Five-Membered Heterocyclic Compounds

Subjects: Chemistry, Medicinal | Chemistry, Organic

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Heterocyclic compounds are a class of compounds of natural origin with favorable properties and hence have major pharmaceutical significance. They have an exceptional adroitness favoring their use as diverse smart biomimetics, in addition to possessing an active pharmacophore in a complex structure. This has made them an indispensable motif in the drug discovery field. Heterocyclic compounds are usually classified according to the ring size, type, and the number of heteroatoms present in the ring.

heterocyclic compounds | nitrogen containing compounds | biological evaluations

1. Introduction

Heterocyclic compounds are compounds with a cyclic ring bearing carbon and other elements, such as oxygen, nitrogen, and sulfur. The simplest of the five-membered heterocyclic compounds are pyrrole, furan, and thiophene, and the compounds contain a single heteroatom. Notably, heterocyclic compounds are the preferred class of compounds of natural origin with pharmaceutical significance. They have an exceptional adroitness to be used as diverse smart biomimetics and an active core in a complex structure, which has made them an indispensable motif in the pharmaceutical field. Several heterocyclic derivatized compounds are known. These numbers continue to expand rapidly, as heterocyclic substitutions can alter the degree of ionization of compounds in the physiological pH, resulting in changes in their basicity and lipophilicity, leading to substantial differences in pharmacokinetic properties [1][2].

2. Five-Membered Heterocyclic Compounds

2.1. Triazole

Heterocyclic systems continue to generate considerable interest due to their broad spectrum of biological activities. Triazole and its derivatives have increased in importance as they represent the structural characteristics of many bioactive compounds. They are known to be included in the structure of many medications, namely, itraconazole, fluconazole, voriconazole, ribavirin, mubritinib, and posaconazole, amongst others. The triazole ring features three nitrogen atoms in the five-membered aromatic ring and is significantly isomeric based on the placement of nitrogen atoms in the ring. Triazole and its derivatives can interact with various enzymes and receptors in the biological system through the diversity of non-covalent interactions, thereby presenting versatile biological activities [3]. Two

significant forms of triazole include 1,2,3-triazole and 1,2,4-triazole. Extensive research on triazole and its derivatives has shown the major pharmacological importance of this heterocyclic nucleus.

2.2. 1,2,3-Triazole

Riu et al. [4] designed and synthesized new and improved benzotriazole–acrylonitrile derivatives incorporating two halogen atoms in positions 5′ and 6′ on the benzotriazole moiety. The compounds were further subjected to biological evaluation. Compound **1** was the most potent in the new series of derivatives. The in vitro XTT assay, flow cytometry analysis, and immunostaining performed on HeLa cancer cells treated with **1** displayed a significant antiproliferative effect, with an IC_{50} value of 3.2 µM. It was demonstrated to block the cells in G2/M-phase, and subsequently cause cell division defects. Additionally, *β*-tubulin staining validated the microtubule as being a potential molecular target of **1**, while the colchicine competition assay indicated that compound **1** vies with colchicine for the binding site on tubulin. Kasemsuk et al. [5] synthesized a novel series of acanthoic acid analogues by substituting a carboxyl functional group of acanthoic acid with methyl ester hybrids bearing a triazole ring through esterification and the CuAAC reaction and considered their cytotoxic activity against cholangiocarcinoma cell lines. Among the evaluated compounds, **2** showed the most significant activity with an IC_{50} value of 18 µM against the KKU-213 cell line, which was eight-fold more effective than acanthoic acid. An assessment of anti-inflammatory, ulcerogenic, platelet activation activities, and the molecular docking studies of COX-2 and P-selectin of the 1,4-diaryl-1,2,3-triazole hybrids has been recently published [6]. The analogs **3**–**5** exhibited anti-inflammatory activity and lacked the induction of gastric lesions in mice when compared to the reference drug, indomethacin. The reduction of polymorphonuclear cells' influx into the peritoneal cavity caused by carrageenan indicated that these active compounds could favor a dual inhibition of COX-2 and 5-LOX enzymes. The hybrids caused a reduction in the expression of P-selectin, which may be liable to mitigate inflammation and thromboembolic events. The molecular docking study with P-selectin showed crucial interactions with the amino acid residue Tyr 48 (see **Figure 1**).

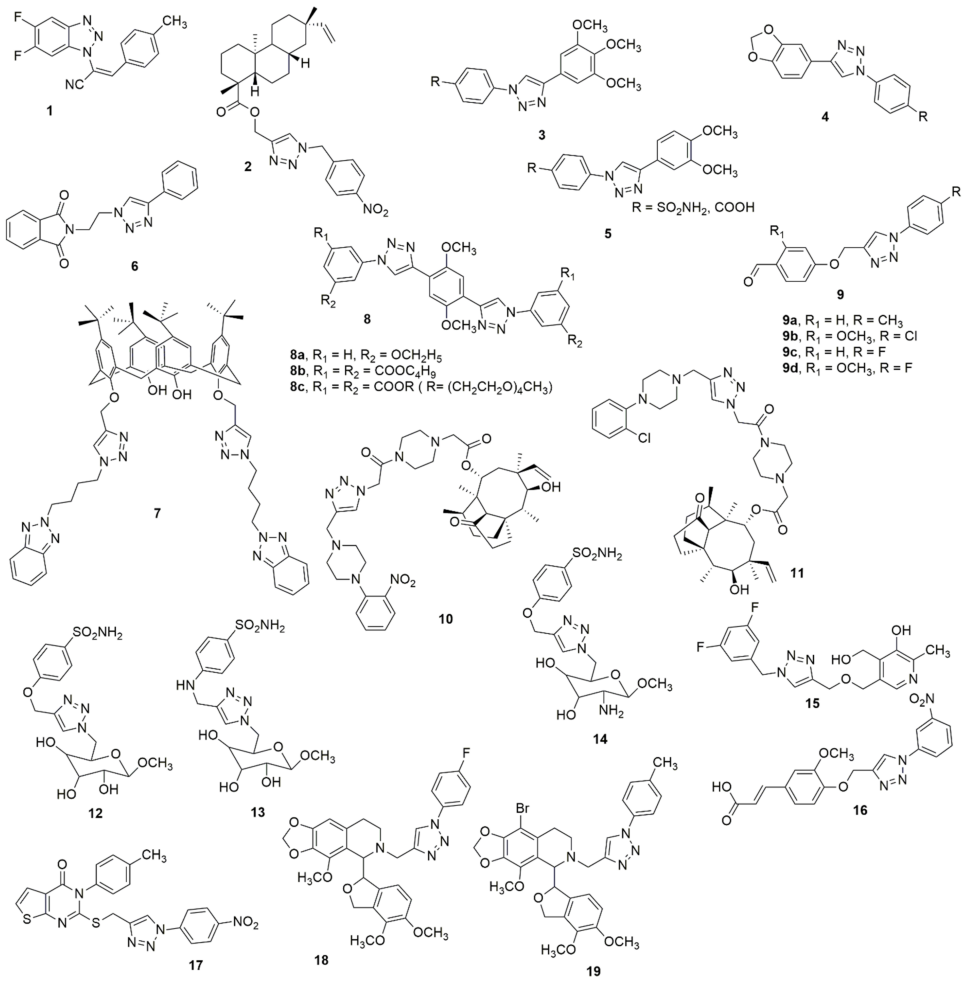

Figure 1. Structures of most active analogues of 1,2,3-triazole molecule.

Holanda et al. [7] utilized the click chemistry approach to efficiently synthesize alkyl-substituted phthalimide 1*H*-1,2,3-triazole derivatives and evaluated their leishmanicidal potential against *Leishmania amazonensis* and *Leishmania braziliensis*. Compound **6** selectively inhibited the increase and existence of promastigote and amastigote forms of *L. amazonensis* and *L. braziliensis*. The molecular docking study indicates that compound **6** is a potential inhibitor of parasite sterol 14α-demethylase due to its interaction with the heme groups of this enzyme. The amalgamation of benzotriazoles and calixarenes through click chemistry produces a new class of p-tert-butyl-calix [8] arene tethered benzotrizolyl dendrimers, which has been reported together with their biological evaluation [9]. Compound **7** was found to be the most potent antibacterial and anti-biofilm agent against drug-resistant and slime-generating organisms with no detected cytotoxicity to the mammalian cell line. Melah et al. [10] reported the design, synthesis, and in vitro antiproliferative activities of novel mono- and bis-1,2,3-triazole molecular hybrids. Compound **8a** exhibited potent activity against HepG-2 when compared to the standard reference anticancer drug doxorubicin whereas compounds **8b** and **8c** demonstrated significant toxicity on the RPE-1 human normal cells. Sahin et al. [11] reported the design and synthesis of several 1,2,3-triazole compounds with aldehyde functional groups. The synthesized compounds were further examined for their antioxidant, anti-cancer, and α-amylase enzyme activity. The DPPH radical scavenging studies showed that all the compounds have a higher activity than the standard BHT and β-carotene. Compound **9a** displayed almost the same scavenging effect with β-carotene and

BHT. Compound **9b** (IC_{50} = 165 µg/mL) was almost 5.5-fold superior to acarbose regarding its α-amylase inhibition activity. The synthesized compounds were screened for anti-cancer activities against the HeLa cell line. Compound **9c** and **9d** with IC_{50}s of 50.12 and 57.07 µg/mL, respectively, displayed mild antitumor activity when compared to cisplatin against the HeLa cell line (see **Figure 1**).

A novel series of pleuromutilin derivatives bearing piperazine and 1,2,3-1H-triazole structures were synthesized by click chemistry methodology under mild conditions [12]. The compounds were further investigated for their MIC and MBC against methicillin-resistant *S. aureus* (ATCC 43300), *S. aureus* (ATCC 29213), *S. aureus* (AD3), *S. aureus* (144), and *E. coli* (ATCC 25922). Compounds **10** and **11** displayed more significant antibacterial activity than other compounds. Compound **10** exhibited rapid kinetics of its bactericidal activity against MRSA and had a longer PAE than tiamulin. The in vivo antibacterial effectiveness of **11** was further studied in a neutropenic murine thigh infection model. The outcomes revealed that compound **10** exhibited more effective in vivo antibacterial activity than tiamulin. In addition, **10** exhibited low to moderate repressing effects on CYP1A2, CYP2E1, CYP2D6, and CYP3A4 enzymes. The design, synthesis, and biological evaluation of a panel of novel aromatic sulfonamides linked to a hydrophilic sugar-tail moiety using rigid 1,2,3-triazole as a spacer have been reported [13]. The newly designed compounds were investigated in vitro and an efficient inhibition against all three CA isoforms, especially the tumor-associated hCA IX, was observed. All the glycoconjugate sulfonamide derivatives exhibited superior inhibitory activity. Compound **12** was the most effective and selective inhibitor of hCA IX with an inhibitory constant (IC_{50}) value of 7 nM, being four-fold superior to acetazolamide (AAZ) whose IC_{50} value is 30 nM. In both hypoxic and normoxic conditions, almost all the compounds exhibited moderate antiproliferative activities against two cancer cell lines (HT-29 and MDA-MB-231). Notably, **12** exhibited superior antitumor activity and cytotoxic activity. In addition, the combined therapy evaluation found noticeable decreases (20–35%) in doxorubicin IC_{50} values in MDA-MB-231 cancer cells in a hypoxic environment in the presence of compounds **12**–**14**, carbonic anhydrase inhibitors, when compared to single therapy (doxorubicin) (see **Figure 1**).

Multi-target natural product-pyridoxine-based derivatives were designed, synthesized, characterized, and evaluated as potential anti-Alzheimer agents [14]. Among the tested compounds, **15** acted as a potent acetylcholinesterase (AChE) inhibitor, (IC_{50} = 1.56 ± 0.02 mM) and exhibited antioxidant activity, having an ORAC-FL value of 1.21 ± 0.28, which is comparable to Trolox. The docking studies showed interactions between the peripheral anionic site of the enzyme (PAS site) with the hydrophobic amino acids Tyr 124 and Phe 338 and the triazole nucleus of **15**. Compound **16** has been reported to selectively inhibit carbonic anhydrase IX (CAIX) with an IC_{50} value of 24 nM [15]. The in silico analysis revealed the binding of **16** with the catalytically significant amino acid residues of CAIX. Additionally, cell-based studies showed that **16** prevents the activity of CAIX, reduces the epithelial-to-mesenchymal transitions, induces apoptosis, and obstructs cell migration and colonization potential of cancer cells (see **Figure 1**).

Suryanarayana et al. [16] reported the synthesis of thieno[2,3-*d*]-pyrimidine fused 1,2,3-triazole scaffolds and their antioxidant activity. Compound **17** exhibited good antioxidant activity against DPPH scavenging with an IC_{50} value of 8.161 µM, as compared to the standard drug ascorbic acid (IC_{50} = 3.073 µM). Notably, electron-removal groups in the *para*-position of the derivatives provided excellent scavenging capacity for all three scavenging methods

when compared to the electron-donating groups. Twenty novel 1,2,3-triazole noscapine derivatives have been synthesized using noscapine as a precursor and were further evaluated for their biological activity [17]. Interestingly the combination of computational and experimental evaluation revealed two potent compounds **18** and **19**, (K_D = 21.5 ± 6.15 and 36.9 ± 4.24 nM, respectively) compared to noscapine (K_D = 579.0 ± 18.7 nM) (see **Figure 1**).

In an attempt to introduce new scaffolds as potent α-glucosidase inhibitors, Sepehri et al. [18] reported a new series of acridine-9-carboxamide-1,2,3-triazole-*N*-phenylacetamide derivatives. They were screened for their in vitro α-glucosidase inhibitory activities. Among the screened compounds, **20** exhibited a superior potency with an IC_{50} of 80.3 ± 0.9μM compared to the standard drug acarbose (IC_{50} = 750.0 ± 10.5μM). Cherif et al. [19] designed and synthesized some new hybrid compounds through the amalgamation of a pyranopyrimidinone moiety with 1,2,3-triazole pharmacophore via 1,3-dipolar cycloaddition using different arylazides. Compounds **21a**–**21d** showed strong capacities of cholinesterase inhibition with IC_{50} values of 6.7 ± 0.2, 8.4 ± 0.4, 7.8 ± 0.2 and 9.1 ± 0.1 μM, respectively. Compound **22** has been reported to be a feasible positron emission tomography (PET) probe that can offer a better understanding of the ASGPR (asialoglycoprotein receptor)-related liver disease [20] (see **Figure 2**).

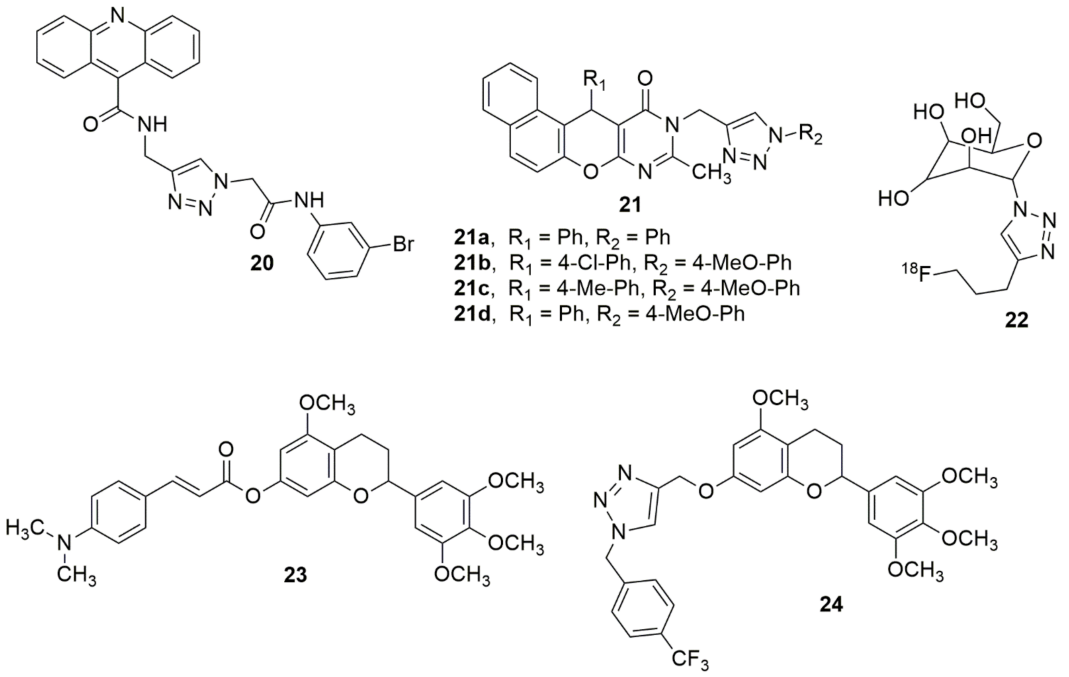

Figure 2. Chemical structures of 1,2,3-triazole hybrids with anti-diabetics (**20**) and anti-Alzheimer activities (**21,23,24**).

Shi and co-workers designed and synthesized 7-*O*-modified galloyltricetiflavan hybrids containing cinnamate, benzoate, phenyl sulfonate, and 1,2,3-triazole scaffolds [21]. Meanwhile, all synthesized compounds were examined for the inhibition of AChE/BuChE (butyrylcholinesterase) and anti-A*β* aggregation activity. Among the evaluated compounds, **23** exhibited the best inhibition of A*β* aggregation (78.81% at 20 μM), and superior AChE inhibitory potencies (IC_{50}, 0.56 μM). Compound **24** exhibited the highest BuChE activity ($IC_{50,}$ 5.77 μM). Compounds **23** and **24** exhibited high potent protective capabilities than Trolox against H_2O_2- induced SH-SY5Y cell injuries. The observed potent compounds lacked visible toxicity in SH-SY5Y cells and could slightly increase

SHSY5Y cell viabilities. Hence, **23** and **24** were reported as promising multi-functional agents for the treatment of Alzheimer's disease (see **Figure 2**).

Tangadanchu et al. [22] designed, synthesized, and evaluated a series of eighteen new 1,2,3-triazole compounds and evaluated their sphingosine kinase-2 (SphK2) inhibitory activity using an ADP-Glo kinase assay. The in vivo anti-tumor bioactivity was further explored. Many of the screened compounds exhibited potent selectivity for SphK2 over SphK1. Compounds **25a**, **26a**–**26c**, **27a**, and **27b** were potent towards SphK2 with IC_{50} values of 0.234, 0.266, 0.254, 0.248, 0.261, and 0.269 µM, respectively, whereas the compounds **25a**, **25d**, **25e**, **26b**–**26f**, **27a**–**27c** showed a high selectivity for SphK2 versus SphK1. In addition, compounds **25b**–**25c**, and **27e** exhibited superior antitumor activity for the human malignant glioblastoma tumor U-251 MG cell line when compared to ABC294640 (see **Figure 3**).

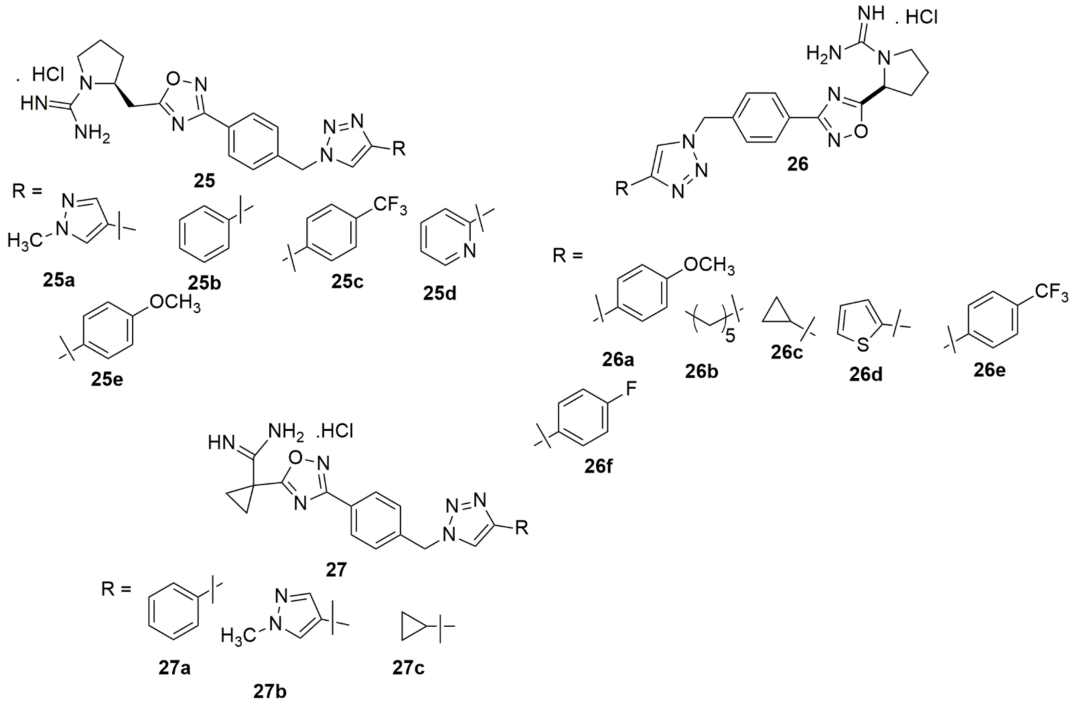

Figure 3. New 1,2,3-triazole series evaluated for SphK2 inhibitory activity using an ADP-Glo kinase assay.

Compound **28** has been reported to exhibit potent antiproliferative activity in U251 cells with an IC_{50} value of 0.94 µM, and it significantly inhibited the colony formation and migration of U251 cells [23]. Chaidam et al. [24] designed and synthesized a series of novel 1,6-bis-triazole-2,3,4-tri-*O*-benzyl-*α*-D-glucoside derivatives. The synthesized compounds were screened for their anti-diabetic activity. Among the examined compounds, **29** showed superior inhibitory activity with IC_{50} values of 3.73 µM, which was 39-fold higher than that of acarbose. Notably, the presence of the ester functional group and menthol moiety played a significant role in its biological activity due to increasing polarity, which enhanced binding against *α*-glucosidase. The library of the cationic tetrahydroisoquinoline–triazole compounds has been synthesized using the copper(II)-catalyzed azide–alkyne cycloaddition [25]. The compounds were evaluated for their antibacterial activity. Compound **30** potently inhibits Gram-positive pathogens and *M. tuberculosis*. The potent compound inhibited *M. tuberculosis* H37Rv at 6 µg/mL

MIC. Compound **30** resulted in lysis and a bulging/swelling phenotype, suggesting compound **30** may target cell wall or membrane homeostasis. The cell passage test demonstrated that *S.aureus* did not develop resistance against **30** even at sub-inhibitory concentrations. A new series of quinazoline–triazole hybrid compounds have been designed, synthesized and evaluated for their anti-AChE activity by Le-Nhat-Thuy and co-workers [26]. Most of the synthesized compounds showed moderate to good AChEI activity. Among the evaluated compounds, *N*-benzyl-6-((1-(2-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)quinazolin-4-amine **31** was shown to have the highest inhibitory activity with an IC_{50} value of 0.23 μM (see **Figure 4**).

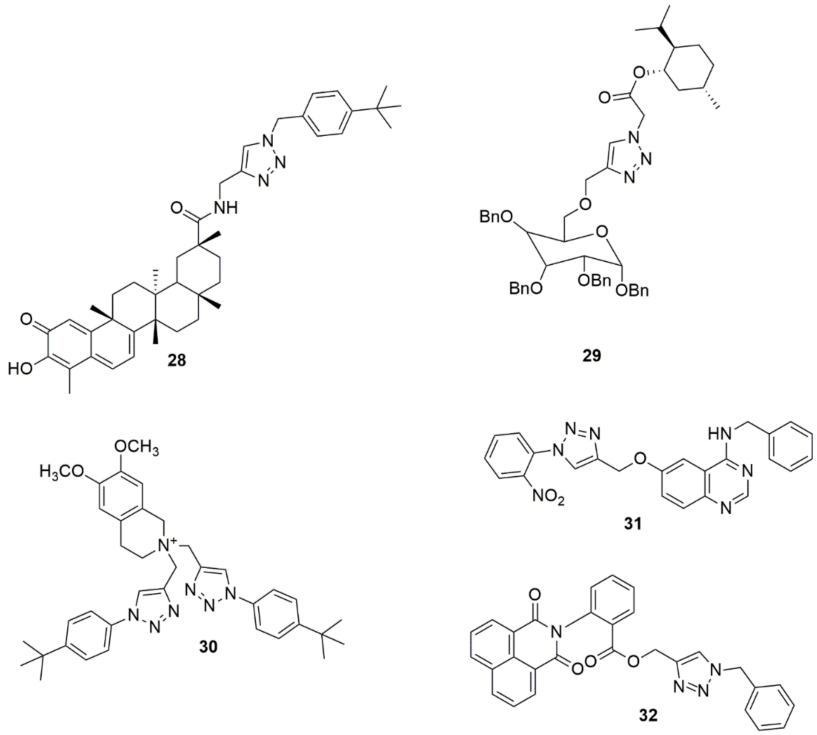

Figure 4. Chemical structures of 1,2,3-triazole hybrids with promising biological activities.

Bengam et al. [27] designed and synthesized novel naphthalimide-1,2,3-triazole tethered heterocycles and evaluated their in vitro anti-inflammatory properties. Among the compounds tested, **32** displayed inhibitions comparable to the reference compound (diclofenac sodium). The compound **32** showed 95.25% inhibition, and the reference drug showed 97.89% inhibition at 200 μM. The molecular docking analysis showed that the triazole ring **32** hydrogens bonded with the amine group of TYR385 and the amine group of TRP387 with the carbonyl group of anthranilic moiety (see **Figure 4**).

Hosseini et al. [28] used a molecular hybridization strategy to design a novel series of naphthoquinone derivatives bearing an acetamide–triazole moiety as novel AChE and BuChE inhibitors. Among the synthesized compounds evaluated for biological activity, **33** with an *ortho*-chlorine substituent exhibited the most potent AChE and BuChE activity with K_i values of 10.16 and 8.04 nM, respectively, compared to the standard compound Tacrine (K_i = 70.61 and 64.18 nM). Notably, the insertion of a chlorine atom at the *ortho* position enhanced the ChEs' inhibition. Compound **33** was well fitted in the AChE and BuChE binding pocket via strong hydrogen bond interactions with

the significant residue of each enzyme. Synthesis of a series of novel 1,2,3-triazole tethered chalcone derivatives and their cytotoxic activity against the human breast cancer cell line (MCF-7), cervical cancer (HeLa), and MDA-MB-231 cell lines have been reported [29]. In vitro cytotoxic activity evaluated using an MTT assay showed that all the synthesized compounds exhibited moderate to substantial cytotoxic activity. Compounds **34**, **35**, and **36** exhibited potent cytotoxic activity with IC_{50} values lower and comparable to cisplatin. Compounds **35** showed the best cytotoxic activity on MCF-7, with IC_{50} values of 1.27 and 0.02 µM at 24 and 48 h, respectively. Compounds with a chloro and methoxy substituent at different positions displayed promising activity. Abdel-Hafez and co-workers [30] designed, synthesized and hybridized acridine and coumarin derivatives, and evaluated their in vitro cancer cell growth inhibition activity. Among the evaluated compounds, **37** presented a good anticancer profile against MCF7 and DU-145 with IC_{50}, values of 2.7 and 26.1 µM, respectively, comparable to doxorubicin (IC_{50} values = 2.0 and 14.2 µM). Compound **37** displayed greater inhibitory activity against topoisomerase (IIB) (IC_{50}, 0.52 µM) when compared with doxorubicin (IC_{50} = 0.83 µM). The novel compounds **38a** and **38b** have been reported as DPP-4 inhibitors with IC_{50} values of 28 and 14 nM, respectively [31] (see **Figure 5**).

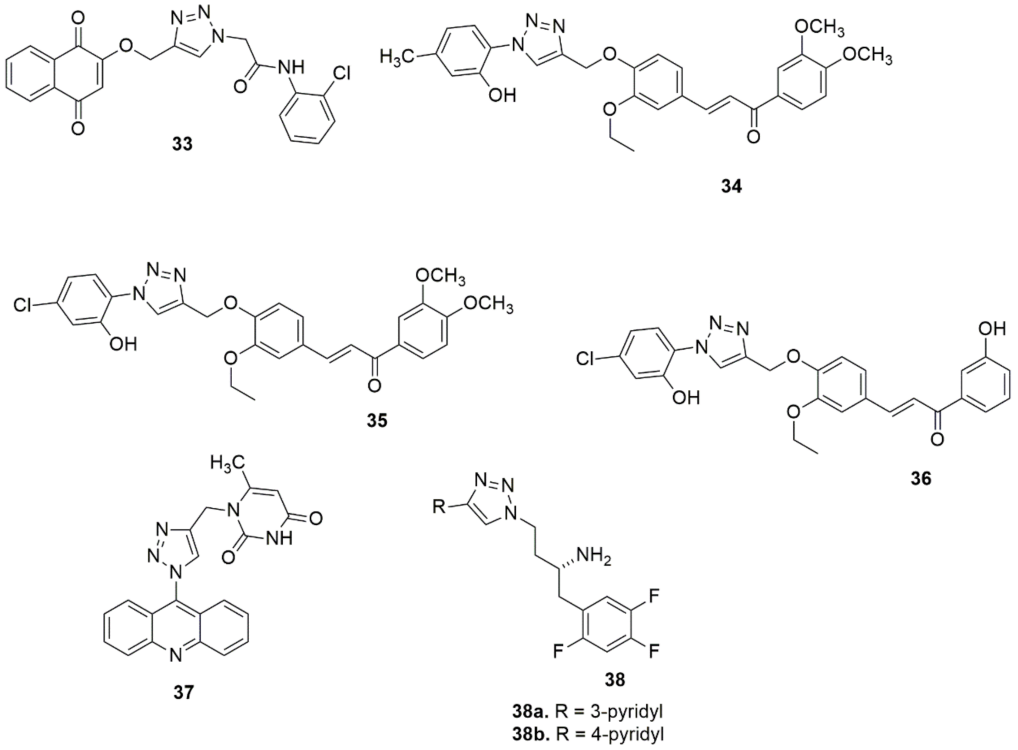

Figure 5. Chemical structures of 1,2,3-triazole hybrids with biological activities.

2.3. 1,2,4-Triazole

A novel series of 3-aryl-6-(*N*-methylpiperazin)-1,2,4-triazolo [3,4-*a*]phthalazines have been synthesized through a facile and economical one-pot copper-catalyzed method from 4-chloro-1-phthalazinyl-arylhydrazones as potential anticancer agents [32]. Most of the evaluated compounds showed anticancer activity against PC-3, MCF-7, and SKBr3 cancer cell lines. Interestingly, **39** displayed apparent anticancer activity with reduced toxicities, and appropriate selectivity indexes, and acted as potassium channel blockers. Meanwhile, the fused triazolo-

phthalazine hybrid and the NO_2 substituent enhanced the biological activity. Compound **40** was reported to be the most effective inhibitor of CB1 activity (0.644 µM) and showed the most effective selectivity of CB2/CB1 (>311) [33]. However, the lack of penetration of **40** through the blood–brain barrier similar to Rimonabant in the MDCK-mdr1 permeability analysis can result in a secondary effect on the CNS. This is apparently caused by the small, obstructed, hydrophobic cyclopropyl group of 1,2,4-triazole. A library of new indole-3-carbaldehyde-triazole hybrids has been synthesized under conventional and microwave-mediated conditions [34]. The antimicrobial assessment of the compounds showed that **41a**–**41b**, bearing a fluoroquinolone scaffold and **42**–**44**, displayed remarkable activities on Gram-positive and Gram-negative bacteria with MIC values < 0.24 µg/mL. In addition, compounds **41a**–**41b**, **42**–**44**, and **45a**–**45c** showed excellent antifungal activities (see **Figure 6**).

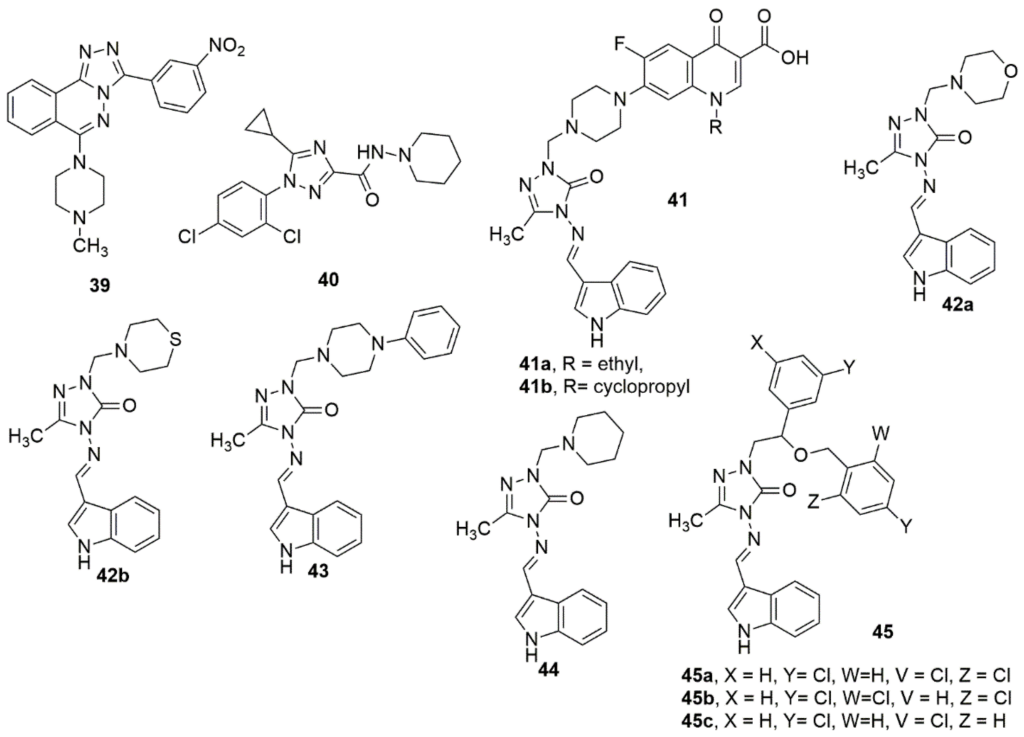

Figure 6. Chemical structures of analogues of 1,2,4-triazole molecule with promising biological activities.

Wang et al. [35] reported a series of interesting compounds and their biological activity evaluation with respect to this tricyclic chemotype of dual PLK1/BRD4 inhibitors to corroborate their effectiveness as anticancer agents. The compounds were synthesized based on the core structure of BI-2536 (PLK1 inhibitor). Among the evaluated compounds, **46** displayed excellent activity for PLK1 (IC_{50} = 22 nM) and BRD4 (IC_{50} = 109 nM), with promising antiproliferative activity against a panel of cancer cell lines. Meanwhile, compound **46** displayed equipotent activity with PLK1 (IC_{50} = 22 nM) and BRD4 (IC_{50} = 109 nM). The SARS detailed that a bulkier group on the piperazine ring will enhance the stabilized potency between PLK1 and BRD4. Depending on the concentration, the potent compound greatly increased the number of Annexin V/PI-positive MV4-11. This indicates its apoptotic induction effect in cancerous cells, which has also been confirmed by the ascending regulation of apoptosis-associated proteins, including cleaved caspase-3 and cleaved PARP, along with the regulation of the anti-apoptosis protein Bcl-2. In addition, **46** demonstrated favorable in vivo anti-tumor activity with 66% tumor growth inhibition (TGI) at a

60 mg/kg dose without evident toxicity. Wu and coworkers [36] synthesized indole-based [1,2,4]triazolo[4,3-a]pyridine hybrids and screened them for their antiproliferative activities, tubulin polymerization inhibition, and cell cycle arrest/apoptosis-initiating effects. In particular, four cancer cell lines, including human cervical cancer cells (HeLa), human adenocarcinoma epithelial cells (A549), human breast cancer cells (MCF-7), and human colon cancer cells (HCT116), were employed in the standard 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Compound **47** bearing an *N*-methyl-5-indolyl substituent at the C-6 position of the [1,2,4]triazolo[4,3-a]pyridine moiety displayed superior activity against all the tested cell lines. In addition, compound **47** displayed potent inhibitory activity with respect to tubulin polymerization with an IC_{50} value of 1.64 ± 0.11 μM, comparable to CA-4 with an IC_{50} of 1.24 ± 0.08 μM. The primary mechanism of action (MOA) studies demonstrated that **47** could inhibit the proliferative of cancer cells by inducing cell cycle arrest at the G2/M phase and cellular apoptosis in HeLa cells in a dose-dependent manner. The active compound was also detected to have the potential ability to inhibit tumor cell migration and metastasis (see **Figure 7**).

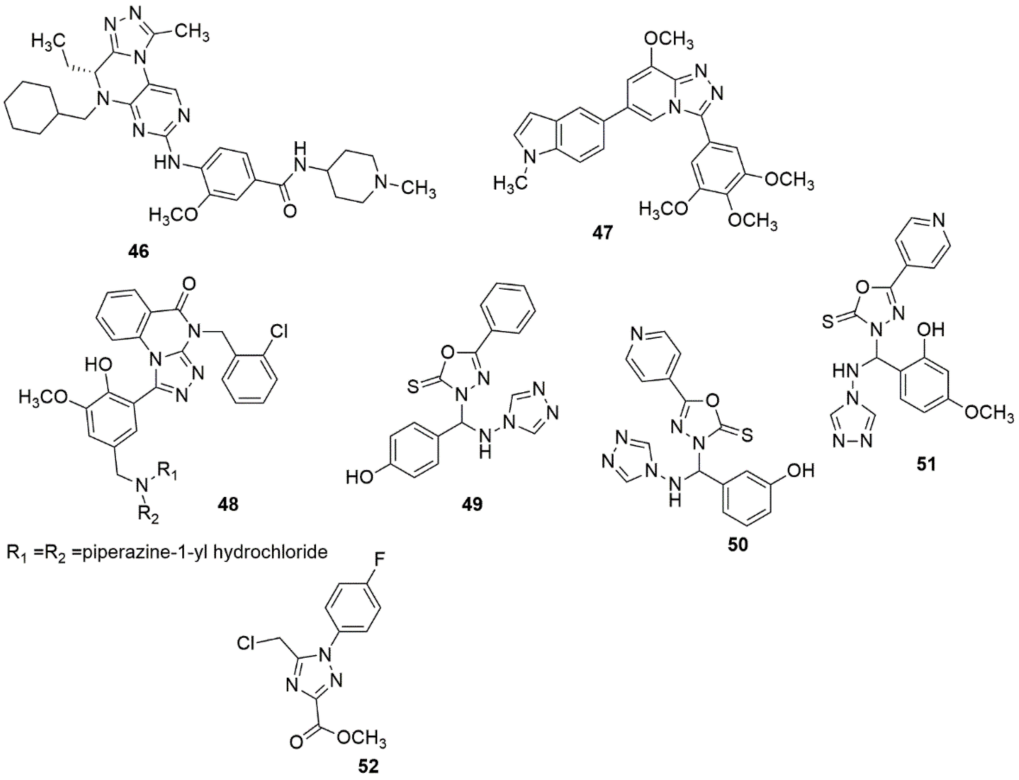

Figure 7. Chemical structures of 1,2,4-triazole hybrids with promising biological activities.

A series of novel triazoloquinazolinone derivatives were designed, synthesized, and evaluated for their inhibitory activity toward the SHP2 protein enzyme [37]. Among the evaluated compounds, **48** displayed the highest inhibitory activity against the SHP2 protein at 10 μM (31.84% inhibition) compared with SHP244. **48** exhibited superior antitumor activities, with an IC_{50} value of 14.67 μM against A375 cells. The SARs revealed that derivatives with hydroxyl substituents at the two-position of the phenyl ring showed significantly higher activity than derivatives with substituents at the four-positions. In addition, the insertion of electron-withdrawing groups, namely methoxy groups, exhibited enhanced inhibitory activity. Compounds **49**–**51** have been reported by Jain et al. as being promising for

the management of cognitive dysfunction [38]. Li et al. [39] designed and synthesized 1,2,4-triazole-3-carboxylates derivatives; the obtained products were subjected to in vitro NO production and cyclooxygenase COX-1/COX-2 inhibition assays. Notably, compound **52** showed the significant inhibition of NO, COX-2 (IC_{50} of 2.87 and 17.9 nM), and substantial selectivity (COX-1/COX-2 = 1080). Meanwhile, compound **52** (5 mg/kg) displayed significant in vivo anti-inflammation and gastric protection results, including paw edema, chemokines, and histological experiments, compared to Indomethacin (10 mg/kg). The presence of a fluorine atom enhanced the COX-2 inhibitory activity. The docked complex of **52** showed a comparable interaction landscape with celecoxib in the active COX-2. The active compound formed three hydrogen bond interactions with His75, Leu338, and Phe504 and eight van der Waals interactions with Val335, Leu338, Ser339, Try341, Phe504, Val509, Gly512, and Ala513, respectively (see **Figure 7**).

A series of novel 3,4,5-trimethoxyphenyl substituted [1,2,4]triazolo[4,3-a]pyridines were designed and synthesized on the basis of triazolopyrimidine **53** as the core compound [40]. The in vitro antiproliferative efficacy of synthesized novel 1,2,4-triazolo[4,3-a]pyridine derivatives were screened against different cancer cell lines using the (MTT) assay. Compound **54** bearing 3-amino-4-methoxyphenyl moiety exhibited the highest activity with an IC_{50} value of 12 nM, equipotent with CA-4(12nM). Also, **54** was 62-fold superior to compound **53**. The active compound **54** also exhibited potent activities against A549, MCF-7, and T47D. The MOA analysis result showed that **54** significantly blocked the cell cycle at the G2/M phase, induced apoptosis in a dose-dependent manner, and disrupted microtubule networks. Compound **54** also exhibited better anti-tubulin activity than CA-4 (see **Figure 8**).

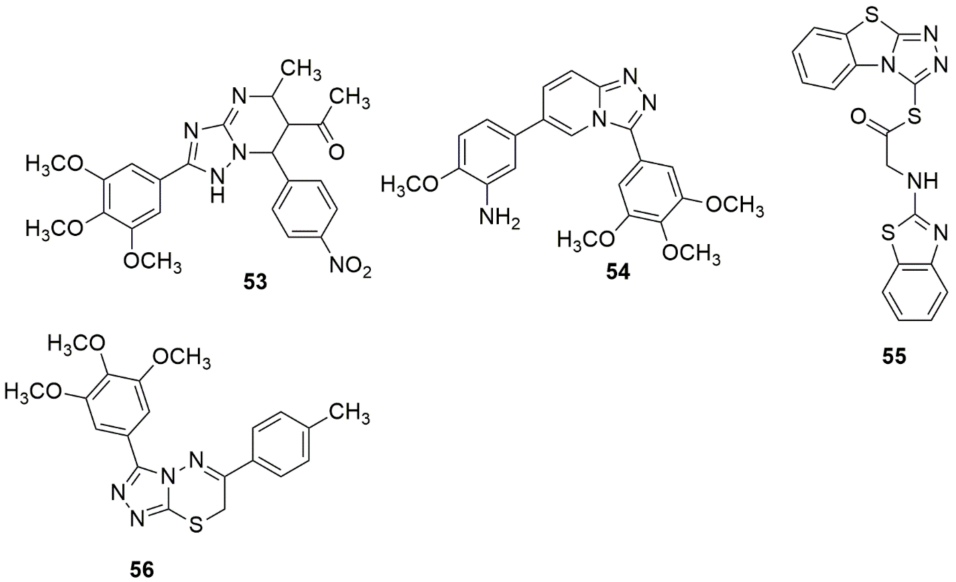

Figure 8. Chemical structures of 1,2,4-triazole hybrids with significant anticancer activities.

Compound **55** has been reported to have substantial apoptosis-inducing activity in A549 cells and inhibited the activity of CDK2/Cyclin A1 with an IC_{50} value of 4.65 μM [41]. Ma et al. [42] synthesized a novel series of triazolothiadiazine hybrids via the ring-merging approach. The compounds were examined for their in vitro antiproliferative efficacy toward a human colon cancer cell line (HT-29) using an MTT assay. Among the evaluated compounds, **56** demonstrated excellent selectivity over the normal human embryonic kidney HEK-293 cells (IC_{50} >

100 μM). Compound **56** strongly blocked tubulin polymerization and disrupted intracellular microtubule networks. Compound **56** effectively inhibited the tumor growth of an A549 lung cancer xenograft mouse model without evident signs of toxicity in the in vivo experimentation (see **Figure 8**).

2.4. Tetrazole

Interest in tetrazole derivatives has increased considerably over the past few decades because of the virtually limitless potential of tetrazole compounds in various fields [43][44][45][46]. They have been successfully applied in pharmaceutical products as a potential replacement for *cis*-peptide binding. In addition, they are used as components in explosives, ligands in coordination chemistry, and precursors in preparing a diversified selection of heterocyclic compounds [47][48]. Considerable advancement was achieved by Wang et al. [49] by describing the synthesis, antiproliferative, tubulin polymerization, analysis of immunofluorescence staining, and cell cycle analysis of new tetrazole derivatives, **57**. Among the compounds synthesized, **57a** showed significant activity against SGC-7901, A549, and HeLa cell lines. The SAR detailed that the insertion of substituent into the ortho-position of the ring attached to the nitrogen atom of the triazole ring significantly improved the antiproliferative activity. The compounds bearing 3,4-dimethoxyl showed significant anticancer activities. The tubulin polymerization result showed that **57a** disrupts the microtubule network, arrests the cell cycle at the G2/M phase, and induces dose- and time-dependent apoptosis. Ulgheri and co-workers [50] reported designing and synthesizing a new class of active non-peptidomimetic and non-covalent caspase-1 inhibitors. Compound **58a** was identified to inhibit IL-1β release in activated macrophages in the low μM range, which corroborates the activities observed for the known covalent inhibitors. Due to the extensive application of altered nucleobases for cancer treatment as a PDE3 inhibitor. Shekouhy et al. [51] presented the synthesis, PDE3 and anticancer properties of some novel nucleobases/tetrazole hybrids using cilostazol as the core structure. Compounds **59a**, **59b** and **59c** are more strong inhibitors of PDE3A than cilostazol, and compound **59b** was observed as being the most effective PDE3A inhibitor (see **Figure 9**).

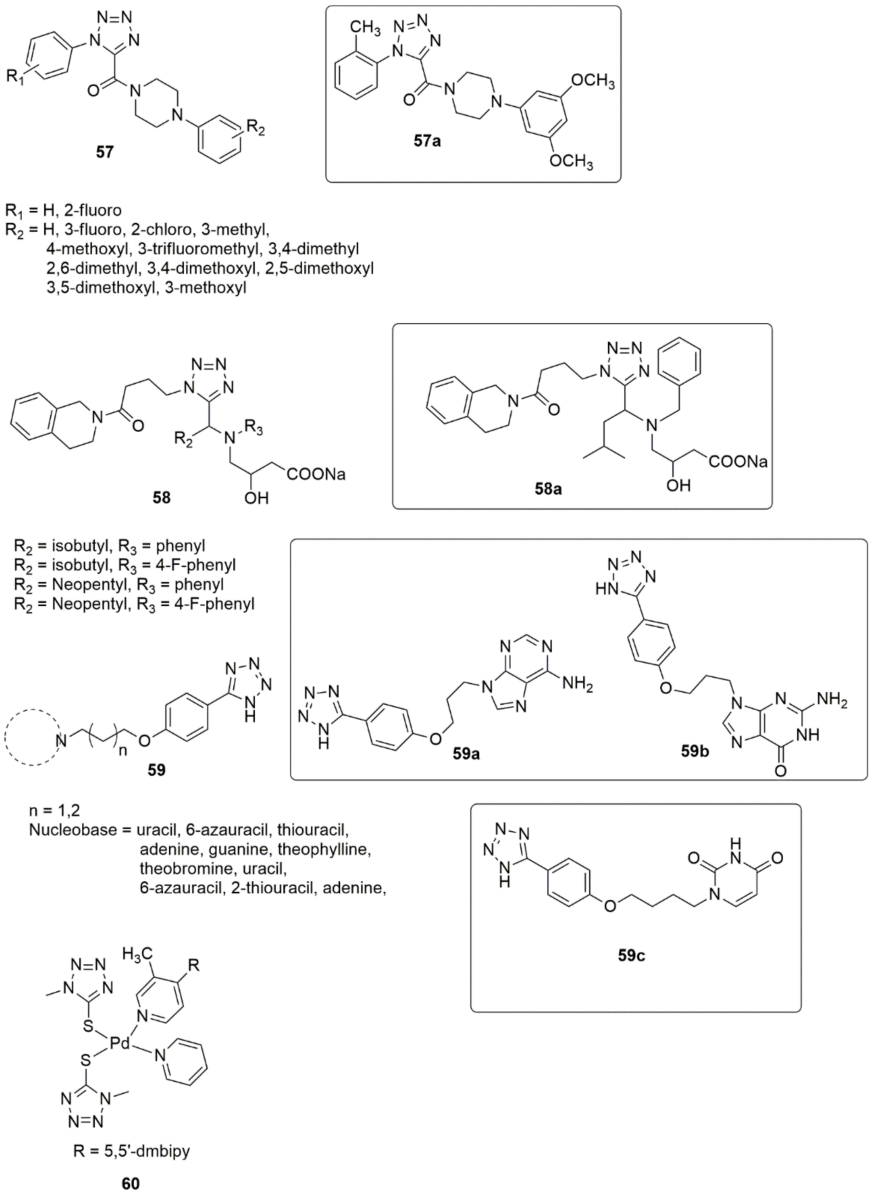

Figure 9. Chemical structures of active tetrazole hybrids with promising anticancer activities.

Additionally, the compounds **59a**, **59b** and **59c** showed significant inhibitory activity against HeLa (IC_{50} = 27.94 ± 0.36 μM) and MCF-7 (IC_{50} = 49.22 ± 1.01 μM) cancer cell lines. The presence of two purine-like nucleobases led to the strongest inhibitory effect against the PDE3A, while the insertion of a pyrimidine-like nucleobase also led to an enhanced inhibitory effect against the PDE3A and cytotoxicity activity against the HeLa and MCF-7 cell lines. Rashidipour et al. [52] reported the effectiveness of **60** on SKBR-3 cell proliferation as being similar to that of cisplatin, and the DNA-binding assay uncovered the ability of the compound to bind to DNA and alter its structure (see **Figure 9**).

2.5. Imidazole/Benzimidazole

A library of new imidazole derivatives **61**, **62** have been prepared and evaluated for their biological activity [53]. Most of the examined compounds have significant inhibitory activities. Compound **61a** (MIC = 62.5, 100, 100

μg/mL) displayed broad-spectrum antibacterial activity against all ESBL, VRE, and MRSA strains, respectively, while **62a** (MIC = 25 μg/mL) showed excellent activity against the ESBL strain. All the examined compounds demonstrated lower activity than the standard drug to inhibit H37Rv strains. The in vitro antimalarial activity against *Plasmodium falciparum* showed that the analogues **61b** (IC_{50}= 0.36 μg/mL), **61a**, and **62b** (IC_{50} = 0.45 μg/mL), exhibited moderate activity compared with the reference drug quinine (0.268 μg/mL). Forty novel naphthoquinone phenacylimidazolium derivatives were synthesized and subsequently evaluated for their antitumor activities against three human cancer cell lines [54]. Compound **63** exhibited remarkable activity against the MCF-7 cell line (IC_{50} = 50 nM) and 256-fold selectivity against normal cells. Furthermore, compound **63** was found to induce apoptosis, activate the pro-apoptotic protein caspase-3, and inhibit survivin expression. Al-Hamashi et al. [55] designed, synthesized, and described a new antimitotic agent class that modulates tubulin polymerization. All the compounds inhibited the growth of HCT 116 cells with GI50 values. The olefin moiety in the linker was crucial for the cytotoxic activity. Hydrogenation of this double bond or conversion to a cyclopropyl moiety obliterated the antiproliferative activity. Substitution of aniline moiety with a cyclohexyl group or a bulky naphthyl moiety lowered the antiproliferative activity, while the substitution of halogen atoms or a trifluoromethyl group at the *para*-position improved the inhibitory activity. Compound **64a** inhibited HDAC1, 2 and 3, while **64a** and **64b** had no effect on SMC3 acetylation. Compound **64a** further destabilized microtubules and accelerated depolymerization. A series of new fluoro-substituted benzimidazole hybrids were designed, synthesized and pharmacologically evaluated [56]. The new compounds were exposed to biological evaluation for their impacts on systolic blood pressure (SBP) and diastolic blood pressure (DBP) in spontaneously hypertensive rats. Of the compounds examined, **65a** and **65b** reduced blood pressure more effectively and had higher and more enduring antihypertensive effects than losartan and telmisartan at the same dose (see **Figure 10**).

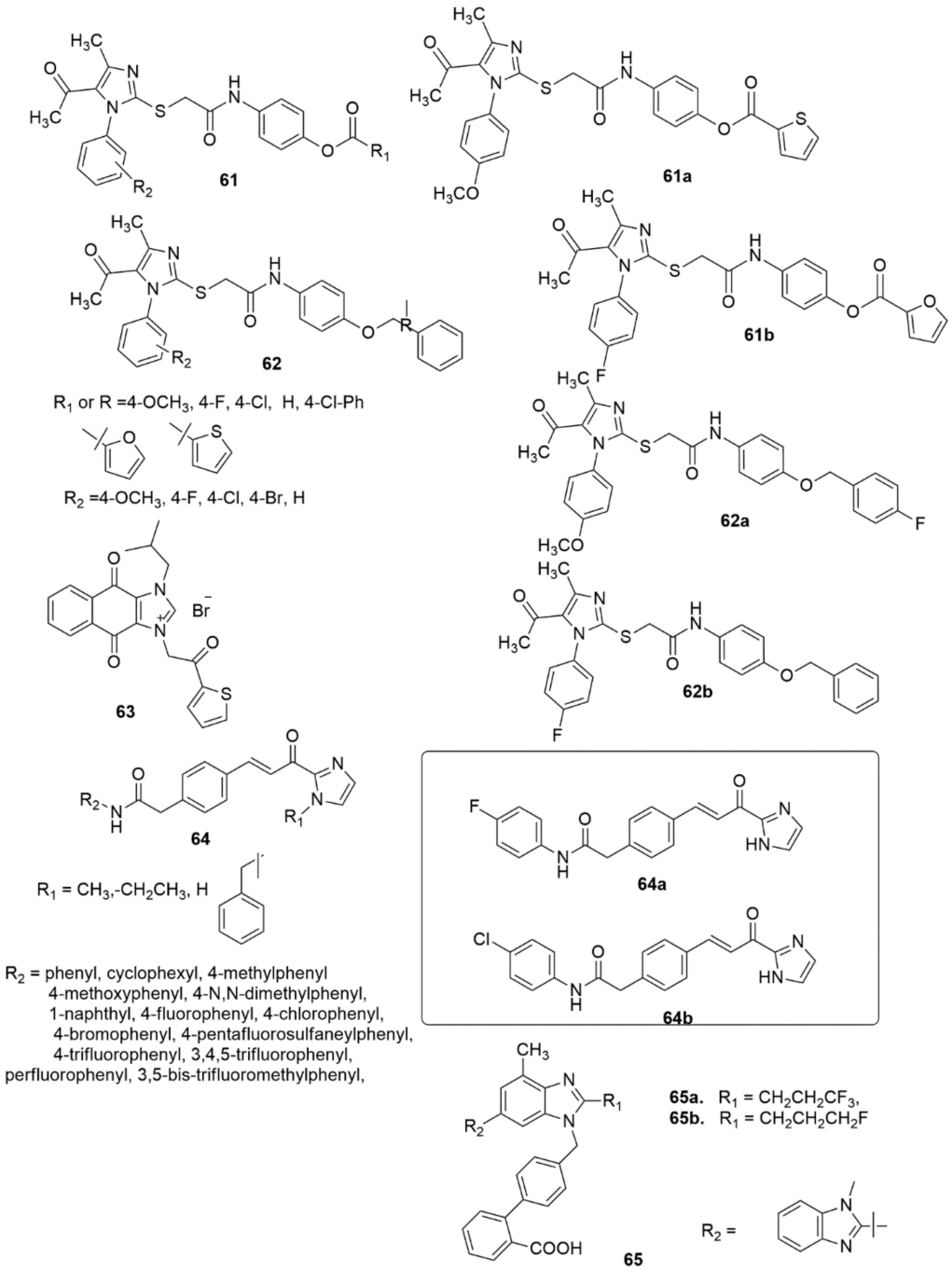

Figure 10. Analogues of imidazole with promising biological activities.

The SARs indicated that the presence of lipophilic benzylamine improved the activity eight-fold in **66b** (MIC 1.56 µg/mL), while as a result of the integration of halogens, namely fluorine and chlorine, at the *ortho* position of the phenyl ring, the inhibitory activity decreased. Among the derivatives with disubstituted halogens, compound **66a** (MIC of 0.78 µg/mL) with 3,4-difluoro substituents demonstrated the highest activity. A four-fold reduction in anti-TB activity has been observed with the integration of the electron-withdrawing 4-trifluoromethyl group, whereas the presence of methyl at the *ortho* position reduced the activity due to the *ortho* steric clash. However, the activity increased upon incorporating the methoxy group at the same second position. In summary, **66a** exhibited the

superior anti-tubercular potential with an MIC of 0.78 µg/mL (2.15 µM), followed by **66b**, **66c**, **66d** and **66e** with an MIC of 1.56 µg/mL (see **Figure 11**).

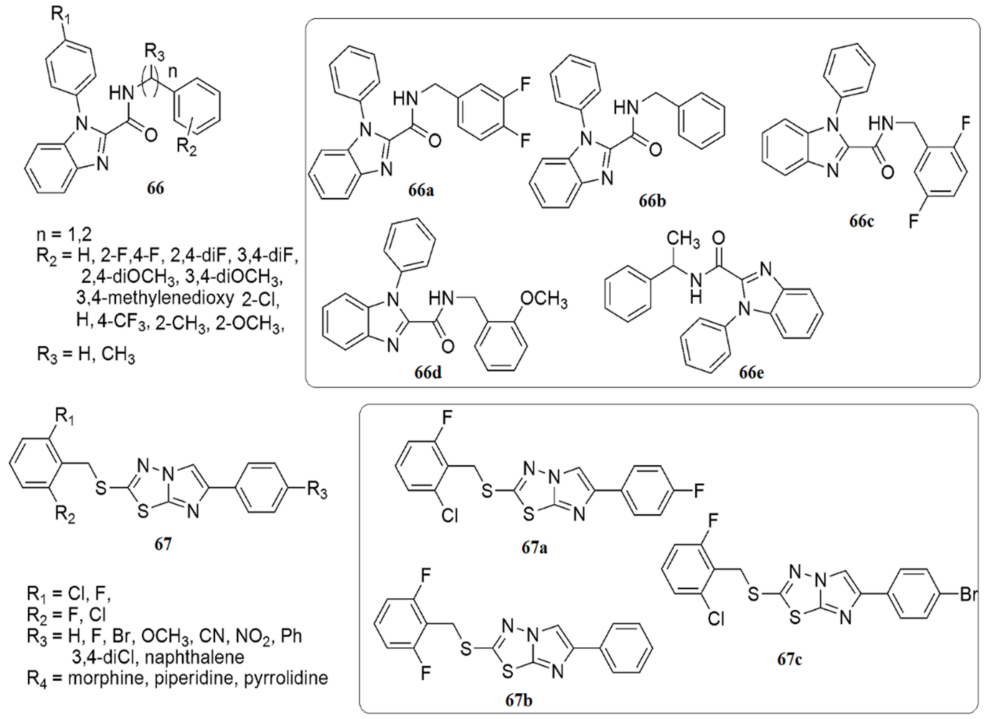

Figure 11. Structures of analogues of imidazole with promising biological activities.

Askin et al. [57] investigated the synthesis, characterization, biological activity, and cytotoxic effects of imidazo[2,1-*b*][1,3,4]thiadiazole derivatives **67**. The novel imidazo[2,1-*b*][1,3,4]thiadiazole derivatives were tested for their ability to inhibit the ubiquitous cytosolic *h*CA I and *h*CA II isozymes and the cholinergic enzyme AChE. All the tested compounds demonstrated low nanomolar inhibitory activity against *h*CA I, *h*CA II, and AChE (*K*Is were 23.44–105.50, 10.32–104.70, and 20.52–54.06 nM, respectively). Moreover, compound **67a** inhibits *h*CA I up to 18-fold compared to acetazolamide, while compound **67b** has a five-fold selectivity towards *h*CA II. **67a**, **67b** and **67c** were the most potent inhibitors of *h*CA I and II isoforms, AChE, and non-toxic agents against the L929 mouse fibroblast cell line at their effective concentrations on target enzymes (see **Figure 11**).

Twenty-six novel 4-phenoxypyridine bearing imidazole-4-carboxamide **68** and 4-methyl-5-oxo-4,5-dihydro-1,2,4-triazole-3-carboxamide **69** hybrids were designed, synthesized, and investigated for pharmacological activities [58]. All the newly synthesized target compounds were evaluated for their in vitro inhibitory activity toward c-Met kinase using a mobility shift assay. **69a** demonstrated the best activity with an IC_{50} value of 0.012 µM. The introduction of a fluorine atom on the phenoxy moiety was crucial for c-Met kinase effective activities for the two series of compounds. Based on an antiproliferative assay, compound **69a** showed remarkable proliferation reduction effects against MKN-45, A549 and H460 cell lines with IC_{50} values of 0.64, 1.92 and 2.68 µM, respectively. Additionally, compound **69a** strongly inhibited A549 cell motility. The results of a colony formation assay indicated that **69a** suppressed the colony formation and prevented the unobstructed increase of A549 cells, and induced apoptosis in MKN-45, A549, and H460 cells, in a concentration-dependent manner (see **Figure 12**).

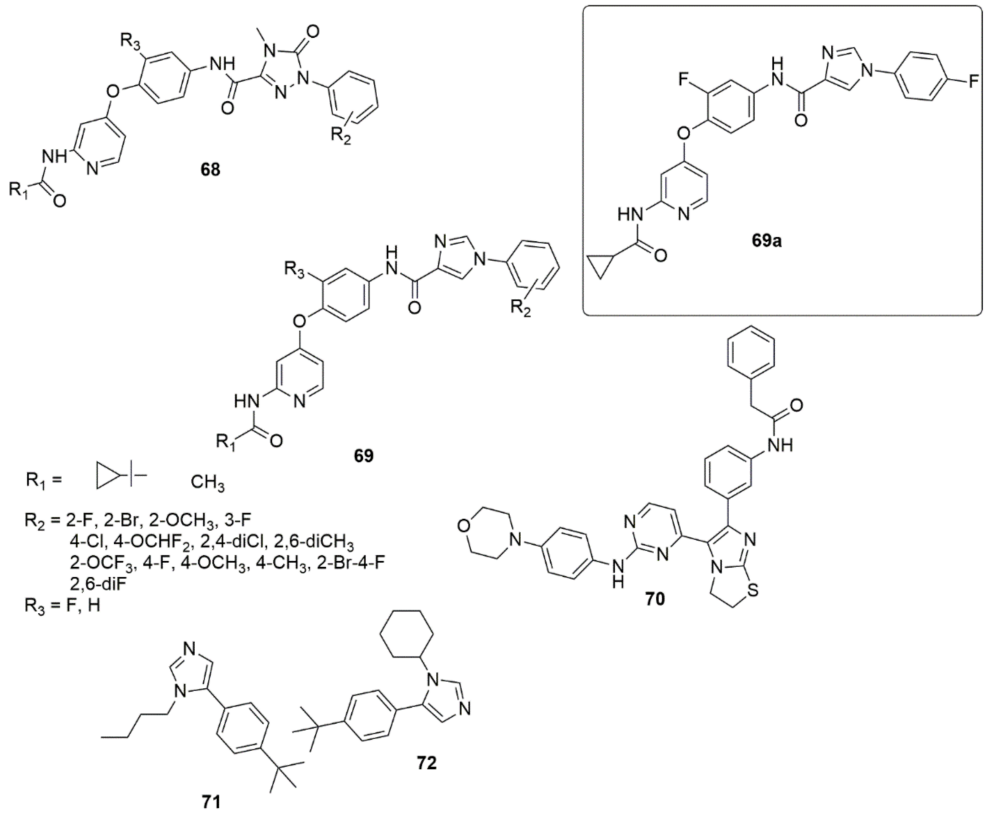

Figure 12. Chemical structures of imidazole hybrids with significant biological activities.

Compound **70** has displayed promising activity with an IC_{50} value of 52 nM against IGF1R and an IC_{50} value of 35.5 nM against EGFR with an acceptable PK profile [59]. Compounds **71** and **72** both exhibited activity against HIV-1 in LEDGF/p75 contact, while **71** displayed a MIC value of 15.6 µg/mL against *S. aureus*, and **72** displayed a comparable MIC value against *B. cereus* [60] (see **Figure 12**).

A new library of 2-(5-aryl-1H-imidazol-1-yl) compounds **73**, **74**, **75** were designed, synthesized, and evaluated for their inhibitory activity against the HIV-1 Vpu and BST-2 protein interaction [61]. The results of the AlphaScreen™ assay showed that **73a** and **74b** displayed IC_{50} values of 11.6 ± 1.1, and 17.6 ± 0.9 µM, respectively, in a dose–response profile, whereas in cytotoxicity and antiviral assays, **73a** displayed significant activity with an EC50 value of 6.3 ± 0.7 µM at non-toxic concentrations (CC50 = 184.5 ± 0.8 µM), while compound **74b** exhibited an EC50 of 157.5 ± 1.2 µM (CC50 = 159.5 ± 0.9 µM). Thus, compound **73a** was identified as a potential inhibitor of HIV-1 Vpu and host BST-2 protein. A series of new 3-(4-phenyl-1H-imidazol-2-yl)-1H-pyrazole derivatives were designed and synthesized as JAK 2/3 and Aurora A/B kinase multi-target inhibitors by Zheng et al. [62]. Many of the compounds examined showed good inhibitory activity against JAK2/3 and Aurora A/B (with IC_{50} values ranging from 0.008 to 2.52 µM). Of all the compounds evaluated, **76a** remarkably decreased the toxic effect on normal human cells, more so than JAK 2/3 and the Aurora A/B kinase multi-target kinase inhibitor (AT9832). Compound **76a** downregulated the phosphorylation of STAT3, STAT5, Aurora A, and Aurora B in K562 and HCT116 cells. This potent compound induced cell cycle arrest in the G2 phase. Notably, the SAR showed that derivatives bearing a morpholine ring at the side chain exhibited superior antiproliferation activity compared to derivatives bearing a piperidine ring. Additionally, the presence of Cl, OCH_3, and NO_2 groups at the benzene ring enhanced the proliferative inhibition.

However, compounds bearing electron-withdrawing groups such as Cl and NO_2 displayed slightly higher K562 proliferative inhibition compared to the compounds containing an electron-donating group (OCH_3) (see **Figure 13**).

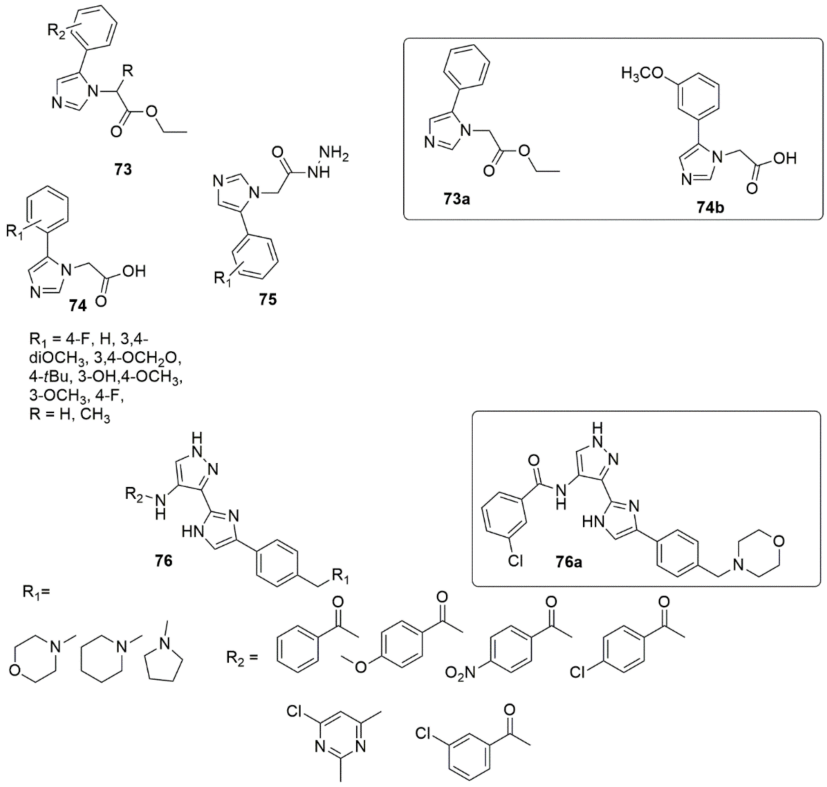

Figure 13. A new library of 2-(5-aryl-1*H*-imidazol-1-yl) compounds with significant biological activities.

Compound **77** showed potent binding affinity to A2A AR (IC_{50}, 9.2 nM), good selectivity against A1 AR (A2A/A1 80-fold) and high potency in cAMP (IC50 31.0 nM) functional and IL-2 (EC50 = 164.6 nM) production assays. A series of dual imidazole-5-yl pyrimidine inhibitors BRAFV600E/p38a were developed and synthesized to overcome resistance to BRAFV600E inhibitors in BRAFV600E metastatic melanoma patients [63]. Among the examined compounds, **78** exhibited superior dual inhibition with IC_{50} values of 2.49 and 85 nM against BRAFV600E and p38a, respectively. Compound **78** exhibited high inhibitory activity with an IC_{50} value of 96.3 nM in the TNF-α production assay. The antiproliferative activity of the targeted compounds was determined using the MTT cytotoxicity assay. Compound **79** showed excellent antiproliferative activity with an IC_{50} value of 0.9 µM. The compound was 11.11-fold more selective against LOX-IMVI melanoma cells than the IOSE-80PC normal cell line. Lei and co-workers have proposed that **80** could be a potential and promising agent for the treatment of thrombotic diseases [64]. Sekiola et al. [65] discovered compound **81** as an attractive candidate for AD treatments. Compound **117** showed high in vitro potency with brain exposure and displayed an unnoticeable inhibition of cytochrome p450 enzymes. Concentrations of Aß42 in the brain of rats were significantly reduced in vivo at a dose of 10 mg/kg, while the dose of 2 mg/kg of **81** for 8 days fully saved the cognitive deficits of AD model mice. Compound **82** has exhibited excellent inhibitory activities against BRD4(1) with an IC_{50} value of 0.035 µM [66]. **82** successfully inhibited the proliferation of pancreatic cancer cells BxPC3. Compound **82** also arrested prostate cancer cells in the G0/G1 phase, induced cell apoptosis by regulating the expression of apoptotic proteins and demonstrated effective

in vivo antitumor activity by inducing the apoptosis of tumor cells. Bu et al. [67] proposed compound **83** as potential MNK1/2 inhibitor [67]. Compound **84** has been shown to be a potential starting point for the development of a lead molecule used for the treatment of leukemia and glioblastoma (see **Figure 14**).

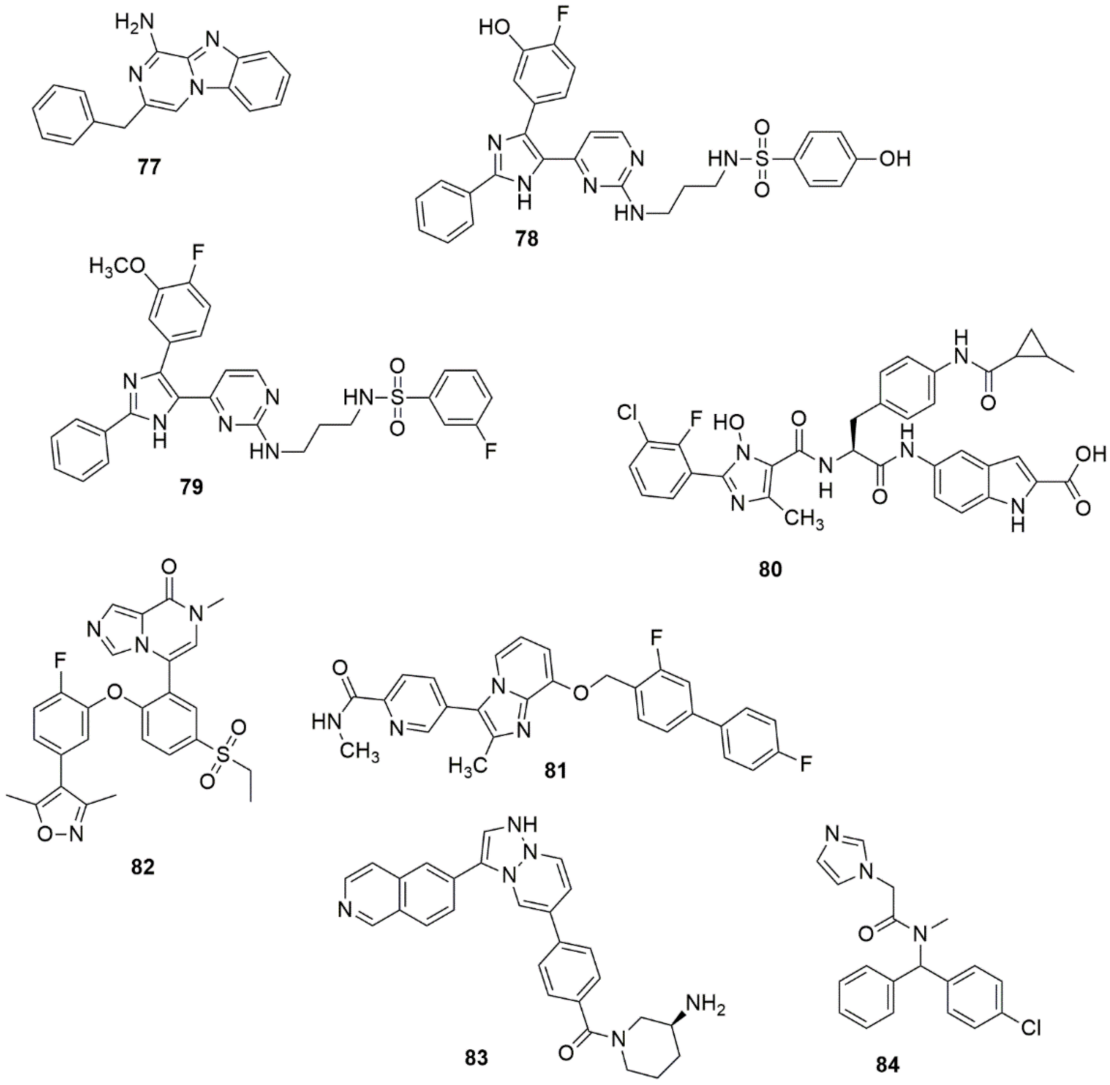

Figure 14. Structures of analogues of imidazole molecule with promising biological activities.

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