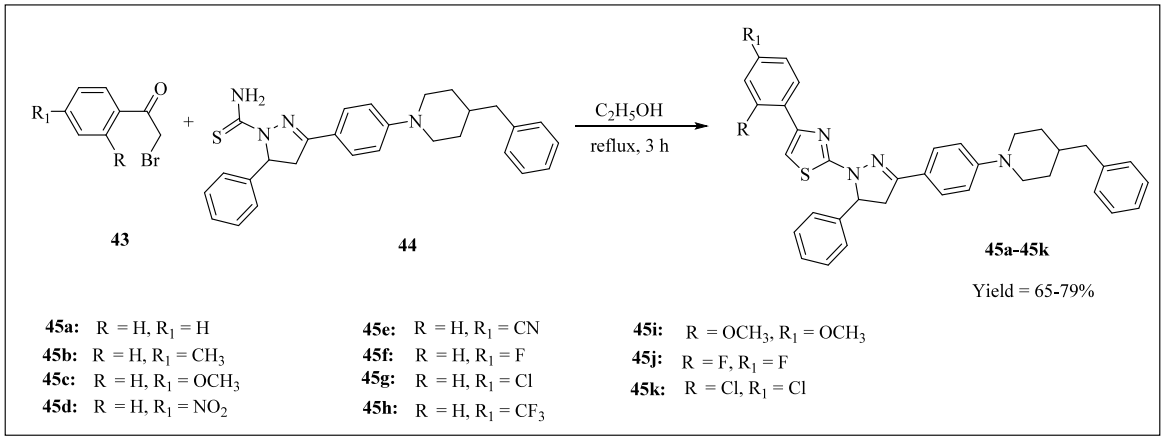


Figure 20. Morpholine-based drugs available in the market.

Sever et al.[73] have disclosed the synthesis of novel thiazolyl-pyrazolines **47a**−**47v**, through the cyclization of the pyrazoline derivative **46** and phenacyl bromide **7** in ethanol under reflux conditions for a precisely controlled duration of 6 h. The resultant reaction exhibited a product spectrum spanning from moderate to outstanding yields. The synthesized derivatives were systematically screened for their antiproliferative activity against A-549, A-375, and MCF-7 cell lines. Remarkably, among the scrutinized derivatives, compounds **47f** and **47q**, namely 1-(4-(4-cyanophenyl)thiazol-2-yl)-3-(4-morpholinophenyl)-5-(4-chlorophenyl)-2-pyrazoline and 1-(4-(4-cyanophenyl)thiazol-2-yl)-3-(4-piperidinophenyl)-5-(4-chloro-

Scheme 17



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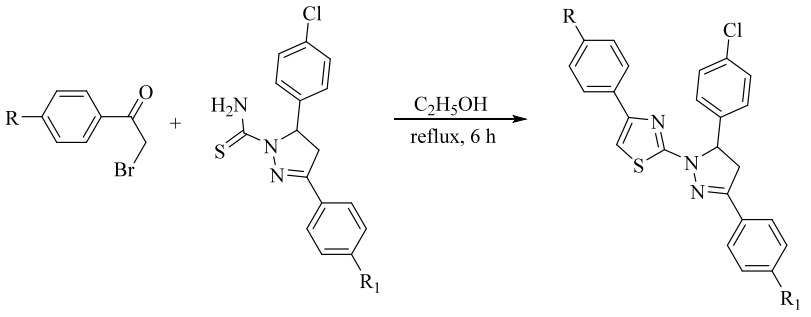
Scheme 18

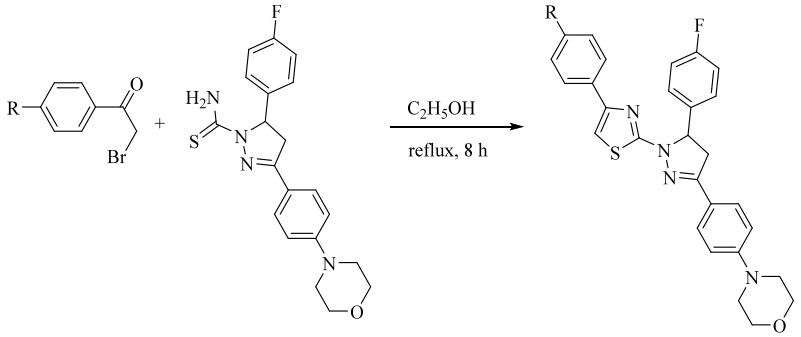


7 **46** **47a-47v**

Yield = 74-86%

47a: R = H, R_1 = Morpholino
47b: R = NO_2, R_1 = Morpholino
47c: R = F, R_1 = Morpholino
47d: R = Cl, R_1 = Morpholino
47e: R = Br, R_1 = Morpholino
47f: R = CN, R_1 = Morpholino
47g: R = CF_3, R_1 = Morpholino
47h: R = CH_3, R_1 = Morpholino
47i: R = OCH_3, R_1 = Morpholino
47j: R = $C_6H_4SO_2CH_3$, R_1 = Morpholino
47k: R = naphthyl, R_1 = Morpholino
47l: R = H, R_1 = Piperidino
47m: R = NO_2, R_1 = Piperidino
47n: R = F, R_1 = Piperidino
47o: R = Cl, R_1 = Piperidino
47p: R = Br, R_1 = Piperidino
47q: R = CN, R_1 = Piperidino
47r: R = CF_3, R_1 = Piperidino
47s: R = CH_3, R_1 = Piperidino
47t: R = OCH_3, R_1 = Piperidino
47u: R = $C_6H_4SO_2CH_3$, R_1 = Piperidino
47v: R = naphthyl, R_1 = Piperidino

Scheme 19



7 **48** **49a-49k**

Yield = 75-91%

49a: R = H
49b: R = NO_2
49c: R = F
49d: R = Cl
49e: R = Br
49f: R = CN
49g: R = CF_3
49h: R = CH_3
49i: R = OCH_3
49j: R = $C_6H_4SO_2CH_3$
49k: R = naphthyl

phenyl)-2-pyrazoline, respectively, exhibited robust and selective biological efficacy against A549 and MCF-7 cell lines in comparison to erlotinib, employed as the standard drug. Moreover, these derivatives showed effective EGFR inhibition activity, as evidenced by their IC_{50} values of 4.34 ± 0.66 μM and 4.71 ± 0.84 μM. Molecular docking studies, conducted to complement the *in vitro* assays, revealed that the derivative containing a morpholino moiety displayed a favorable affinity for the ATP binding sites of HER2 and EGFR (Scheme 18).

Sever and group[74] reported the synthesis of thiazolyl-pyrazolines **49a−49k**, which are morpholine-based, through the ring closure reaction of the thiocarbamoyl moiety **48** and phenacyl bromide **7**. This synthesis was achieved by refluxing in ethanol on a water bath for a time period of 8 h, resulting in yields ranging from good to excellent. The significance of these compounds lies in their potential therapeutic relevance to Alzheimer's disease (AD), as human carbonic anhydrases (hCAs), crucial targets for AD therapy, were specifically addressed through a recent evaluation utilizing Verporte and Ellman's assay. *In vitro* analyses were conducted on all synthesized derivatives to assess their inhibition activity against acetylcholinesterase (AChE) and carbonic anhydrase (hCA). Among the studied derivatives, 1-(4-phenylthiazol-2-yl)-3-(4-morpholinophenyl)-5-(4-fluorophenyl)-2-pyrazoline (**49a**), 1-[4-(4-cyanophenyl)thiazol-2-yl]-3-(4-morpholinophenyl)-5-(4-fluorophenyl)-2-pyrazoline (**49f**) and 1-[4-(4-chlorophenyl)thiazol-2-yl]-3-(4-morpholinophenyl)-5-(4-fluorophenyl)-2-pyrazoline (**49c**) exhibited the most promising activities against hCAI, hCAII, and AChE, respectively.

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Moreover, a comprehensive *in silico* screening was conducted using Schrödinger Suite software to ascertain the binding affinities of the candidate substances. This analysis was based on Glide XP scoring, MM-GBSA calculation, and subsequent validation procedures (Scheme 19).

2.3.3. Pyridine-Linked Hybrids. Pyridine, characterized by the chemical formula C_5H_5N, stands as a foundational heterocyclic organic compound, as depicted in Figure 21.

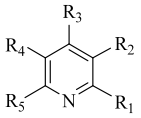

Figure 21. Structure of pyridine.

Analogous to benzene, it manifests a conjugated system comprising six π-electrons, which undergo delocalization throughout the heterocyclic ring. This compound finds extensive applications in pharmacology, serving as a herbicidal, antibacterial, antiviral, antihistaminic, and antiallergic agent (Figure 22).[75]

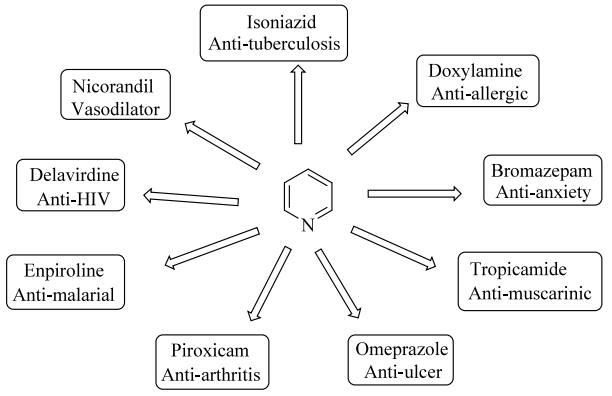

Figure 22. Pyridine-based therapeutic molecules.

Jadav et al.[76] proficiently conducted the synthesis of a series of pyrazoline-thiazole linked pyridine hybrids **51a−51t**. This synthetic protocol entailed the reaction between pyrazoline derivatives **50** and phenacyl bromide **7** in ethanol, resulting in good yields within reaction duration of 30 to 45 min. It is interesting that some derivatives showed significant antiviral activity against the dengue virus. In a seminal publication appearing in the *Proceedings of the National Academy of Sciences of the United States of America* in 2003 (Proc. Natl. Acad. Sci. U.S.A. 2003, 100, 6986), the identification of the β-OG pocket within the flavivirus envelope (*E*) protein was disclosed. This cavity was recognized as a promising target for the development of antiviral therapeutics aimed at hindering virus entry into the host cell (Scheme 20).

Elbayaa and coauthors[77] elucidated the synthetic pathway for the preparation of 2-(4,5-dihydro-5-(pyridin-2-yl)-3-*p*-tolylpyrazol-1-yl)thiazol-4(5*H*)-one **53** with a satisfactory yield. The synthesis involved refluxing 1-thiocarbamoyl pyrazole derivatives **52** and phenacyl bromide **40** in ethanol for 2 h. Characterization of the resultant compounds was conducted, and their potential antiinflammatory properties were assessed using a carrageenan-induced granuloma bioassay, employing celecoxib as the standard drug for comparative analysis. Furthermore, the evaluated derivatives were subjected to scrutiny for potential anticancer activities through the utilization of the National Cancer Institute's (NCI) *in vitro* disease-oriented human cells screening panel assay. In order to gain insights into the impact of the tested compounds on liver tissue in the context of their antiinflammatory effects, a histopathological investigation was undertaken. This study involved the examination of rat livers subjected to carrageenan injections. The comprehensive scientific evaluation of these synthesized compounds contributes valuable information to the fields of medicinal chemistry and pharmacology, providing insights into their therapeutic potential for both antiinflammatory and anticancer applications (Scheme 21).

2.3.4. Pyrazine-Linked Hybrids. Pyrazine is an electron-deficient member of the 1,4-diazines family, which includes an important group of biologically active heterocycles that can be chemically synthesized or isolated naturally from plants or animals (Figure 23). Numerous pharmaceutically approved compounds featuring a pyrazine nucleus are depicted in Figure 24, such as sulfalene, acipimox, glipizide, flavipiravir, fluitmide, pyraziamide, bortezomib, varenicline, amiloride, and telaprevir.[78]

Hassan and co-workers[79] accomplished the synthesis of 2-[5-(3,4-dimethoxyphenyl)-3-(pyrazin-2-yl)-4,5-dihydro-1*H*-pyrazol-1-yl]-4-phenylthiazole **55** via the reaction between 5-(3,4-dimethoxyphenyl)-3-(pyrazin-2-yl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide **54** and phenacyl bromide **25** in ethanol under reflux conditions over a duration of 6 h. The chemical reaction resulted into moderate yields of the intended product. Subsequently, the *in vitro* antitubercular activity of the synthesized pyrazoline-thiazole derivatives against the *Mycobacterium tuberculosis H37Rv* strain was examined using the Microplate Alamar Blue Assay (MABA) method (Scheme 22).

2.3.5. Miscellaneous. da Rosa et al.[80] developed an effective methodology for the synthesis of 2-(3,5-diaryl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-phenylthiazoles **57a−57d**, achieving a moderate yield. The synthetic methodology employed herein entailed the reaction between 1-thiocarbamoyl-4,5-dihydro-1*H*-pyrazoles **56** and phenacyl halide **40** in an ethanol medium, utilizing reflux conditions implemented on a water bath over a period of 4 h. The resultant hybrid compounds were subjected to comprehensive evaluation for both cytotoxicity and utility as latent fingermark (LFM) agents. Among the evaluated hybrids, 2-(3,5-diphenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-phenylthiazole **57a** exhibited superior attributes, exhibiting low cytotoxicity and exceptional performance in friction ridge morphometry. Notably, compound **57a** displayed heightened sensitivity, particularly on sebaceous fingermarks. Fingerprints play a pivotal role in criminal investigations, representing one of the most prevalent physical traces encountered at crime scenes. Their ubiquitous applicability extends globally, serving as a crucial means of person identification (Scheme 23).

Fakhry and co-workers[81] communicated the synthesis of 2-(3-(3,4-dimethoxyphenyl)-5-(aryl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(aryl) thiazoles **59a−59l**. This synthetic procedure involves the chemical interaction between 3-(3,4-dimethoxyphenyl)-5-(4-aryl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide **58** and phenacyl bromide **7** in ethanol, with DMF serving as the catalytic agent. The reaction was conducted under reflux conditions on a water bath for duration of 5 h, yielding the desired compounds, in good yield. The fabricated compounds were screened to assess their inhibitory effects on cell proliferation in MCF-7 and MCF-10 cell lines, which serve

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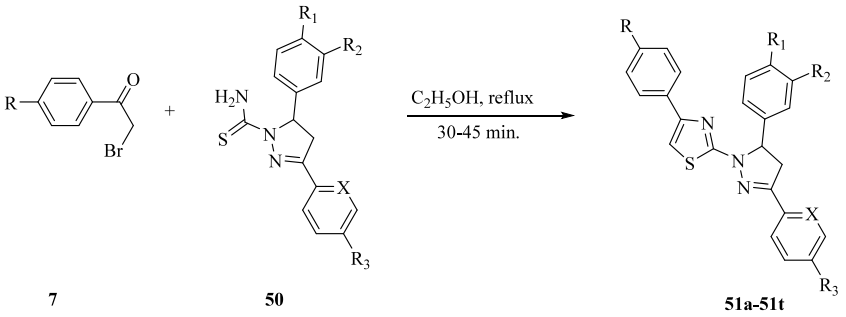
Scheme 20

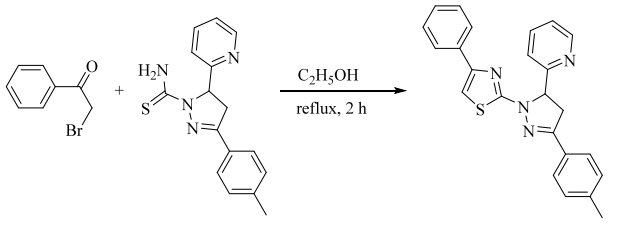


7 50 51a-51t

Yield = 60-78%

51a: R = Cl, R_1 = H, R_2 = H, R_3 = H, X = CH
51b: R = Cl, R_1 = H, R_2 = H, R_3 = Cl, X = CH
51c: R = Cl, R_1 = H, R_2 = H, R_3 = OH, X = CH
51d: R = Cl, R_1 = H, R_2 = H, R_3 = OCH_3, X = CH
51e: R = Cl, R_1 = H, R_2 = H, R_3 = NO_2, X = CH
51f: R = Cl, R_1 = H, R_2 = H, R_3 = H, X = N
51g: R = Cl, R_1 = OH, R_2 = OCH_3, R_3 = Cl, X = CH
51h: R = Cl , R_1 = OH, R_2 = H, R_3 = Cl, X = CH
51i: R = Cl, R_1 = OH, R_2 = OCH_3, R_3 = OCH_3, X = CH
51j: R = Cl, R_1 = OH, R_2 = H, R_3 = OCH_3, X = CH
51k: R = C_6H_5, R_1 = H, R_2 = H, R_3 = H, X = CH
51l: R = C_6H_5, R_1 = H, R_2 = H, R_3 = Cl, X = CH
51m: R = C_6H_5, R_1 = H, R_2 = H, R_3 = OH, X = CH
51n: R = C_6H_5, R_1 = H, R_2 = H, R_3 = OCH_3, X = CH
51o: R = C_6H_5, R_1 = H, R_2 = H, R_3 = NO_2, X = CH
51p: R = C_6H_5, R_1 = H, R_2 = H, R_3 = H, X = N
51q: R = C_6H_5, R_1 = OH, R_2 = OCH_3, R_3 = Cl, X = CH
51r: R = C_6H_5, R_1 = OH, R_2 = H, R_3 = Cl, X = CH
51s: R = C_6H_5, R_1 = OH, R_2 = OCH_3, R_3 = OCH_3, X = CH
51t: R = C_6H_5, R_1 = OH, R_2 = H, R_3 = OCH_3, X = CH

Scheme 21



40 52 53

Yield = 61%

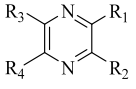


Figure 23. Structure of pyrazine.

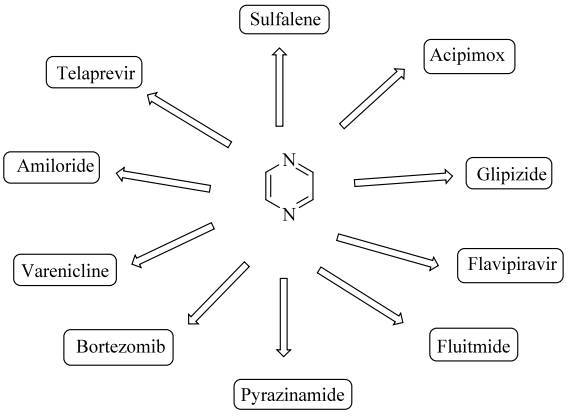


Figure 24. Pyrazine-based drugs.

as models for cancer and normal breast cells, respectively. Among the array of analogs investigated, compound 2-(3-(3,4-dimethoxyphenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-phenylthiazole **59e** and 2-(5-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(4-fluorophenyl)thiazole **59k** demonstrated significant dual inhibitory activity against EGFR and HER2 receptors, when correlated with standard drug lapatinib. Compound **59e** exhibited an IC_{50} values of 0.009 and 0.051 μM, while compound **59k** displayed an IC_{50} values of 0.013 and 0.027 μM. To further elucidate their potential therapeutic utility, comprehensive ADMET tests, computational modeling studies, and toxicity predictions were executed. The amalgamation of *in vitro*, *in vivo*, and *in silico* investigations underscored the promising therapeutic profile of 2-(3-(3,4-dimethoxyphenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-phenylthiazole **59e**, which emerged as a compelling candidate for the development of future anticancer agents. Remarkably, compound **59e** demonstrated a dual inhibitory effect against EGFR and HER2 receptors, positioning it as a potential cornerstone for the advancement of anticancer therapeutics (Scheme 24).

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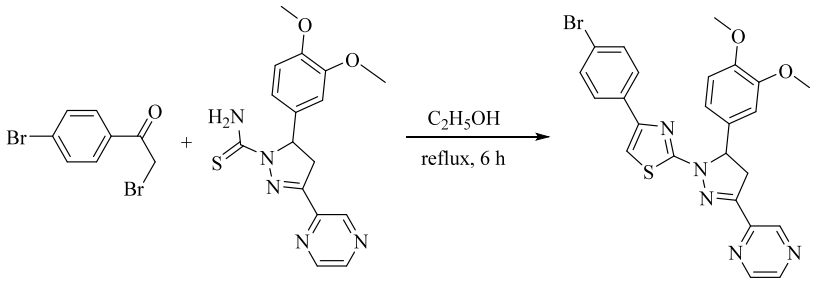
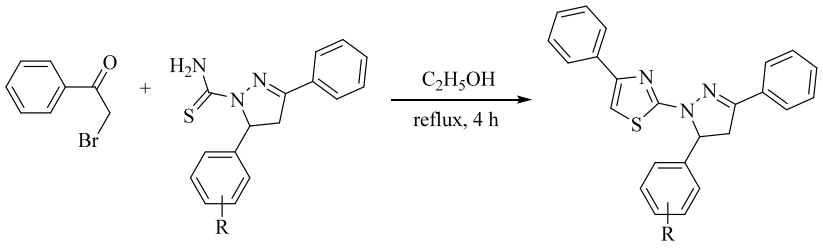
Scheme 22



25 **54** **55**

Yield = 50%

Scheme 23



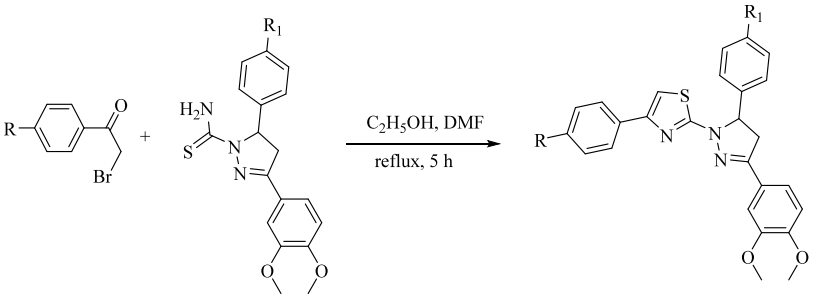
40 **56** **57a-57d**

57a: R = H **57c:** R = Cl

57b: R = OCH_3 **57d:** R = Br

Yield = 70-77%

Scheme 24



7 **58** **59a-59l**

Yield = 36.6-81.3%

59a: R = H, R_1 = H **59e:** R = H, R_1 = OCH_3 **59i:** R = H, R_1 = Cl

59b: R = F, R_1 = H **59f:** R = F, R_1 = OCH_3 **59j:** R = F, R_1 = Cl

59c: R = Cl, R_1 = H **59g:** R = Cl, R_1 = OCH_3 **59k:** R = Cl, R_1 = Cl

59d: R = CH_3, R_1 = H **59h:** R = CH_3, R_1 = OCH_3 **59l:** R = CH_3, R_1 = Cl

Sharifzadeh et al.[82] have devised an environmentally conscious approach for crafting novel bioactive thiazolyl-pyrazoline derivatives **61a−61c** and **63a−63f**. This method involves the acid-catalyzed cyclocondensation of diverse chalcones **60** or **62**, phenacyl bromide **40**, and thiosemicarbazide **20** in ethanol under reflux on a water bath for 4 to 6 h, resulting in moderate to good yields. The procedure stands out for its simplicity, efficient atom economy, straightforward execution, favorable yields, and utilization of economically viable starting materials, contributing to an ecologically benign process. Several of the produced pyrazoline derivatives were assessed for their antibacterial properties, with a striking efficacy observed against *Pseudomonas aeruginosa*. The compounds **63a** and **63f** comprising electron-releasing group methoxy and thiophene nucleus exhibited notably auspicious bacteriostatic efficacy against *Pseudomonas aeruginosa* (Scheme 25).

Suwunwong and colleagues[83] have explored the synthesis of thiazolyl-pyrazolines **66a−66d** via the cyclization of pyrazoline derivative **65** with phenacyl bromide **64**. The catalytic influence of sodium hydroxide was employed in this reaction, which transpired in an ethanol milieu under reflux conditions, utilizing a water bath, with a reaction duration spanning 4 to 5 h. The ensuing chemical entities were found to be in moderate to excellent yields. The thiazole conjugates demonstrated distinct green fluorescence properties at approximately 506−508 nm (excited at 370 nm) in both solution and solid states. Furthermore, a thermal gravimetric study was performed on 2-

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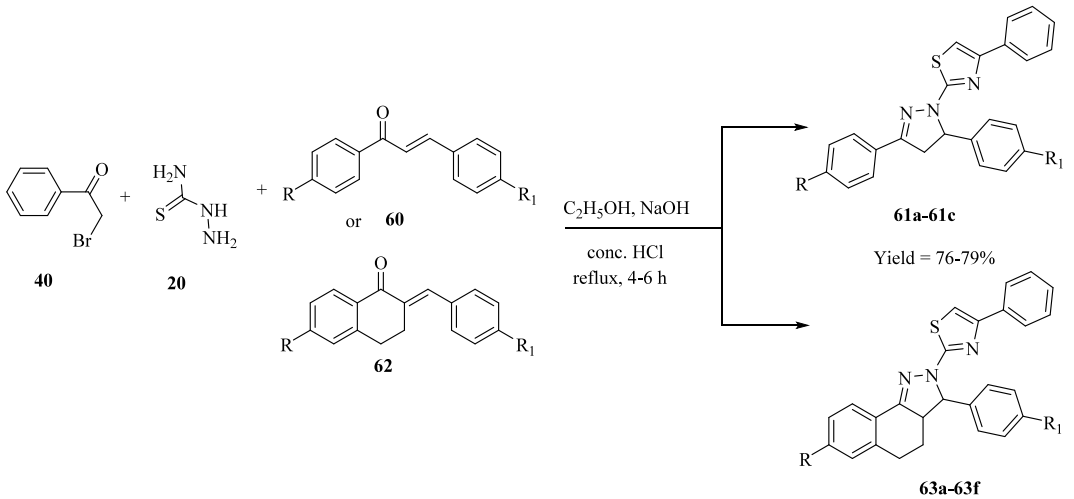
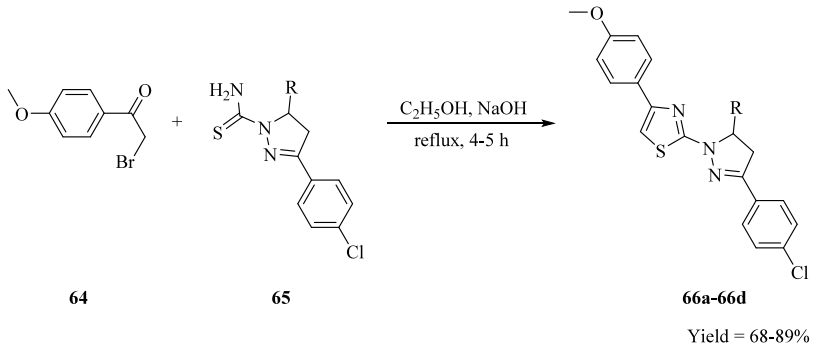
Scheme 25



61a: R = H, R_1 = OCH_3
61b: R = H, R_1 = Cl
61c: R = H, R_1 = thienyl
63a: R = H, R_1 = OCH_3
63b: R = OCH_3, R_1 = OCH_3
63c: R = OCH_3, R_1 = CH_3
63d: R = CH_3, R_1 = CH_3
63e: R = CH_3, R_1 = OCH_3
63f: R = H, R_1 = thienyl

Scheme 26



66a: R = C_6H_5
66b: R = 4-$OCH_3C_6H_4$
66c: R = 4-$OC_2H_5C_6H_4$
66b: R = 2-naphthyl

(3-(4-chlorophenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(4-methoxyphenyl)thiazole **66a**, and an analysis of the effects of pH on the characteristics of fluorescence was conducted. Especially, within an acetonitrile−water matrix, the thiazole derivative exhibited notable thermal stability, enduring temperatures up to approximately 250 °C. Additionally, the compound displayed high stability across a range of pH values (Scheme 26).

Bayomi and co-workers[84] have elucidated the synthesis of some novel hybrid compounds **68a−68b** and **70a−70h** and screened for their anticancer potentials. These compounds were meticulously crafted by means of a cyclization reaction, wherein thiocarbamoyl pyrazole derivatives **67** and **69** underwent a chemically orchestrated coupling with phenacyl bromides **40** and **7**, all within the structural framework of curcumin. The synthesis was carried out in ethanol under reflux conditions for 2 h, yielding moderate yields of the desired compounds. Further, the anticancer efficacy of these synthesized conjugates was investigated through both *in vivo* and *in vitro* studies using the Ehrlich ascites carcinoma (EAC) cell line. Within the scope of the examined compounds, the derivative identified as 4-(4-chlorophenyl)-2-(5-ethyl-7-(4-methoxybenzylidene)-3-(4-methoxyphenyl)3,3*a*,4,5,6,7-hexahydro-2*H*-pyrazolo[4,3-*c*]pyridin-2-yl)thiazole **70h** exhibited remarkable antineoplastic activity in comparison of the reference drug cisplatin. Furthermore, *in silico* modeling studies were conducted, revealing that the majority of bioactive derivatives demonstrated antitumor properties through the inhibition of telomerase (Scheme 27).

Wang et al.[85] have meticulously detailed the synthesis of thiazole hybrids conjoined with a pyrazoline scaffold **73a−73r** through the refluxing of dihydropyrazole derivatives **72** with phenacyl bromide **71** in the presence of DMF at ambient temperature for the time period of 6 h, affording products in moderate yields. The antineoplastic efficacy of all synthesized compounds was assessed against MCF-7, HepG2, and HeLa cells, revealing a majority of them to exhibit superior activities compared to the positive control drugs gefitinib and celecoxib. Augmentation of activities was observed upon the introduction of fluoro and bromo substituents at the R_1 and R_3 positions in the resultant compounds. The following derivatives underwent evaluation for their specific inhibitory effect on Matrix

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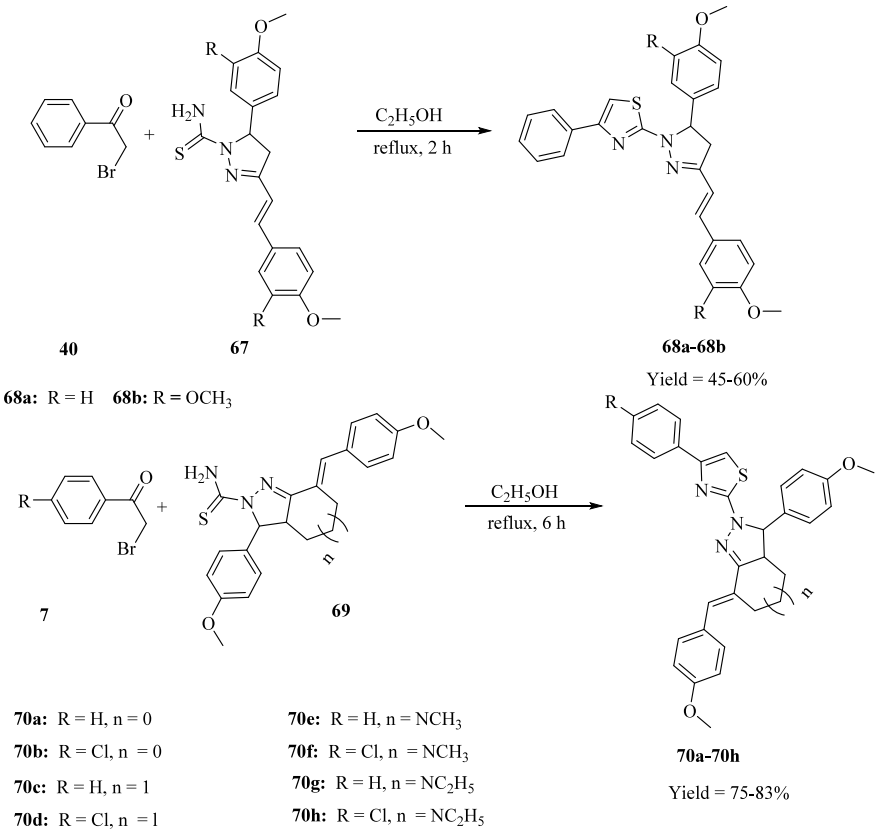
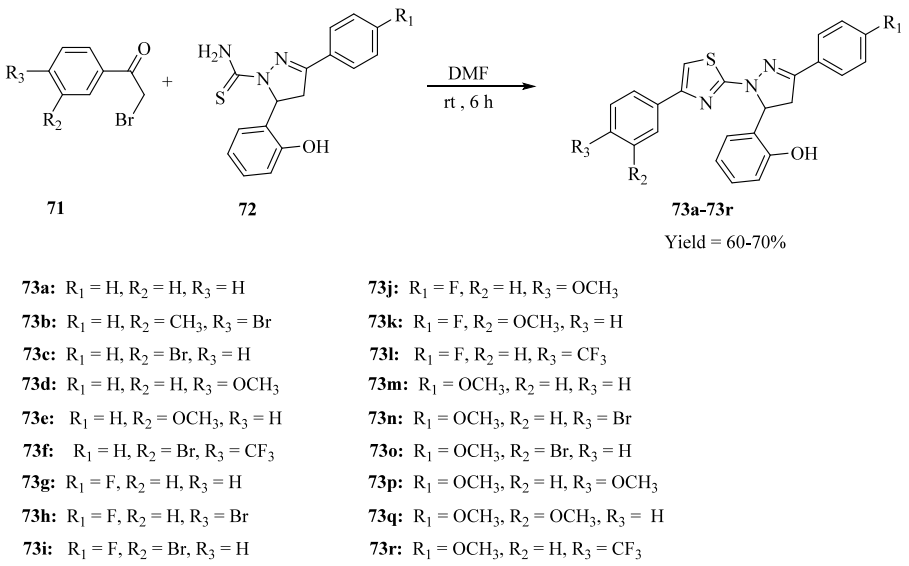
Scheme 27



Scheme 28



Metalloproteinase-2 (MMP-2). Among the assessed derivatives, 2-(3-(4-methoxyphenyl)-1-(4-(3-methoxyphenyl)thiazol-2-yl)-4,5-dihydro-1*H*-pyrazol-5-yl)phenol **73q** demonstrated the most notable inhibitory potential for MMP-2, exhibiting an IC_{50} value of 2.80 μM, surpassing the reference drug CMT-1 with an IC_{50} value of 1.29 μM (Scheme 28).

Masoud and group[86] described the synthesis of pyrazoline-thiazole hybrids **75a−75h** as antimicrobial agents through the cyclization reaction involving phenacyl bromide **7** and thiamide **74**, conducted in the presence of ethanol as the solvent. The reaction transpired under reflux conditions on a water bath for 4 h, yielding moderate outcomes. The synthesized compounds underwent comprehensive assessment for antimicrobial efficacy against a diverse array of microorganisms including, *Staphylococcus aureus, Klebsiella pneumoniae, Bacillus subtilis, Pseudomonas aeruginosa, Candida albicans, Aspergillus fumigatus, Syncephalastrum racemosum, Penicillium expansum*, and *Aspergillus fumigates*. Of the scrutinized analogs, 2-(5-(benzo[*d*][1,3]dioxol-5-yl)-3-(3,4-dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(4-phenyl)thiazole **75e** and 2-(5-

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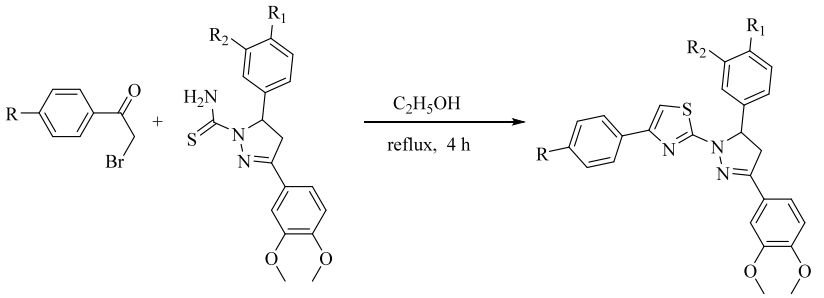
Scheme 29

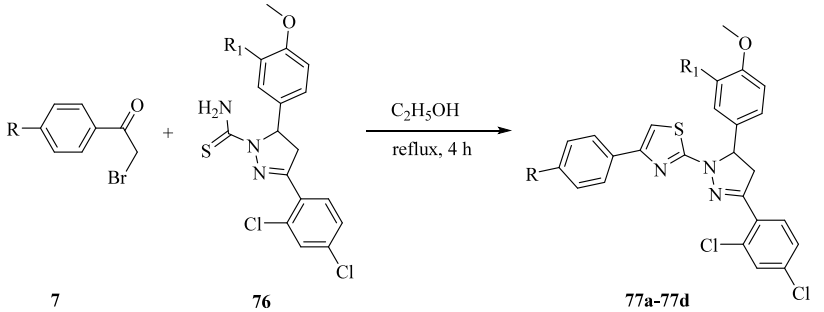


7 74 75a-75h

Yield = 62-72%

75a: R = H, $R_1 = R_2 = OCH_3$
75b: R = F, $R_1 = R_2 = OCH_3$
75c: R = Cl, $R_1 = R_2 = OCH_3$
75d: R = Br, $R_1 = R_2 = OCH_3$
75e: R = H, $R_1 = R_2 = -OCH_2O-$
75f: R = F, $R_1 = R_2 = -OCH_2O-$
75g: R = Cl, $R_1 = R_2 = -OCH_2O-$
75h: R = Br, $R_1 = R_2 = -OCH_2O-$

Scheme 30

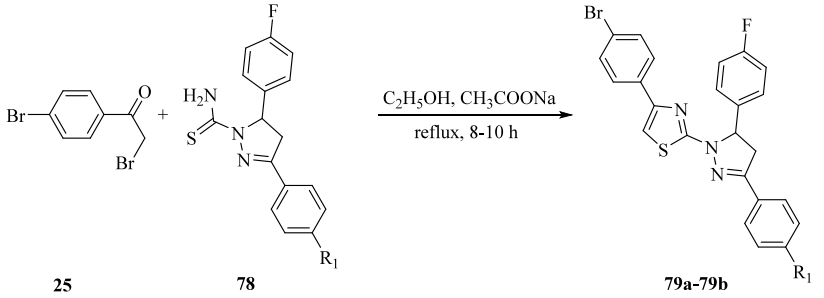


7 76 77a-77d

Yield = 55-79%

77a: R = H, R_1 = H
77b: R = H, R_1 = Cl
77c: R = OCH_3, R_1 = H
77d: R = OCH_3, R_1 = Cl

Scheme 31



25 78 79a-79b

Yield = 75-82%

79a: R_1 = H **79b:** R_1 = F

(benzo[*d*][1,3]dioxol-5-yl)-3-(3,4-dimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(4-chlorophenyl)thiazole **75g** demonstrated remarkable antimicrobial activity, particularly against *Penicillium expansum* and *Aspergillus flavus*, displaying inhibitory zones of 2.3 mm and 2.2 mm, respectively. The observed inhibitory activity was greater than that of griseofulvin, the reference medication (Scheme 29).

Abdelsalam and co-workers[87] have described a systematic methodology for synthesizing 4-(aryl)-2-(3-(2,4-dichlorophenyl)-5-(4-aryl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazoles **77a**−**77d**. This synthetic route involves the condensation of carbothioamide derivatives **76** with phenacyl bromide **7** in ethanol under reflux conditions for 4 h, resulting in the targeted compounds with a moderate yield. The cytotoxicity of the synthesized thiazole derivatives was evaluated against nonsmall lung cancer cells (NSCLC), A-549 and H441 cell lines. Additionally, their inhibitory potency against the kinases EGFR and VEGFR-2 was investigated. The results of SAR analysis revealed that compounds 3-(2,4-dichlorophenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl-4-phenylthiazole **77a** and 4-(4-chlorophenyl)-2-(3-(2,4-dichlorophenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole **77b** exhibited superior EGFR inhibition activity than derivative with two methoxy groups, as evidenced by their IC_{50} values of 145.1 ± 2.0 and 114.2 ± 0.4 nM respectively. Furthermore, the substitution pattern on the pendant phenyl moieties imparted distinct

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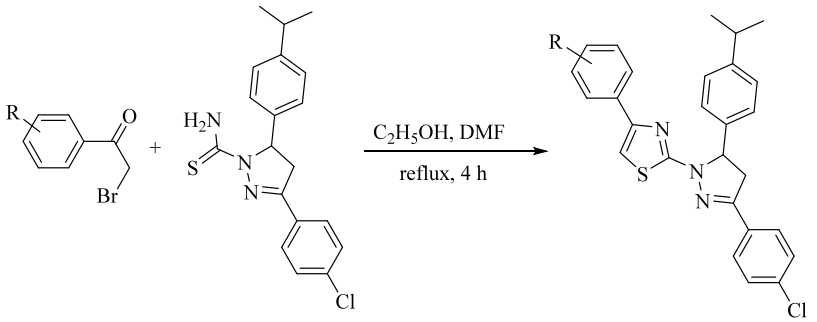
Scheme 32

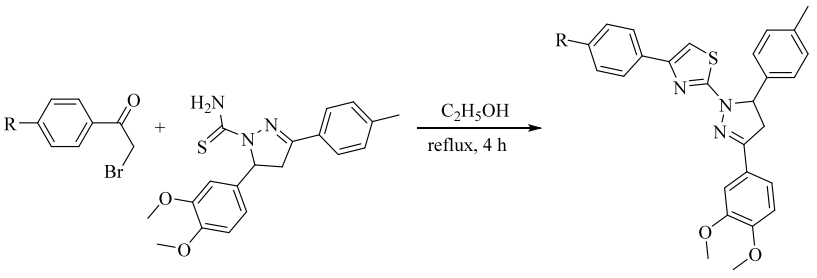


80 **81** **82a-82l**

Yield = 71-88%

82a: R = H
82b: R = 4-Cl
82c: R = 4-F
82d: R = 4-Br
82e: R = 4-CH_3
82f: R = 4-OH
82g: R = 4-NH_2
82h: R = 4-NO_2
82i: R = 4-CH_3
82j: R = 2,4-$(Cl)_2$
82k: R = 2,4-$(OH)_2$
82l: R = 2-OH-5-OCH_3

Scheme 33



7 **83** **84a-84d**

Yield = 80-83%

84a: R = H
84b: R = Cl
84c: R = Br
84d: R = CH_3

electronic and lipophilic environments, thereby influencing the activity profile of the resultant thiazoles. This information underscores the importance of strategic structural modifications in tailoring the pharmacological properties of these compounds, shedding light on potential avenues for further drug development in the field of kinase inhibition (Scheme 30).

Abbas et al.[88] devised a synthetic methodology to synthesize thiazole-based pyrazolines **79a−79b** as potential anticancer agents. The synthesis involved the reaction of pyrazole-1-carbothioic acid amide derivatives **78** and phenacyl bromide **25** in ethanol, catalyzed by anhydrous sodium acetate. The ensuing reaction mixture underwent reflux on a water bath for 8 to 10 h, consistently yielding high product yields. The antiproliferative efficacy of the synthesized thiazoles was analyzed against MCF-7 human breast cancer cell lines utilizing the sulforhodamine-B (SRB) assay. A comprehensive SAR investigation was conducted, revealing that 4-(4-bromophenyl)-2-[5-(4-fluorophenyl)-3-phenyl-4,5-dihydropyrazol-1-yl]thiazole **79a** demonstrated notable biological activity, when compared to the established reference drug tamoxifen, as evidenced by an IC_{50} value of 9.30 μg/mL (Scheme 31).

Salian and group[89] reported the synthesis of a diverse array of thiazole-linked pyrazoline scaffolds **82a−82l** and their subsequent assessment for antimicrobial and antioxidant potential. The synthesis involved the refluxing of 3-(4-chlorophenyl)-5-[4-(propan-2-yl)phenyl]-4,5-dihydro-1*H*-pyrazole-1-carbothioamide derivatives **81** and phenacyl bromide **80** in a mixture of ethanol and DMF for a duration of 4 h, affording desired products with satisfactory yields. The synthesized compounds underwent *in vitro* evaluation for their antioxidant and antimicrobial properties against *Staphylococcus aureus*, *Escherichia coli*, *Bacillus cereus*, *Serratia marcescens*, *Aspergillus niger*, *Candida albicans*, *Trichophyton mentagrophytes*, and *Candida parapsilosis*. This evaluation employed the free radical DPPH assay and the agar well diffusion method. The antimicrobial screening exhibited noteworthy results, with derivatives 4-{2-[3-(4-chlorophenyl)-5-(4-(propan-2-yl)phenyl-4,5-dihydro-1*H*-pyrazol-1-yl]-1,3-thiazol-4-yl}phenol **82f** and 4-{2-[3-(4-chlorophenyl)-5-(4-(propan-2-yl)phenyl)-4,5-dihydro-1*H*-pyrazol-1-yl]-1,3-thiazol-4-yl}aniline **82g** demonstrating significant antioxidant activity, evidenced by IC_{50} values of 63.11 μg/mL and 67.93 μg/mL, respectively. To further support the antimicrobial assessment, an *in silico* molecular docking study was conducted. Markedly, single crystal investigations on the synthesized compounds elucidated their varying radical scavenging capacities, ranging from poor to moderate, attributed to the destabilization of radicals generated during oxidation (Scheme 32).

Fathy and group[90] synthesized several thiazole-based pyrazoline scaffolds **84a−84d** through the cyclization reaction

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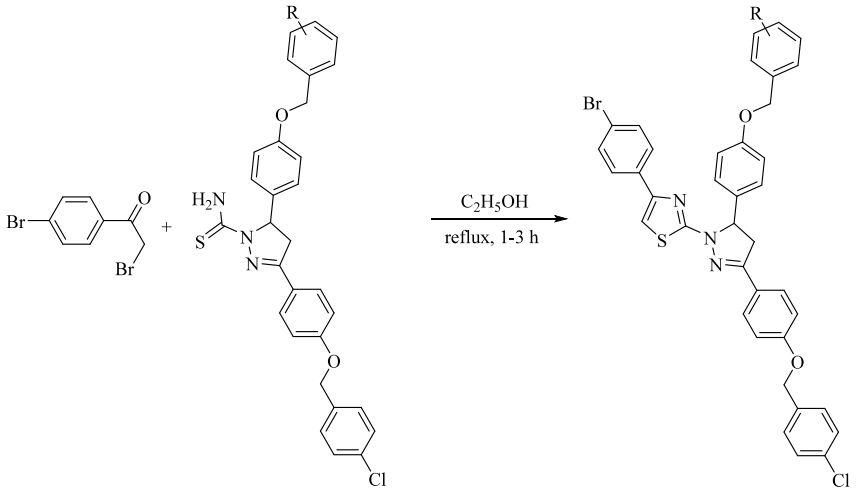
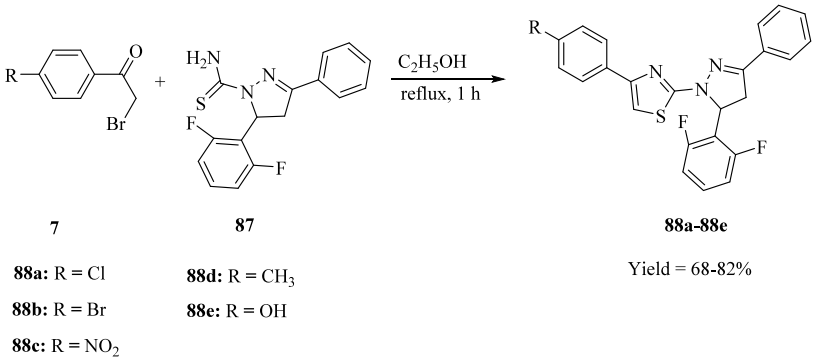
Scheme 34



Scheme 35



between phenacyl bromide **7** and thiamide **83** in ethanol under reflux conditions. This methodology yielded good to excellent yields within a 4 h time frame. The anticancer efficacy of the synthesized scaffolds was evaluated using the SRB assay on MCF-7, A549, and HepG-2 cancer cell lines. Remarkably, 4-(4-bromophenyl)-2-(5-(3,4-dimethoxyphenyl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-thiazole **84c** emerged as the most promising compound, demonstrating potent activity against all three tested cell lines. Structural-activity relationship (SAR) analysis displayed a positive correlation between the incorporation of chloro, bromo, and fluoro electron-withdrawing groups in the pyrazoline-thiazole derivatives and an enhancement in anticancer activity (Scheme 33).

Salih and group[91] have explored the synthesis of a discerningly chosen set of thiazole-linked pyrazoline conjugates, **86a−86b**. These compounds were derived through the reaction of pyrazoline derivatives **85** and phenacyl bromide **25**. The synthetic procedure was conducted in ethanol under reflux conditions, employing stirring for a duration ranging from 1 to 3 h, resulting in exemplary yields. Further, the *in vitro* antimicrobial efficacy of the synthesized derivatives was meticulously evaluated using both the well-diffusion method and MIC test against microbial strains *Candida albicans*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Acinetobacter baumannii*. Particularly, the examined derivatives demonstrated significant antimicrobial activity, in contrast to well-established pharmaceutical standards, namely ciprofloxacin and fluconazole. Furthermore, bioinformatics investigations elucidated the nontoxic profile and favorable pharmacokinetics of the two scrutinized conjugates, **86a** and **86b**. However, it was observed that both derivatives exhibited suboptimal bioavailability. Molecular docking studies and Density Functional Theory (DFT) analyses provided insights into the superior biological activities of derivative **86b**, distinguished by a nitro substituent on the phenyl ring, in comparison to derivative **86a** featuring a chloro substituent. This heightened efficacy was attributed to the increased binding affinity and a reduced HOMO−LUMO gap associated with **86b** (Scheme 34).

Rajendra Prasad and co-workers[92] synthesized a few novel anticancer and antimicrobial agents **88a−88e** through the condensation reaction of phenacyl bromide **7** with 5-(2,6-difluorophenyl)-3-phenyl-4,5-dihydropyrazole-1-carbothioamide **86** in ethanol under reflux conditions for a duration of 1 h, resulting in satisfactory to excellent yields. The efficacy of these hybrid compounds was evaluated for their *in vitro* inhibitory potential against the growth of Hela, MCF-7, A549, BGC-823, and A2780 cell lines using the MTT assay. Additionally, the antimicrobial properties of the synthesized compounds were investigated using the broth dilution method.

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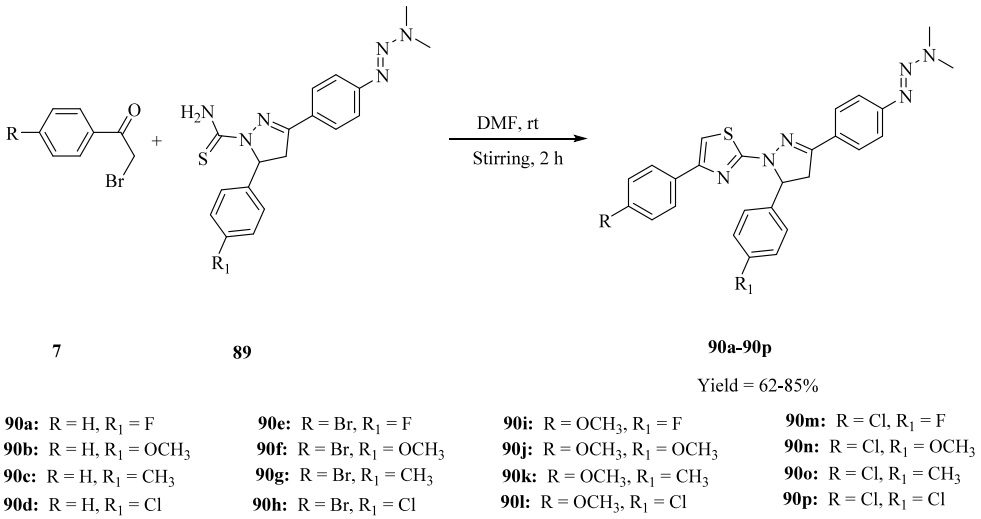
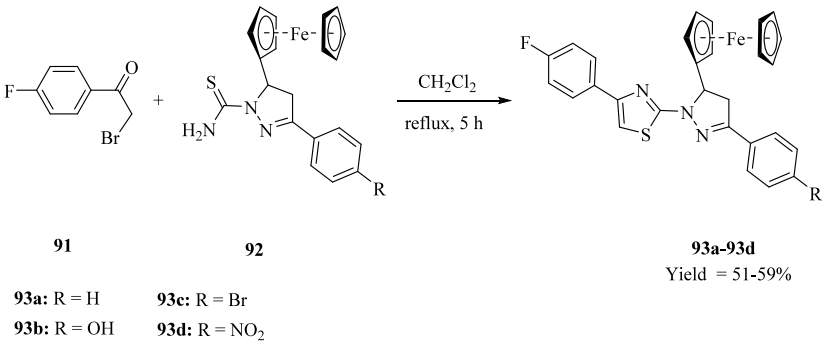
Scheme 36



Scheme 37



Among the analyzed conjugates, 5-(2,6-difluorophenyl)-3-phenyl-1-(4-*p*-tolylthiazol-2-yl)-4,5-dihydro-1*H*-pyrazole **88d** exhibited effective anticancer activity in contrast to the reference medication cisplatin. Especially, the 4-methyl-substituted derivative **88d** demonstrated significant inhibition against tested Gram-positive bacteria with MIC values ranging from 4 to 8 μg/mL (Scheme 35).

Ravula and co-workers[93] devised a methodological approach for the synthesis of thiazolyl-pyrazoline hybrids incorporating dimethyl triazene functionalities **90a−90p** by the reaction of thiamides **89** derivatives and phenacyl bromide **7** in the presence of DMF and stirring for about 2 h at room temperature, in moderate to excellent yield. The synthesized compounds were examined for their *in vitro* anticancer activity against human colon cancer (HT-29) cell lines and human breast cancer (MCF-7) cell lines using the MTT assay. Amongest them, (*E*)-4-(4-chlorophenyl)-2-(3-(4-(3,3-dimethyltriaz-1-enyl)phenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole hybrid **90n** with IC_{50} values of 9.04 and 10.65 μg/mL having methoxy and chloro as substituents displayed potent biological activities against human colon cancer (HT-29) cell lines and human breast cancer (MCF-7) cell lines in comparison with the standard drug cisplatin (Scheme 36).

Parveen et al.[94] orchestrated the synthesis of 2-(5-ferrocenyl-3-aryl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(4-substituted-phenyl)-thiazoles **93a−93d** and systematically evaluated their antimicrobial efficacy. The synthetic protocol involved the cyclization of 5-ferrocenyl-3-substituted aryl-4,5-dihydro-1*H*-pyrazol-1-carbothioamide **92** with phenacyl bromide **91** in dichloromethane. The reaction transpired under reflux and stirring conditions within a nitrogen atmosphere for of 5 h, resulting in the generation of moderate yield of the target compounds. All newly synthesized compounds underwent antimicrobial *in vitro* testing against microorganisms, including *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Streptococcus bovis*, *Escherichia coli*, *Enterobacter cloacae*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus mutans*, *Candida dubliniensis*, *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida kefyr*, *Candida parapsilosis*, and *Candida krusei*. The antifungal evaluation outcomes demonstrated that compound **93d**, distinguished by the presence of a nitro group in the benzene ring of the pyrazoline moiety, exhibited superior efficacy compared to the other compounds under investigation (Scheme 37).

2.4. Fused Ring-Linked Heterocyclic Hybrids. In the context of fused moieties, a singular ring engages in the sharing of two or more of its edges with another ring, exemplified by chemical entities such as naphthalene, benzofuran, coumarin and indole. Fused ring systems manifest ubiquitously in natural products, pharmaceuticals and a spectrum of synthetic compounds. Their presence imparts manifold applications, exerting discernible influence on the chemical and physical attributes of the host molecules.

2.4.1. Indole-Linked Hybrids. A bicyclic molecular structure composed of a pentagonal pyrrole ring conjoined with a

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benzene moiety is designated as indole, colloquially referred to as benzopyrrole (Figure 25). Indole exhibits diverse biological activities like analgesic, antifungal, antibacterial, antitubercular, antidiabetic, anticancer, etc. (Figure 26).[95]

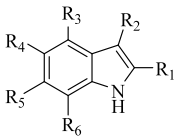


Figure 25. Structure of indole.

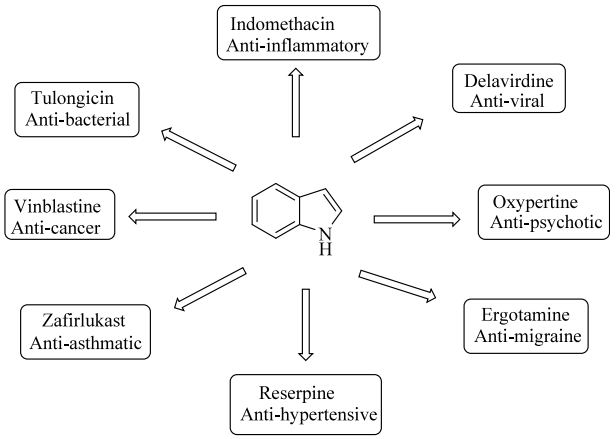


Figure 26. Pharmaceutical importance of indole.

Faritha and group[96] synthesized a few indole appended pyrazole-thiazoles **96a−96g** in the presence of acetic acid; the indolyl chalcones **94** underwent cyclization with hydrazinothiazole **95** in ethanol with stirring about 30 min followed by refluxing for 10 to 22 h, in moderate to excellent yield. All the synthesized compounds were assessed for their *in vitro* antibacterial activity against *Bacillus subtilis, Staphylococcus aureus, Escherichia coli, Salmonella typhi*, and *Pseudomonas aeruginosa* using an agar well diffusion method as well as antifungal activity against *Candida tropicals, Aspergillus fumigants, Trycophyton mentagrophytes*, and *Candida albicans* using the same cup plate method with PDA medium. The pyrazoline derivative **96c** bearing a methoxy group exhibited a notable antifungal effect on tested microbes when compared with the standard drug gentamicin. The antimicrobial activity of thiazole derivatives was enhanced by the inclusion of an electron-withdrawing group such as nitro and bromo on the phenyl ring (Scheme 38).

2.4.2. Benzofuran-Linked Hybrids. Benzofuran represents a heterocyclic molecular entity characterized by the fusion of a benzene ring with a furan nucleus (Figure 27). This compound

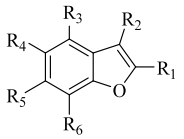


Figure 27. Structure of benzofuran.

exhibits significant inhibitory activity against a diverse array of pathological agents, including but not limited to illnesses, viruses, bacteria, fungi, and enzymes. Certain naturally occurring derivatives of benzofuran, exemplified by cicerfuran, which shows antifungal attributes, were initially isolated from the roots of wild chickpea species. In contrast, conocarpan demonstrated insecticidal, fungicidal, and antitrypanosomal properties. Notably, ailanthoidol has been associated with a myriad of biological actions, encompassing anticancer, antiviral, immunosuppressive, antioxidant, antifungal, and antifeedant properties. Moreover, synthetic benzofuran derivatives such as bufuralol and amiodarone have garnered well-established utility in the medical domain (Figure 28).[97]

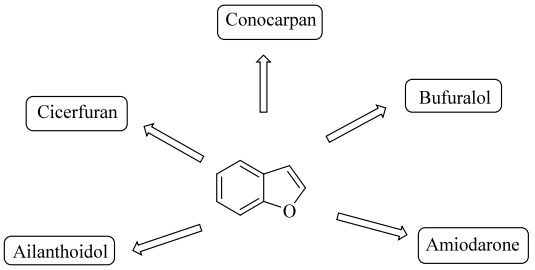
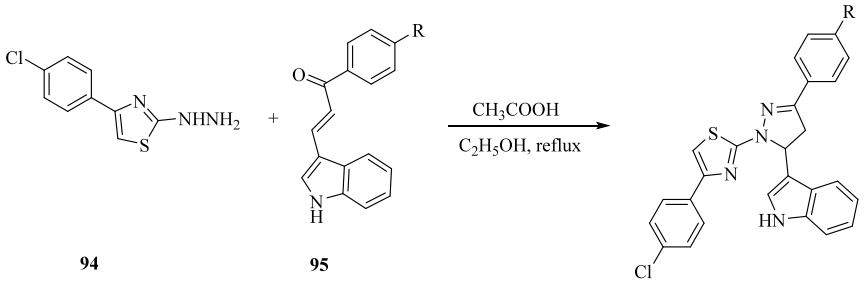


Figure 28. Natural and synthetic bioactive benzofuran derivatives.

Gouhar and colleagues[98] achieved the synthesis of (*E*)-2-(5-(naphthalen-2-yl)-3-(5-((3-(trifluoromethyl) phenyl)-diazenyl)benzofuran-2-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-phenylthiazole incorporating a naphthalene moiety **98**. The resultant compound was obtained through the reaction of

Scheme 38



94 **95**

96a-96g

96a: R = H
96b: R = CH_3
96c: R = OCH_3
96d: R = Cl
96e: R = Br
96f: R = OH
96g: R = NO_2

Yield = 70-80%

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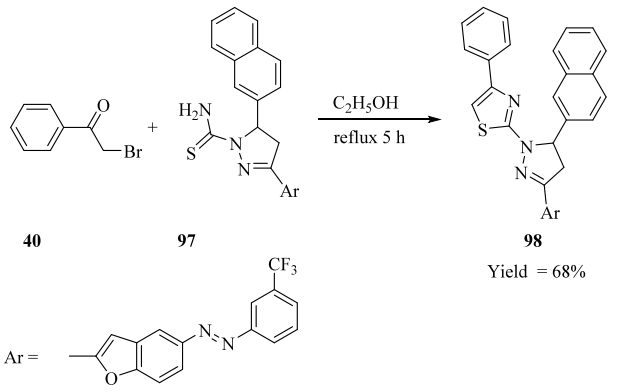
the pyrazole-1-carbothioamide derivative **97** and phenacyl bromide **40** in ethanol under reflux conditions for 5 h, yielding the desired product in a moderate yield. The anticancer efficacy of the synthesized derivative was screened against human breast carcinoma (MCF-7) cell lines, and a comparative analysis was conducted with the standard treatment, doxorubicin. The synthesized derivatives demonstrated significant antitumor activity, suggesting their potential in the field of cancer therapeutics (Scheme 39).

Scheme 39



40 **97** **98**

Yield = 68%

Mohamed et al.[99] developed a synthetic procedure for the synthesis of fluorinated 2-(3-(benzofuran-2-yl) pyrazol-1-yl)thiazole **100a−100b** through the cyclization of *N*-thiocarboxamide-2-pyrazoline **99** with phenacyl bromide **7** under reflux conditions in ethanol for a duration of 4 h, resulting in a moderate yield. The newly synthesized thiazole derivatives underwent analysis using the agar well diffusion method to assess their antimicrobial efficacy against *Bacillius Subtilis, Staphylococcus aureus, Bacillius Megaterium, Klebsiella pneumonia, Sarcina lutea, Pseudomonas aeruginosa, Escherichia coli, Saccharomyces cerevisiae*, and *Candida albicans*. Among the examined conjugates, 2-(3-(benzofuran-2-yl)-5-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(4-bromophenyl)thiazole **100b** demonstrated significant bioactivity against *Staphylococcus aureus*, with an inhibition zone measuring 22 mm. The introduction of chloro substituents in the targeted derivatives was observed to enhance the antimicrobial activity of the synthesized compounds (Scheme 40).

2.4.3. Benzodioxole-Linked Hybrids. The 1,3-benzodioxole ring system is prevalent in various naturally occurring compounds, such as myristicin, sesamol, piperonal, and saffrole (Figure 29). Additionally, this structural motif serves as a

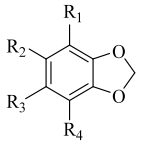


Figure 29. Structure of benzodioxole.

fundamental component in the molecular architecture of two recently developed antiepileptic medications, namely stiripentol and antiepilepserine. Numerous reports have documented diverse biological activities attributed to the benzodioxole ring system, encompassing anticancer, anticonvulsant, antidepressant, antiinflammatory, antihypertensive, anti-oxidant, antiprotozoal, antivitiligo, and immunomodulatory effects (Figure 30).[100]

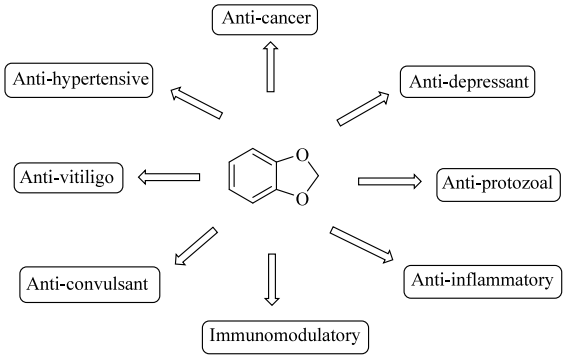
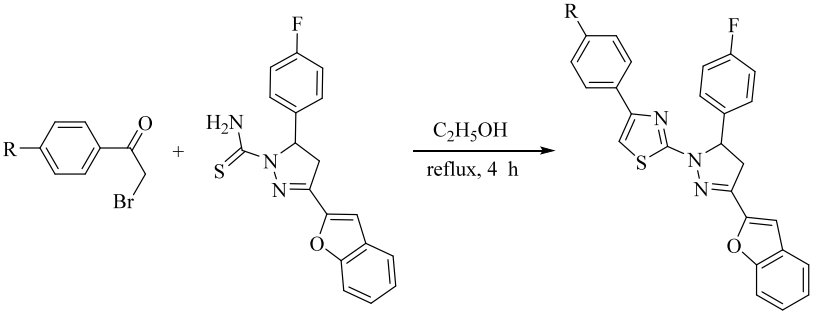


Figure 30. Pharmaceutical applications of benzodioxole.

Mansour and group[101] recently communicated the synthesis of benzodioxole-linked thiazolyl-pyrazolines **102a−102b** through the ring closure reaction of 4,5-dihydro-1*H*-pyrazoles **101** and phenacyl bromide **7**. The reaction was conducted under reflux conditions on a water bath for 3 h, resulting in

Scheme 40



7 **99** **100a-100b**

Yield = 49-58%

100a: R = Cl

100b: R = Br

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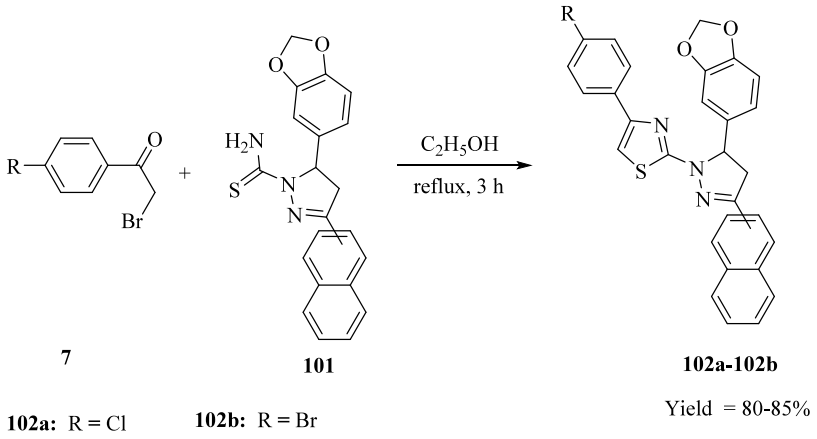
Scheme 41

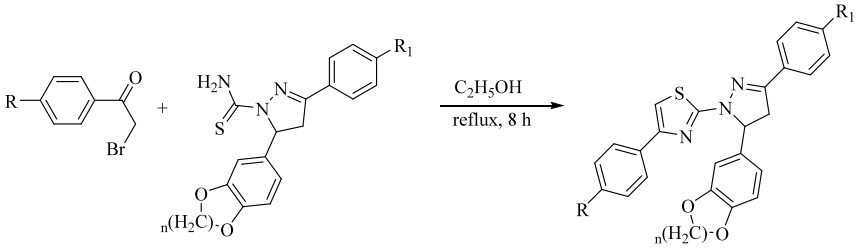


7 **101** **102a-102b**

102a: R = Cl **102b:** R = Br

Yield = 80-85%

Scheme 42



7 **103** **104a-104t**

Yield = 68-84%

104a: R = OCH_3, R_1 = F, n = 1
104b: R = Br, R_1 = F, n = 1
104c: R = OCH_3, R_1 = Cl, n = 1
104d: R = Br, R_1 = Cl, n = 1
104e: R = OCH_3, R_1 = Br, n = 1
104f: R = Br, R_1 = Br, n = 1
104g: R = OCH_3, R_1 = CH_3, n = 1
104h: R = Br, R_1 = CH_3, n = 1
104i: R = OCH_3, R_1 = OCH_3, n = 1
104j: R = Br, R_1 = OCH_3, n = 1
104k: R = OCH_3, R_1 = F, n = 2
104l: R = Br, R_1 = F, n = 2
104m: R = OCH_3, R_1 = Cl, n = 2
104n: R = Br, R_1 = Cl, n = 2
104o: R = OCH_3, R_1 = Br, n = 2
104p: R = Br, R_1 = Br, n = 2
104q: R = OCH_3, R_1 = CH_3, n = 2
104r: R = Br, R_1 = CH_3, n = 2
104s: R = OCH_3, R_1 = OCH_3, n = 2
104t: R = Br, R_1 = OCH_3, n = 2

favorable yields. The synthesized conjugates were subjected to assessment for their antimicrobial and antiproliferative properties using MIC values. Among the compounds evaluated, 2-(5-(benzo[*d*][1,3]dioxol-5-yl)-3-(naphthalen-2-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(4-chlorophenyl)thiazole **102a** exhibited remarkable inhibitory activity against HCT-116 cancer cells. This compound demonstrated a significant inhibitory effect with an IC_{50} value of 6.19 μM, establishing itself as a promising antiproliferative agent against HCT-116 cancer cells (Scheme 41).

Wang and co-workers[102] synthesized some thiazolyl-pyrazoline derivatives **104a−104t** linked to a benzodioxole moiety by cyclization of thiamides derivatives **103** with substituted phenacyl bromide **7** in ethanol with refluxing for 8 h, with a good yield. The synthesized compounds displayed potent antiproliferative activities and HER-2 inhibitory activities against B16-F10 cell lines and MCF-7 cell lines. The outcomes of antiproliferative assays demonstrated that 2-(5-(benzo[*d*]-[1,3]dioxol-5-yl)-3-(4-bromophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(4-bromophenyl)thiazole **104f** displayed a robust *in vitro* antiproliferative impact on both MCF-7 and B16-F10 cell lines having an IC_{50} values of 0.09 μM and 0.12 μM, respectively. Furthermore, it exhibited superior inhibitory efficacy against HER-2 cells, with IC_{50} values of 0.18 μM. These values were commensurate with the performance of the standard drug erlotinib (Scheme 42).

2.4.4. Benzimidazole-Linked Hybrids. Benzimidazole is a bicyclic aromatic heterocyclic compound in which a imidazole moiety is fused with a benzene ring (Figure 31). The structural

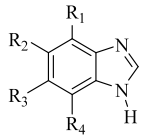


Figure 31. Structure of benzimidazole.

similarity between benzoimidazole and purines allows it to interact with a wide range of biomolecules with ease. The pharmacological profile shown by it can be categorized into antimicrobial, anti-inflammatory, analgesic, antitubercular, antidiabetic, anticonvulsant, antioxidant, antiprotozoal, anti-trichinellosis, anticancer, antiviral, antiulcer, antihypertensive, antiparasitic agents, diuretic, antimalarial activity, and

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acetylcholinesterase inhibitors (Alzheimer's disease) enzyme attributes (Figure 32).[103]

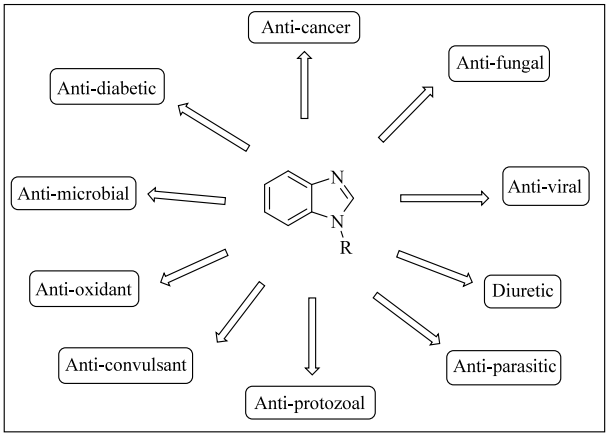
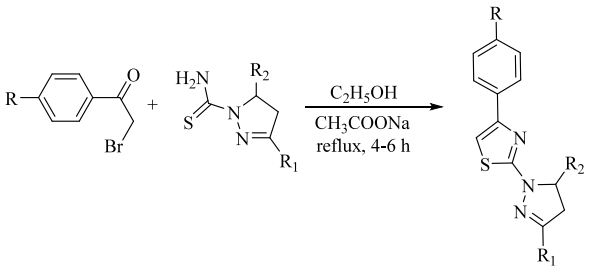


Figure 32. Biological attributes of benzimidazole analogs.

Nofal et al.[104] have devised a highly effective synthetic methodology for the production of thiazolyl-pyrazolines **106a−106l**. This innovative approach involves the cyclization of the pyrazoline *N*-thioamide derivative **105** and substituted phenacyl bromide **7** through refluxing for 4 to 6 h in ethanol, utilizing a catalytic amount of anhydrous sodium acetate. The reaction yielded products in moderate to excellent yields. To screen the antimicrobial properties of the newly synthesized hybrids, the researchers employed the Gram-positive bacterium *Staphylococcus aureus* and the Gram-negative bacterium *Escherichia coli*. A comparative analysis was conducted with established reference drugs such as ampicillin, chloramphenicol, and kanamycin. Undesirably, none of the evaluated derivatives exhibited noteworthy antibacterial activity in the conducted assays (Scheme 43).

Scheme 43



7 **105** **106a-106l**

Yield = 68-88%

106a: R = H, R_1 = NCH_3 benzimidazolyl, R_2 = C_6H_5
106b: R = Br, R_1 = NCH_3 benzimidazolyl, R_2 = C_6H_5
106c: R = H, R_1 = NH benzimidazolyl, R_2 = 4-ClC_6H_4
106d: R = Br, R_1 = NH benzimidazolyl, R_2 = 4-ClC_6H_4
106e: R = H, R_1 = NCH_3 benzimidazolyl, R_2 = 4-ClC_6H_4
106f: R = Br, R_1 = NCH_3 benzimidazolyl, R_2 = 4-ClC_6H_4
106g: R = H, R_1 = NH benzimidazolyl, R_2 = 4-FC_6H_4
106h: R = H, R_1 = NH benzimidazolyl, R_2 = thienyl
106i: R = Br, R_1 = NH benzimidazolyl, R_2 = thienyl
106j: R = H, R_1 = NCH_3 benzimidazolyl, R_2 = NH indolyl
106k: R = H, R_1 = C_6H_5, R_2 = NH indolyl
106l: R = Br, R_1 = C_6H_5, R_2 = NCH_3 indolyl

2.4.5. Coumarin-Linked Hybrids. Coumarin, chemically represented as (2*H*-1-benzopyran-2-one), features a fused benzene ring and an α-pyrone ring, rendering it a prominent constituent within a broad spectrum of naturally occurring compounds, as depicted in Figure 33. This class of compounds

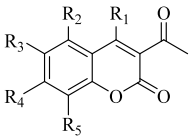


Figure 33. Structure of coumarin.

is renowned for its multifaceted pharmacological profiles like anticoagulant, antiinflammatory, antibacterial, antiviral, antifungal, anticancer, antitubercular, antihypertensive, anticonvulsant, antiadipogenic, antioxidant, antihyperglycemic, and neuroprotective activities, as illustrated in Figure 34.[105]

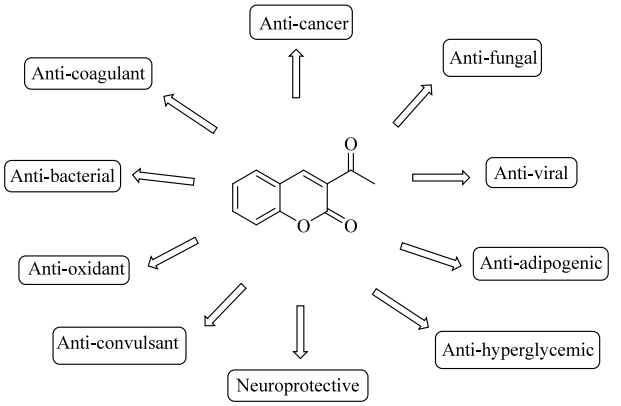


Figure 34. Medicinal importance of coumarin-based derivatives.

Mohamed and group[106] elucidated a procedural framework for the synthesis of coumarin-linked pyrazoline-thiazoles **108a−108b** intended for deployment as anticancer agents. This synthesis involved subjecting coumarinyl thiocarbamoyl **107** to reflux conditions with phenacyl bromide **40** in ethanol over a time period of 6 to 8 h, employing anhydrous sodium acetate as a catalytic agent. The reaction yielded the desired compounds in a commendable range of good to excellent yields. The synthesized pyrazoline derivatives were subjected to thorough examination for their *in vitro* anticancer potential against a panel of five distinct human cell lines, namely MCF-7, prostate PC3, lung A549, liver HepG2, and normal melanocyte HFB4. Especially, the compound 3-(5-(4-(dimethylamino)-phenyl)-4,5-dihydro-1-(4-phenylthiazol-2-yl)-1*H*-pyrazol-3-yl)-4-hydroxy-2*H*-chromen-2-one **108b** displayed a moderate level of biological activity, as evidenced by IC_{50} values of 23.40 μM (Scheme 44).

Saeed and co-workers[107] reported the synthesis of pyrazoline-thiazole hybrid **110a−110o** based on coumarin, employing coumarinyl thiocarbamoyl derivatives **109** and phenacyl bromide **25** as reactants in ethanol, with anhydrous sodium acetate as a catalyst under reflux conditions for 4 h, resulting in moderate yields. The synthesized conjugates were assessed for their radical-scavenging abilities using the DPPH technique. Additionally, the derivatives exhibited remarkable inhibitory effects against tyrosinase, surpassing the efficacy of the standard drug, kojic acid. Among the tested analogs, 3-(5-(4-

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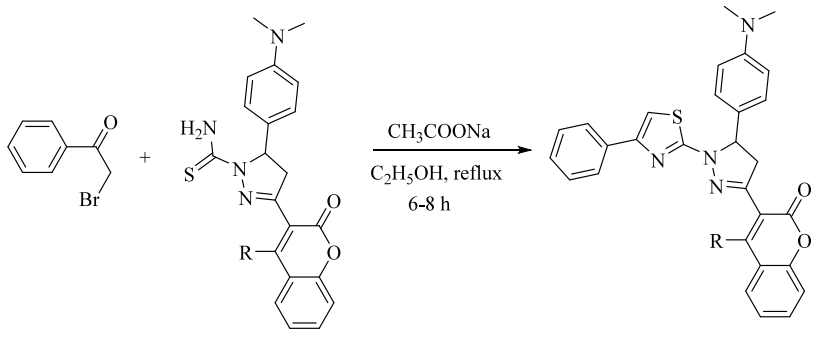
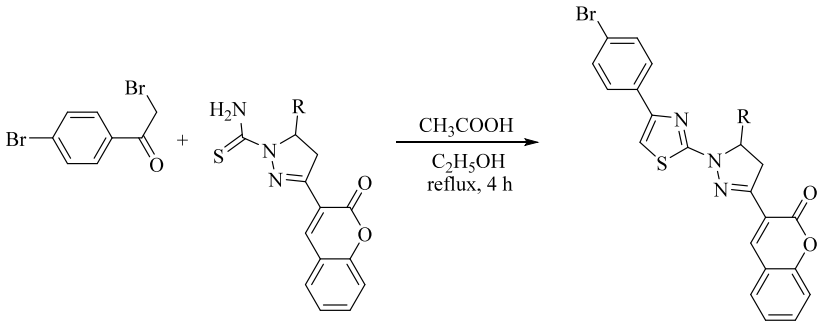
Scheme 44



40 **107** **108a-108b**

108a: R = H **108b:** R = OH Yield = 83-85%

Scheme 45



25 **109** **110a-110o**

Yield = 70-76%

110a: R = 4-CH_3-3-$NO_2C_6H_3$
110b: R = 9-ethyl-9*H*-carbazol-3-yl
110c: R = 1*H*-indol-3-yl
110d: R = 4-OH-5-$NO_2C_6H_3$
110e: R = 4-benzyloxyC_6H_3
110f: R = 4-ClC_6H_4
110g: R = 2-OHC_6H_4
110h: R = 3-OH-4-$OCH_3C_6H_3$
110i: R = 2-Cl-5-$NO_2C_6H_3$
110j: R = 4-benzyloxy-3-$(OCH_3)C_6H_3$
110k: R = furan-2-yl
110l: R = 4-BrC_6H_4
110m: R = 2-OH-3-$OCH_3C_6H_3$
110n: R = C_6H_5
110o: R = 4-$N(CH_3)_2C_6H_4$

(benzyloxy)-3-methoxyphenyl)-1-(4-(4-bromophenyl)thiazol-2-yl)-4,5-dihydro-1*H*-pyrazol-3-yl)-2*H*-chromen-2-one **110j** demonstrated the most potent tyrosinase inhibitory activity, displaying an IC_{50} value of 0.00458 ± 0.00022 μM, in contrast to kojic acid with an IC_{50} value of 0.84 ± 0.052 μM. Furthermore, the inhibition mechanism was analyzed using Lineweaver−Burk plots, revealing that derivative **110j** inhibited tyrosinase in a noncompetitive manner (Scheme 45).

2.4.6. Quinoline-Linked Hybrids. Quinoline, possessing a molecular formula of C_9H_7N, is a tertiary amine characterized by an aromatic heterocyclic structure featuring the fusion of a benzene ring with a nitrogen atom (Figure 35). This chemical entity is prevalent in numerous naturally occurring compounds, exhibiting noteworthy biological efficacy. As delineated in Figure 36, quinoline exhibits diverse pharmacological properties, including antifungal, antimalarial, anthel-

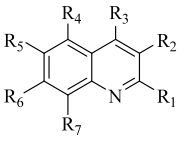


Figure 35. Structure of quinoline.

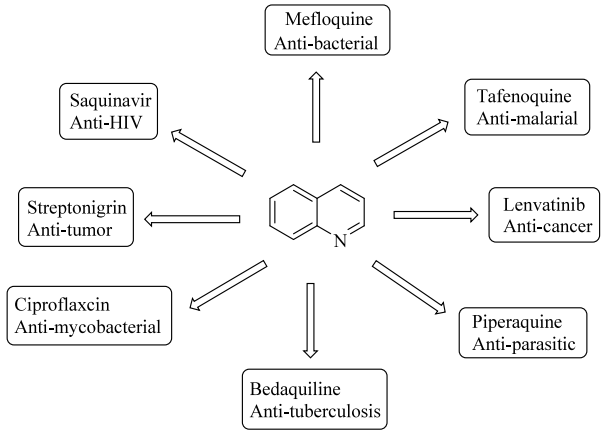


Figure 36. Quinoline-based drugs available in the market.

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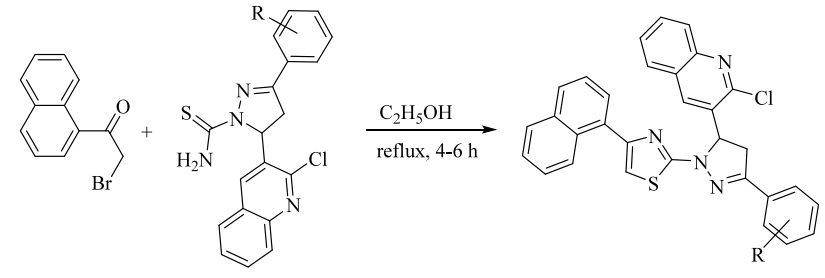
Scheme 46

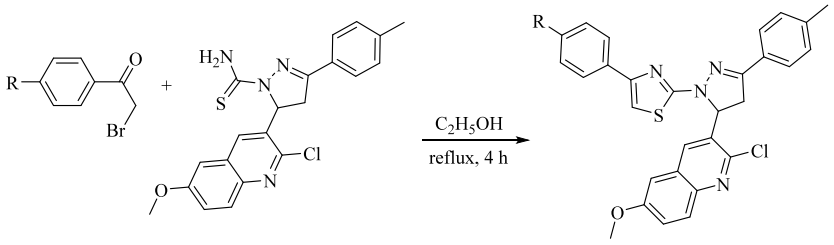


111 **112** **113a-113d**

113a: R = 2-Cl **113c:** R = 3-F Yield = 50-65%

113b: R = 2-F **113d:** R = 4-F

Scheme 47



7 **114** **115a-115d**

115a: R = H **115c:** R = F Yield = 60-70%

115b: R = Cl **115d:** R = CH_3

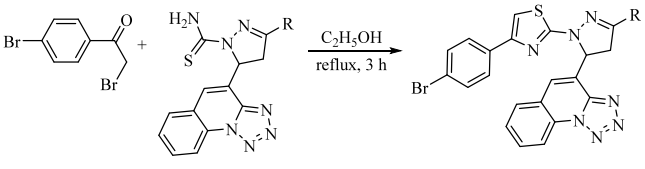
mintic, antibacterial, cardiotonic, antispasmodic, antiinflammatory, and analgesic activities.[108]

Imran and group[109] recently elucidated the synthesis of naphthalenyl thiazole derivatives based on a quinoline-pyrazoline scaffold **113a−113d** with a modest yield. This synthetic endeavor involved the cyclization reaction of 5-(2-chloroquinolin-3-yl)-3-substitutedphenyl-4,5-dihydro-1*H*-pyrazole-1-carbothiamides **112** and phenacyl bromide **111** in ethanol under reflux conditions for a duration of 4 to 6 h. A serial plate dilution technique was performed to screen the antimicrobial action of the produced derivatives, and their MIC values were also studied. Among screened derivatives, 2-(5-(2-chloroquinolin-3-yl)-3-(*p*-fluorophenyl)-4,5-dihydropyrazol-1-yl)-4-(naphthalen-2-yl)thiazole derivatives **113d** having an MIC value of 25 μg/mL with a 4-fluoro substituent in the phenyl ring demonstrated the greatest antibacterial activities when compared to ofloxacin and ketoconazole as standard antimicrobial agents (Scheme 46).

George and co-workers[110] executed the synthesis of 4,5-dihydro-1-(4-phenylthiazol-2-yl)-1*H*-pyrazoles **115a−115d** via the cyclization of carbothioamide derivatives **114** and phenacyl bromide **7** in ethanol under reflux conditions for a duration of 4 h. The resulting derivatives were subjected to scrutiny for their antiproliferative effects against HeLa, MCF-7, DLD1 cancer cell lines, and the normal fibroblast WI-38. Notably, among the investigated derivatives, the 4-fluorophenylthiazole derivative **115c** exhibited superior biological potential with an IC_{50} value of 31.80 nM, with respect to the positive control gefitinib with an IC_{50} value of 29.16 nM. This underscores the observation that the incorporation of quinoline-pyrazoline hybrids yielded enhanced activity compared to the presence of the quinoline core alone (Scheme 47).

Radini and the research group[111] successfully synthesized pyrazolinyl-thiazoles **117a−117c** featuring a tetrazolo[1,5-*a*]quinoline moiety through the cyclization of pyrazoline derivatives **116** with phenacyl bromide **25** under refluxing ethanol conditions for a duration of 3 h, resulting in yields ranging from good to excellent. The thiazole derivatives underwent *in vitro* antimicrobial testing against *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, *Candida albicans*, and *Pseudomonas aeruginosa* using the agar well diffusion technique, with ciprofloxacin serving as the reference drug. The antimicrobial assessment demonstrated that the biological efficacy follows the sequence: furyl > pyridinyl > thienyl (Scheme 48).

Scheme 48



25 **116** **117a-117c**

Yield = 83-85%

117a: R = 2-furyl **117b:** R = 2-thienyl **117c:** R = 2-pyridinyl

2.4.7. Miscellaneous. Abdel-Samii et al.[112] delineated a meticulous procedure for the synthesis of an anticancer and antimicrobial agent **119a−119p** derived from 3-(4-substitutedphenyl)-5-(naphthalen-1-yl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide **118** and phenacyl bromide **7**. The synthesis was conducted through reflux for 2 h on a water bath in glacial

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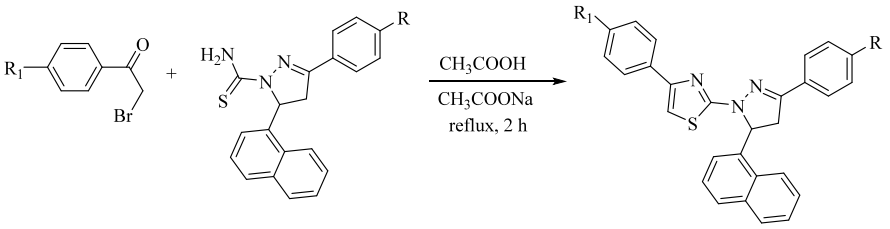
Scheme 49



7 118 119a-119p

119a: R = H, R_1 = OCH_3
119b: R = H, R_1 = CH_3
119c: R = H, R_1 = Br
119d: R = H, R_1 = NO_2
119e: R = OCH_3, R_1 = OCH_3
119f: R = OCH_3, R_1 = CH_3
119g: R = OCH_3, R_1 = Br
119h: R = OCH_3, R_1 = NO_2
119i: R = Br, R_1 = OCH_3
119j: R = Br, R_1 = CH_3
119k: R = Br, R_1 = Br
119l: R = Br, R_1 = NO_2
119m: R = Cl, R_1 = OCH_3
119n: R = Cl, R_1 = CH_3
119o: R = Cl, R_1 = Br
119p: R = Cl, R_1 = NO_2

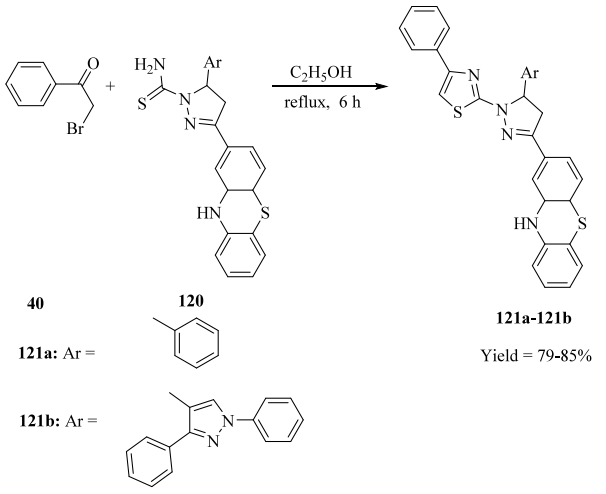
Yield = 57-89%

acetic acid, facilitated by the presence of sodium acetate, resulting in a commendable yield. The newly synthesized compounds underwent screening for their anticancer and antimicrobial attributes. A majority of the examined compounds exhibited substantial anticancer efficacy against colon carcinoma (HCT-116) and breast carcinoma (MCF-7) cell lines, concurrently exhibiting noteworthy antimicrobial properties against *Candida albicans*. Particularly, among the scrutinized bioactive derivatives, 2-(3-(4-bromophenyl)-5-(naphthalen-1-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-(*p*-tolyl)thiazole **119j** emerged as the most potent, demonstrating remarkable biological activities against colon carcinoma (HCT-116) and breast carcinoma (MCF-7) cell lines, with IC_{50} values of 1.22 μg/mL and 1.01 μg/mL, respectively (Scheme 49).

Hamama and co-workers[113] detailed the synthesis of 2-(4,5-dihydro-5-phenyl-1-(4-phenylthiazol-2-yl)-1*H*-pyrazol-3-yl)-10*H*-phenothiazine **121a** and 2-(4,5-dihydro-5-(1,3-diphenyl-1*H*-pyrazol-4-yl)-1-(4-phenylthiazol-2-yl)-1*H*-pyrazol-3-yl)-10*H*-phenothiazine **121b** from thioamides **120** and phenacyl bromide **40** in ethanol under reflux conditions for a duration of 6 h, yielding exceptional results. Employing the ABTS method, newly synthesized compounds were assessed for their antioxidant properties. Remarkably, it was observed that the molecules appended to phenothiazine derivatives exhibited superior antioxidant properties compared to the established pharmaceutical standard, ascorbic acid (Scheme 50).

Budak et al.[114] conducted a study wherein pyrazolyl-thiazole conjugates **123a−123i** featuring a methanoisoindol-1,3-dion unit were synthesized through the refluxing of a novel 4,5-dihydropyrazole **122** and phenacyl bromide **25** in ethanol for a duration of 1 h, resulting in a commendable yield. The antibacterial efficacy of the synthesized conjugates was evaluated against *Bacillus subtilis*, *Candida albicans*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Proteus vulgaris*, and *Escherichia coli* using the disk diffusion method on Mueller-Hilton agar medium. Upon biological evaluation, compounds bearing methyl, chloro, and furyl substituents exhibited notable activity, with inhibitory areas ranging from 16 to 19 mm, with respect to performance of standard drugs sulbactam/cefoperazone. Furthermore, the synthesized conjugates underwent assessment for their inhibition activity against acetylcholinesterase (AChE) enzyme and human carbonic anhydrase (hCA) I and II isoforms. Enzymatic assessments revealed that

Scheme 50



40 120 121a-121b

121a: Ar =

121b: Ar =

Yield = 79-85%

derivative **123c**, characterized by a chloro substituent, displayed the most potent inhibitor for hCA I and II isoforms, exhibiting K_i values of 5.72 ± 5.72 and 18.90 ± 2.37 nM, respectively. Additionally, derivative **123i** containing a furyl substituent demonstrated substantial inhibitory activity against AChE, with a K_i value of 25.47 ± 11.11 *n*M (Scheme 51).

Gürdere et al.[115] successfully executed the synthesis of 1,4-phenylene-bis-pyrazolylthiazoles **125a−125h** through the condensation reaction involving 1,4-phenylene-bis-*N*-thiocarbamoylpyrazole **124** and phenacyl bromide **25** under reflux conditions with alcoholic KOH for a duration of 1 h, yielding products in the range of good to excellent. Subsequently, the *in vitro* anticancer activity of all synthesized hybrids against C6 and HeLa cancer cell lines was evaluated using the BrdU ELISA assay. However, the results indicated that all the hybrids exhibited inactivity against both cell lines when compared to the standard reference, 5-fluorouracil (Scheme 52).

3. THIAZOLYL-PYRAZOLE HYBRIDS

These hybrid entities are concomitantly engendered through the merging of pyrazole and thiazole fragments into a singular structural unit employing a hybridized methodology. This strategic synthesis is undertaken with the intent of elucidating their prospective utility as novel pharmaceutical candidates or

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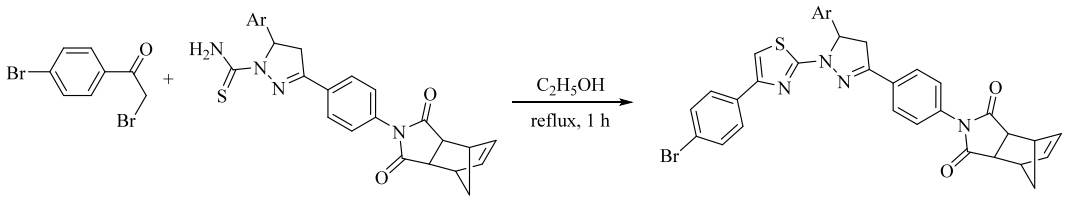
Scheme 51

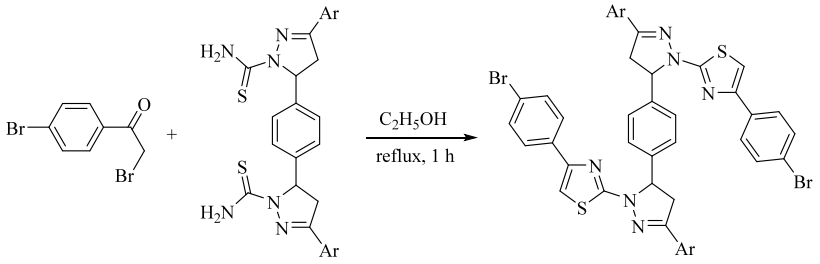


25 **122** **123a-123i**

Yield = 76-92%

123a: Ar = 4-$OCH_3C_6H_4$
123b: Ar = 4-$CH_3C_6H_4$
123c: Ar = 4-ClC_6H_4
123d: Ar = 4-BrC_6H_4
123e: Ar = 2-thienyl
123f: Ar = 3-$OCH_3C_6H_4$
123g: Ar = 3-$CH_3C_6H_4$
123h: Ar = 3-ClC_6H_4
123i: Ar = 2-furyl

Scheme 52



25 **124** **125a-125h**

Yield = 40-85%

125a: Ar = 1-naphthyl
125b: Ar = 3-thienyl
125c: Ar = 2-thienyl
125d: Ar = 2-furyl
125e: Ar = C_6H_5
125f: Ar = 4-$CH_3C_6H_4$
125g: Ar = 4-$OCH_3C_6H_4$
125h: Ar = 4-ClC_6H_4

chemical probes, specifically tailored for engagement with diverse biological targets (Figure 37).

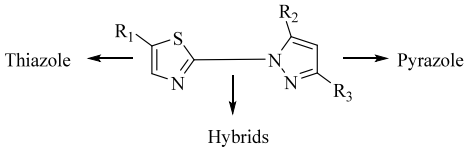


Figure 37. Thiazolyl-pyrazole hybrids.

Pyrazole belongs to the 1,2-azole class, characterized by the presence of two nitrogen atoms in contiguous positions within its five- membered ring structure (Figure 38). This molecular

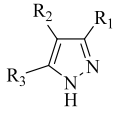


Figure 38. Structure of pyrazole.

framework imparts diverse biological, chemical, agrochemical, and pharmacological activities to pyrazole. Especially, pyrazole compounds are prevalent in numerous FDA-approved drugs, including celecoxib, lonazolac, mavacoxib, sulphaphenazole, acomplia, and deracoxib (Figure 39).[116,117]

3.1. Coumarin-Linked Hybrids. Mamidala and co-workers[118] described the synthesis of several thiazolyl-pyrazole carbaldehydes in one-pot, **127a−127n** sequential Hantzsch-thiazole synthesis, and Vilsmeier−Haack reaction, in excellent yield. The reaction was carried out in ethanol utilizing phenacyl bromide **7**, thiosemicarbazide **20**, and substituted 3-acetylcoumarins **126** followed by the addition of Vilsmeier−Haack reagent under stirring conditions for 3 to 4 h. The synthesized compounds were evaluated for their *in vitro* anticancer activity using nocodazole as the standard drug. Among the examined bioactive compounds, 3-(8-methoxy-2-oxo-2*H*-chromen-3-yl)-1-(4-(4-methoxyphenyl) thiazol-2-yl)-1*H*-pyrazole-4-carbaldehyde **127m** exhibited good potency against MCF-7, A549, and HeLa cancer cell lines with an IC_{50} value of 9.05 μM, 7.12 μM, and 6.34 μM, respectively. Additionally, to establish an effective lead molecule for next anticancer drug discovery activities, *in silico* ADME/T profiles were also performed. Moreover, molecular docking studies confirmed that pyrazole carbaldehyde derivatives bind to the colchicine binding site of β-tubulin, and results were comparable with an *in vitro* anticancer data (Scheme 53).

Aggarwal et al.[119] have developed an efficacious and solvent-free synthetic methodology for the production of 4-substituted-2-(3,5-dimethylpyrazol-1-yl)thiazoles **130a−130j**. This innovative approach involves the mechanical grinding of phenacyl bromide **128** with 3,5-dimethylpyrazol-1-thiocarboxamide **129** in the presence of sodium carbonate, carried out for a brief duration of 5 min at room temperature, resulting in exemplary yields. The method exhibits versatility across a wide range of applications and circumvents the formation of undesirable byproducts such as thiocyanatoketone and 3,5-dimethylpyrazole, while mitigating issues associated with low yields, protracted reaction times, expensive catalysts, and the use of potentially hazardous solvents (Scheme 54).

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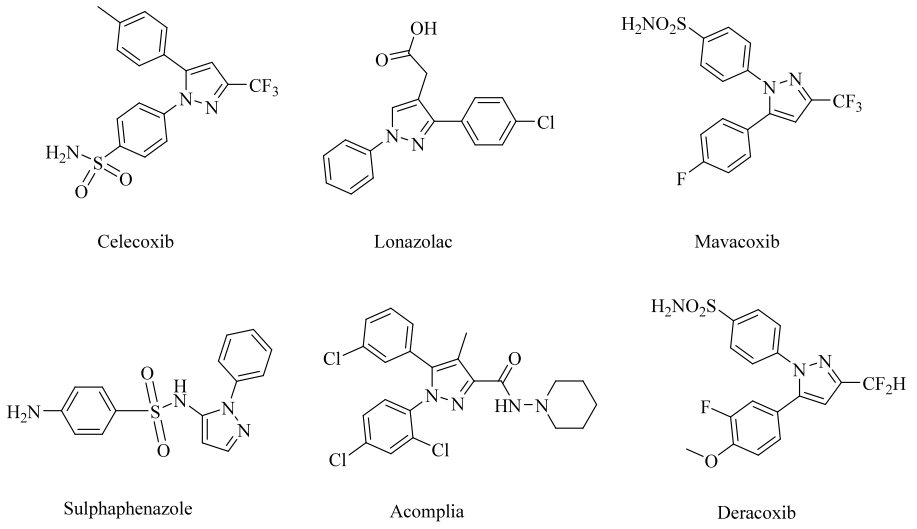
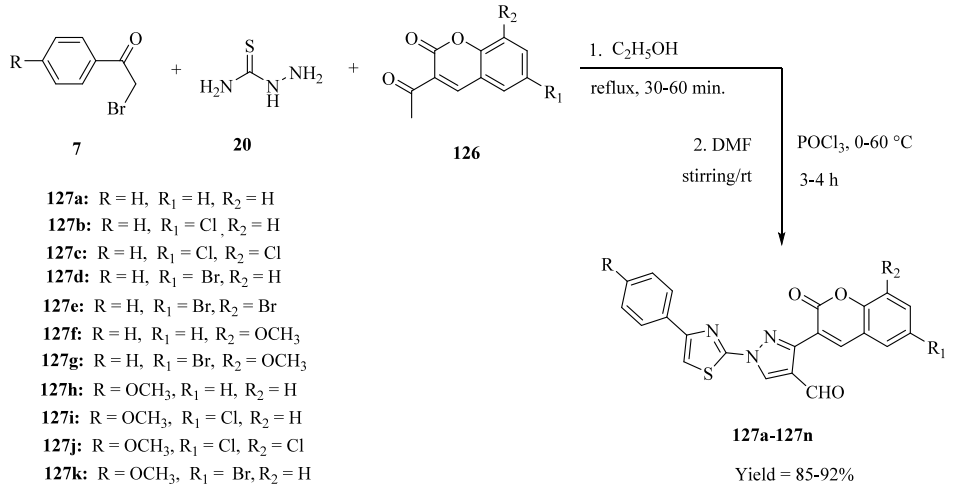


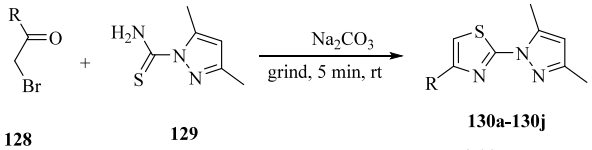
Figure 39. Pyrazole-based drugs available in the market.

Scheme 53



127a: R = H, R_1 = H, R_2 = H
127b: R = H, R_1 = Cl, R_2 = H
127c: R = H, R_1 = Cl, R_2 = Cl
127d: R = H, R_1 = Br, R_2 = H
127e: R = H, R_1 = Br, R_2 = Br
127f: R = H, R_1 = H, R_2 = OCH_3
127g: R = H, R_1 = Br, R_2 = OCH_3
127h: R = OCH_3, R_1 = H, R_2 = H
127i: R = OCH_3, R_1 = Cl, R_2 = H
127j: R = OCH_3, R_1 = Cl, R_2 = Cl
127k: R = OCH_3, R_1 = Br, R_2 = H
127l: R = OCH_3, R_1 = Br, R_2 = Br
127m: R = OCH_3, R_1 = H, R_2 = OCH_3
127n: R = OCH_3, R_1 = Br, R_2 = OCH_3

Scheme 54



130a: R = C_6H_5
130b: R = 4-ClC_6H_4
130c: R = 4-$CH_3C_6H_4$
130d: R = 4-$NO_2C_6H_4$
130e: R = 4-BrC_6H_4
130f: R = coumarin-3-yl
130g: R = 6-chlorocoumarin-3-yl
130h: R = 2-thienyl
130i: R = 3-pyridyl
130j: R = 4-pyridyl

3.2. Benzimidazole Hybrids. Bakthavatchala Reddy and group[120] have communicated the synthesis of a series of innovative benzimidazoles featuring pyrazolyl-thiazole moieties **132a−132g**. This synthesis involved the utilization of pyrazole derivatives **131** and phenacyl bromide **90**, employing a refluxing procedure conducted on a water bath in ethanol for 5 h, yielding products in good to moderate yields. The synthesized compounds underwent assessment for their antimicrobial efficacy against *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Aspergillus niger*, and *Penicillium chrysogenum* through the agar well diffusion method. Remarkably, among the examined compounds, the derivative 2-(5-(1*H*-benzimidazol-2-yl)-3-(*p*-nitrophenyl)-1*H*-pyrazol-1-yl)-4-(4-fluorophenyl)thiazole **132d**, featuring nitro substituents on the aromatic ring, demonstrated the most potent antifungal and antibacterial activities. Specifically, compound **132d** exhibited substantial inhibition zones measuring 41 mm and 34 mm against *Penicillium chrysogenum* and *Pseudomonas aeruginosa*, respectively. For comparative purposes, the effectiveness of the synthetic thiazole conjugates was benchmarked against commonly employed antibacterial (chloramphenicol) and antifungal (ketoconazole) agents. The findings underscore the pronounced antimicrobial potential of compound **132d**, establishing it as a promising candidate for further exploration in the development of therapeutic agents (Scheme 55).

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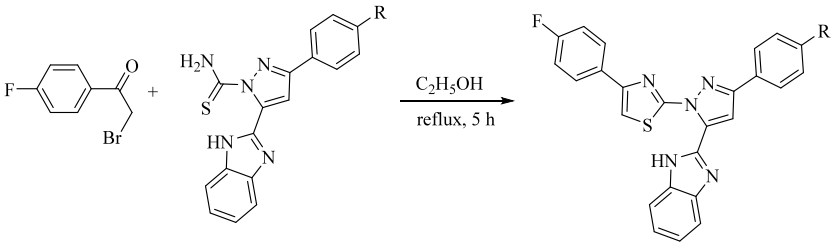
Scheme 55

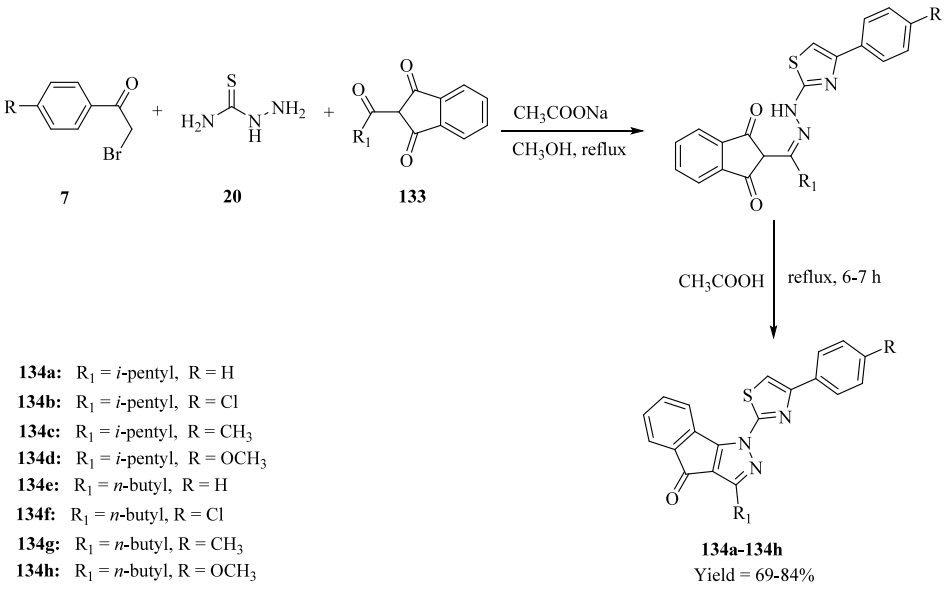


90 131

132a: R = H
132b: R = CH_3
132c: R = OCH_3
132d: R = NO_2
132e: R = F
132f: R = Cl
132g: R = Br

132a-132g
Yield = 71-78%

Scheme 56



7 20 133

134a: R_1 = *i*-pentyl, R = H
134b: R_1 = *i*-pentyl, R = Cl
134c: R_1 = *i*-pentyl, R = CH_3
134d: R_1 = *i*-pentyl, R = OCH_3
134e: R_1 = *n*-butyl, R = H
134f: R_1 = *n*-butyl, R = Cl
134g: R_1 = *n*-butyl, R = CH_3
134h: R_1 = *n*-butyl, R = OCH_3

134a-134h
Yield = 69-84%

3.3. Miscellaneous. Mor et al.[121] synthesized indenopyrazolones **134a−134h** via the reaction between 2-acyl-(1*H*)-indene1,3-(2*H*)-dione **133** and thiosemicarbazide **20** in dry methanol. Subsequent treatment with phenacyl bromides **7** in the presence of anhydrous sodium acetate yielded *N*-thiazolyl hydrazones, followed by the addition of glacial acetic acid under reflux conditions lasting 6 to 7 h, resulting in moderate to excellent yields. The *in vitro* antimicrobial activity of the synthesized compounds against bacterial strains, namely *Bacillus subtilis*, *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*, as well as fungal strains *Candida albicans* and *Aspergillus niger*, was assessed using the serial dilution method. Additionally, the *in vitro* antioxidant activity of indenopyrazolones was evaluated employing a 2,2-diphenyl-1-picrylhydrazyl radical scavenging assay, with ascorbic acid serving as a reference drug. Among the screened compounds, 3-butyl-1-(4-(4-chlorophenyl)thiazol-2-yl)indeno[1,2-*c*]-pyrazol-4(1*H*)-one **134f** exhibited the highest radical scavenger activity, as evidenced by an IC_{50} value of 33.14 μg/mL. Molecular docking investigations were conducted to elucidate the binding interactions between indenopyrazolones and lanosterol 14-demethylase, confirming the reported antibacterial activity results (Scheme 56).

Mor and group[122] have presented a streamlined three-component, one-pot synthesis protocol for the production of indeno[1,2-*c*]pyrazoles **135a−135l**. This synthetic approach involves the utilization of 1,3-diketones **133**, thiosemicarbazide **20**, and phenacyl bromide **7** in a methanol reflux for 6−7 h on a water bath, facilitated by the presence of sodium acetate and glacial acetic acid. In the next step, the synthesized indeno[1,2-*c*]pyrazol-4-ones thiazole **134** undergoes a Wolf-Kishner reduction in ethylene glycol and hydrazine hydrate under reflux conditions for 5 h, yielding moderate to good overall yields. The resultant indenopyrazoles were evaluated for their *in vitro* anticancer activity assessments against various human cancer cell lines, including A-498 (human renal carcinoma), MCF-7 (human breast adenocarcinoma), HT29 (human colorectal adenocarcinoma), and HepG2 (human hepatocellular carcinoma). Notably, among the evaluated derivatives, 2-(3-isobutylindeno[1,2-*c*]pyrazol-1(4*H*)-yl)-4-phenylthiazole **135i**, 2-(3-isobutylindeno[1,2-*c*]pyrazol-1(4*H*)-yl)-4-(4-methoxyphenyl)thiazole **135l**, and 4-(4-methoxyphenyl)-2-(3-propylindeno[1,2-*c*]pyrazol-1(4*H*)-yl)thiazole **135h** exhibited exceptional potency against the HT29 cancer cell line, with IC_{50} values of 34.77 μM, 35.07 μM, and 35.10 μM, respectively. To gain insights into the structural basis of anticancer activity exhibited by the synthesized indenopyrazoles against HepG2 cell lines, QSAR studies were conducted using multiple linear regressions. These analyses aimed to discern trends and relationships between molecular structures

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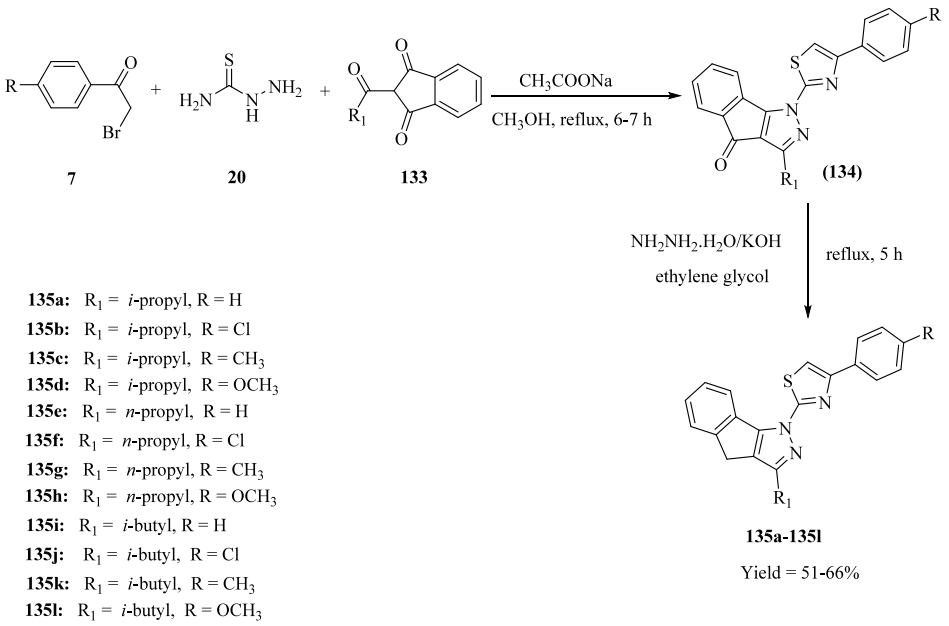
Scheme 57

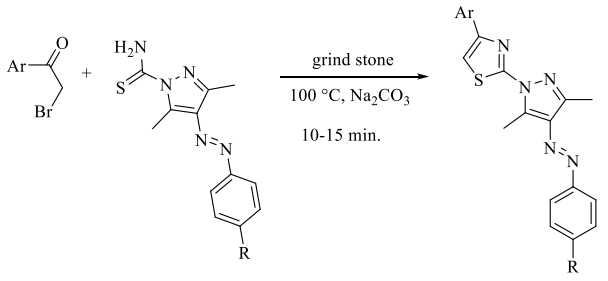


135a: R_1 = *i*-propyl, R = H
135b: R_1 = *i*-propyl, R = Cl
135c: R_1 = *i*-propyl, R = CH_3
135d: R_1 = *i*-propyl, R = OCH_3
135e: R_1 = *n*-propyl, R = H
135f: R_1 = *n*-propyl, R = Cl
135g: R_1 = *n*-propyl, R = CH_3
135h: R_1 = *n*-propyl, R = OCH_3
135i: R_1 = *i*-butyl, R = H
135j: R_1 = *i*-butyl, R = Cl
135k: R_1 = *i*-butyl, R = CH_3
135l: R_1 = *i*-butyl, R = OCH_3

and observed anticancer activities, providing valuable information for further optimization of these compounds in the context of therapeutics (Scheme 57).

Kaur and co-workers[123] delineated a solvent-free methodology for the synthesis of novel (*E*)-2-(3,5-dimethyl-4-(aryldiazenyl)-1*H*-pyrazol-1-yl)-4-arylthiazoles **137a−137p** through the mechanochemical amalgamation of (*E*)-3,5-dimethyl-4-(*p*-tolyldiazenyl)-1*H*-pyrazole-1-carbothioamide **136** and phenacyl bromide **128** in the presence of sodium carbonate, affording substantial yields within a reaction time span of 10 to 15 min. The synthesized compounds were analyzed for their antibacterial, antioxidant, UV-mediated DNA damage-protective, and photocleavage activities to discern their biological potential. Among the compounds subjected to screening, the methyl group-incorporated derivative **137e** exhibited antifungal efficacy comparable to the reference medication. In contrast, the chloro-substituted derivative **137c** demonstrated superior antifungal activity compared to reference drugs ciprofloxacin and amphotericin-B against *Candida albicans*. A subset of the synthesized derivatives displayed activity against *Escherichia coli*, while none of the evaluated derivatives manifested activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Saccharomyces cerevisiae*, and *Pseudomonas aeruginosa*. In the realm of DNA-based analysis, compounds **137b** and **137p** emerged as the most active DNA damage-protecting and DNA photocleavage agents, respectively. Markedly, none of the compounds exhibited efficacy in scavenging DPPH radiation (Scheme 58).

Scheme 58



137a: R = H, Ar = C_6H_5
137b: R = H, Ar = 4-FC_6H_4
137c: R = H, Ar = 4-ClC_6H_4
137d: R = H, Ar = 4-BrC_6H_4
137e: R = H, Ar = 4-$CH_3C_6H_4$
137f: R = H, Ar = naphthyl
137g: R = CH_3, Ar = C_6H_5
137h: R = CH_3, Ar = 4-FC_6H_4
137i: R = CH_3, Ar = 4-ClC_6H_4
137j: R = CH_3, Ar = 4-BrC_6H_4
137k: R = CH_3, Ar = 4-$CH_3C_6H_4$
137l: R = CH_3, Ar = naphthyl
137m: R = F, Ar = C_6H_5
137n: R = F, Ar = 4-FC_6H_4
137o: R = F, Ar = 4-ClC_6H_4
137p: R = F, Ar = 4-BrC_6H_4

4. CONCLUSION

In conclusion, an overview of recent advancements in the synthesis of thiazole-linked hybrids through the molecular hybridization approach and their subsequent pharmacological implications has been provided. The majority of these synthesized hybrids have demonstrated noteworthy bioactive properties, encompassing anticancer, antibacterial, anticonvulsant, antifungal, antiviral, and antioxidant activities. The therapeutic efficacy of these hybrids has prompted the exploration of diverse pharmacophores, with the primary objective of addressing resistance to multiple drugs, mitigating toxicity, and augmenting the efficacy of therapeutic interventions. The trajectory of this field suggests continued evolution as researchers delve into innovative methodologies, potentially yielding groundbreaking discoveries with applications across various domains.

The outlook for this research area is promising, with an expected emergence of an expanding array of inventive synthetic routes for thiazole-based hybrids in the future.

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Author Contributions

All the authors contributed equally.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

MAO	monoamine oxidase
DMF	dimethylformamide
hCAs	human carbonic anhydrases
AD	Alzheimer's disease
DABCO	(1,4-diazabicyclo[2.2.2] octane)
NaOAc	sodium acetate
PEG	polyethylene glycol
MW	microwave
SRB	sulforhodamine-B
LFM	latent fingermark

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