Review Article

Quinazolinone-based hybrids with diverse biological activities: A mini-review

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Quinazolinone and quinazoline have been shown different pharmacological activities, namely anticancer, anti-inflammatory, anti-hyperlipidemia, analgesic, antihypertensive, and antibacterial. On the other hand, molecular hybridization is a structural modification technique in the design of new ligands which consist of two or more pharmacologically active molecules in one structure. Therefore, due to the importance of the biological activities of quinazolinones for the development of new therapeutic agents, this review emphasizes current findings on various quinazolinone-based hybrids in medicinal chemistry. Moreover, it highlights the biological activities and structure-activity relationship of these hybrids.

Key words: Biological activities, hybrid, quinazoline, quinazolinone, synthesis

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INTRODUCTION

The first quinazoline nucleus was synthesized by the reaction of anthranilic acid with cyanogens in 1869.[1] After that, Gabriel synthesized quinazoline derivatives in 1903.[2] Many years later, the synthesis of quinazolinone derivatives was done by the different methods such as Niementowski's synthesis, Grimmel, Guinther, and Morgan's synthesis.[3,4] In the past decades, many scientists were synthesized quinazolinone nucleus by the different techniques.[5-7] Due to the importance of these fused heterocyclic compounds, medicinal chemistry researchers had much attention in biological assay of the quinazoline/quinazolinone derivatives.[8] Quinazolinone are nitrogenated scaffolds that were extensively gained much attention due to pharmacological activities, including anticancer,[9-11] anti-inflammatory,[12] antimicrobial,[13,14] antihypertensive,[15] dihydrofolate reductase (DHFR) inhibition,[16] Tyrosine Kinase inhibition,[17] etc. Molecular hybridization is a strategy for designing hybrid compounds that two or more small molecules such as quinazolinone, thiazole, triazole, benzofuran, and imidazole covalent and noncovalent linked.[18] These new hybrid molecules improved the pharmacological activity[11] through interaction with biological targets such as aromatase, cyclooxygenase (COX), DHFR enzymes, and epidermal growth factor receptor (EGFR).[19] There are diverse synthetic quinazoline-based drugs such as gefitinib and erlotinib (EGFR inhibitors), alfuzosin and prazosin (α1 blockers), which are used in clinics [Figure 1].[20,21] Hybrid compounds, including quinazolinone and other pharmacologically active heterocycles, have resulted in new chemical drugs with reduced multidrug resistance. The activity of quinazolinone-based hybrid derivatives has been demonstrated in some literature.[22,23] This review focuses on the important biological activities of quinazolinone-based hybrids including anti-cancer, antibacterial, urease enzyme inhibition, COX enzyme inhibition, β-site amyloid precursor protein cleaving

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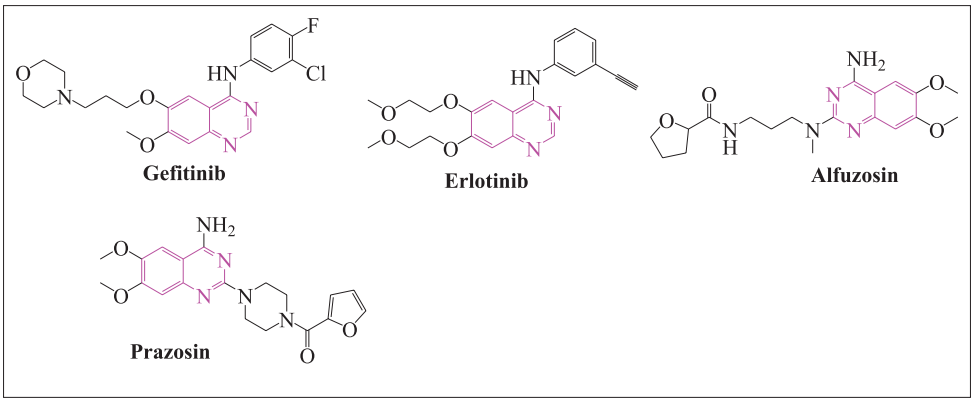

Figure 1: Synthetic quinazoline-based drugs in the clinic

enzyme 1 (BACE1) inhibition, dipeptidyl peptidase IV (DPP-4) inhibition and antimalarial activities, also the impact of different substituents on the biological activities were discussed in some compounds.

ANTI-CANCER ACTIVITIES

Piperazine is a significant heterocycle anchor for improving novel therapeutic compounds, in particular cytotoxic agents.[24] Piperazine-1-carbothioyl and piperazine-1-carbodithioate derivatives have shown cytotoxicity against hepatocellular and gastric carcinomas. Hence, Zhang *et al*. reported two series of hybrid compounds, including quinazoline and piperazine moiety. Then, these new compounds were assayed against MCF-7, A549, and HCT-116 cell lines. The structures (1–3) presented in Figure 2 inhibited the proliferation of three cancer cell lines with IC_{50} values <10 μM. These results revealed that replacing the cyclohexyl group with aliphatic or alkyl heterocyclyl groups decreased antiproliferative potency.[25]

Among the various synthesized compounds of quinazolinones, 2-styryl quinazolinones, and 2-methyl quinazolinones derivatives showed pharmacologically active properties due to inhibitory effects on tubulin polymerization and DNA repair enzyme poly (Adenosine diphosphate-ribose) polymerase, respectively.[26] More ever, pyrrolobenzodiazepines, a natural antibiotic, are associated with antitumor activity by interaction with double-stranded DNA and forming a covalent bond.[27] In a hybridization strategy, these two pharmacophores were combined by Kamal *et al*. in good yield through different alkane spacers. Compounds 4 and 5 [Figure 2]. Compound 4 showed GI_{50} values of <0.1 μM against 60 human cancer cell lines [Figure 2].[28]

Vodnala *et al*. have designed new hybrid compounds that consist of dihydropyranochromene as a privileged oxa-heterocyclic unit at the C-2 position of quinazoline ring. Final structures were prepared in a one-pot three-component synthesis. Then, these hybrids were assayed against the breast cancer cell lines of MDA-MB 231 and MDA-MB 453. Compound 6 [Figure 2] with substitution chlorine and bromine at phenyl ring of oxa-heteroaryl scaffold found as an active molecule with IC_{50} values at 45.7 μM and 28.3 μM concentrations in MDA-MB453 and MDA-MB 231 cell lines, respectively. Molecular docking results of this structure into the receptor site of ERa protein (3UUD) showed the best docking score results. Bromo and chloro substituents in phenyl ring oriented toward the hydrophobic pockets cause a positive influence in binding affinity with protein.[29]

In the research for developing more potent anticancer agents, Kamal *et al*. have modified podophyllotoxin structure using hybridization strategy. Some derivatives of podophyllotoxin-based quinazolinone were synthesized by stable alkane spacers and amide bonds. Some of these hybrids compound 7 have the potentiality to control breast cancer cell growth by affecting tumor angiogenesis and invasion [Figure 2].[30]

Asadi *et al*. have synthesized a unique series of hybrid molecules by the connecting of quinazolinone, benzofuran, and imidazolium moiety, followed by the evaluation of their cytotoxic activity. Among the synthesized hybrids, compound 8 has reported the most potent cytotoxicity, with IC_{50} values of 0.59 μM against the MCF-7 cell line [Figure 2]. Structure-activity relationship (SAR) consideration declared the important role of the methoxy substituent on benzofuran ring in the growth inhibition. Furthermore, the results of the docking analysis of these hybrids to aromatase were paralleled with the results of the experimental study (PDB ID: 3EQM).[31]

Alkylphospholipids have shown antitumor activities.[32-35] Miltefosine and edelfosine are two essential antitumor lipids [Figure 2].[36] On the other hand, erlotinib is a famous EGFR inhibitor.[37] In the search for developing multitarget anticancer agents, Alam *et al.* reported two series of hybrid compounds. Antitumor phospholipid molecule via linking erlotinib as the pharmacophoric moiety (EGFR inhibitor) were prepared through an amide or ester group at the *sn*-2

position. Then, these new hybrids were assayed against four cell lines (A-549, MCF-7, HepG2, and A-431) using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay. In contrast with ester analogs, the amide series with long alkyl chain enhanced cytotoxic activity. Notably, compound 9 had the best efficacy against MCF-7 cell line than reference erlotinib and miltefosine [Figure 2].[38]

Ghorab *et al.* synthesized benzenesulfonamide-linked benzo quinazolinone-based hybrids as dual EGFR/human epidermal growth factor receptor 2 inhibitors, succeeded by *in vitro* anticancer screening against the MDA-MB-231 cell line. All the hybrids showed the IC_{50} in the range of 0.36–40.90 μM. Among these, compound 10 exhibited the highest EGFR inhibitory profile (63.00%) in compared to erlotinib (68.30%) [Figure 2]. The SAR analysis revealed that bulky groups linked to the acetamide moiety are necessary for biological activity. Furthermore, the results of the molecular docking analysis were paralleled with the results of the cytotoxicity study (PDB code: 1M17).[39]

Thiazole, which is an active heterocycle,[40-44] was combined with 4-(3H)-quinazolinone through molecular hybridization by Hosseinzadeh *et al*. These hybrid compounds were synthesized, succeeded by *in vitro* anticancer evaluation against three human cancer cell lines (MCF-7, PC-3, and HT-29). SAR consideration

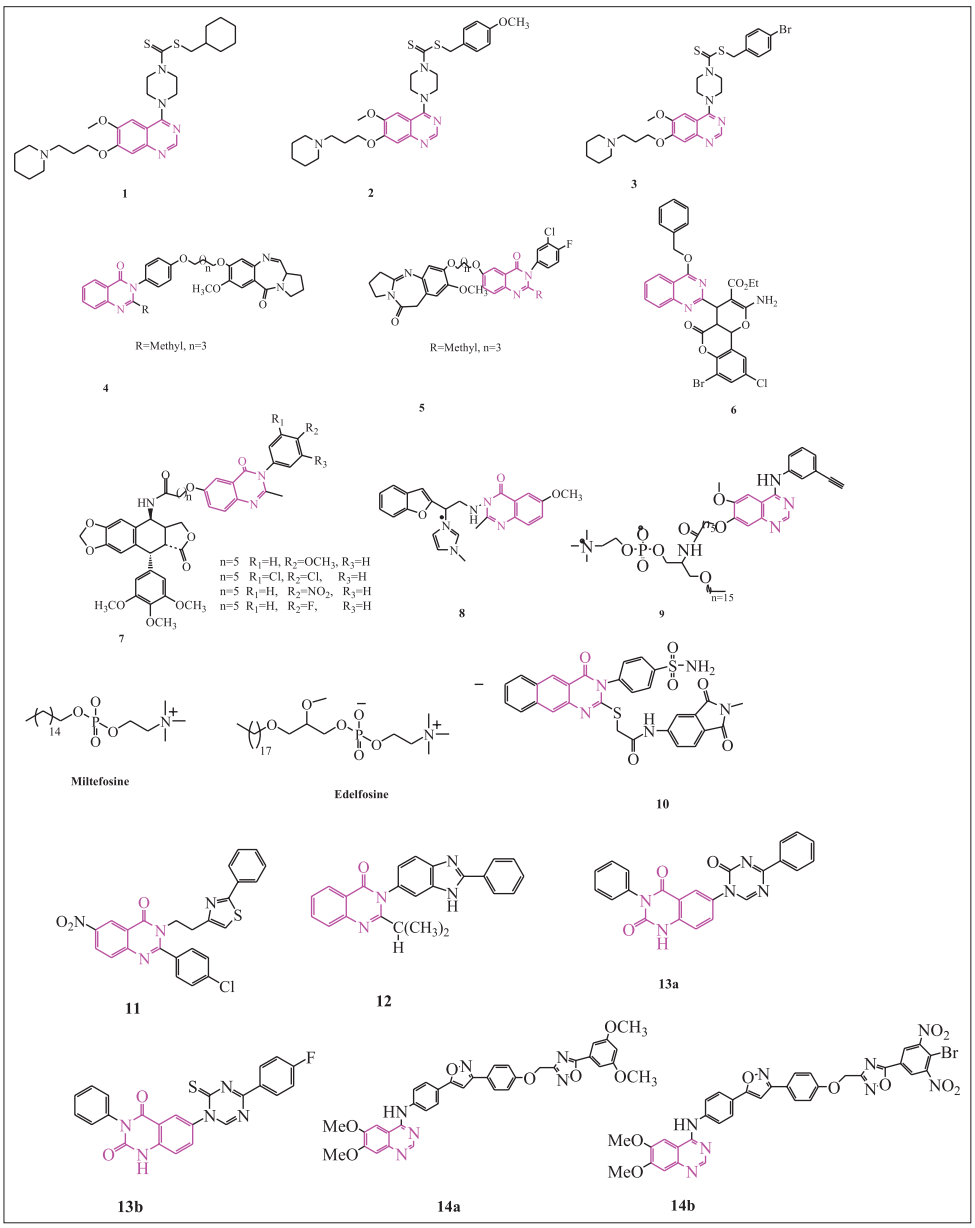

Figure 2: Quinazoline hybrids with anticancer activity

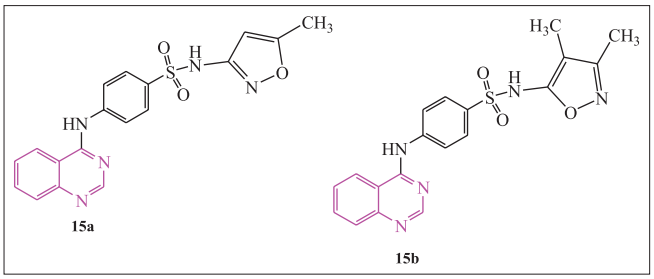

Figure 3: 4-Aminoquinazoline- and sulfonamide-based hybrids

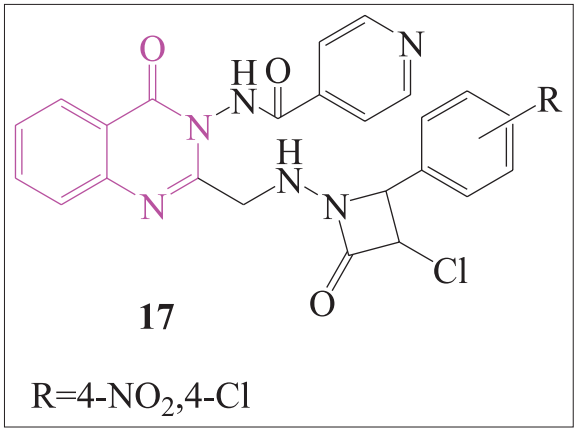

Figure 5: Azetidinyl-quinazolinone hybrids

revealed the important role of the halogen group (Cl) at the 2th position. Among hybrids, compound 11 was active against three cell lines [Figure 2].[45]

Considering the importance of benzimidazole as a biologically active heterocycle,[46-48] Taherian *et al*. designed a unique series of quinazolinone-benzimidazole hybrids. After cytotoxic evaluation, compounds displayed remarkable cytotoxic activity against MCF7 and Hela cell lines. SAR analysis showed that alkyl substituent had more important effect than phenyl substituent at the 3th position. Notably, compound 12 was active with IC_{50} 50 µM against the Hella cell line [Figure 2].[49]

Triazole, triazine, and sulfone have shown to increase the activity of many bioactive backbones.[50-52] Al-Romaizan *et al*. have designed and synthesized quinazoline diones-based derivatives by attaching the triazole, triazine, and sulfone moiety on quinazolinone structure. Among three series of hybrids, triazine derivatives exhibited more potent activity than triazole and sulfone analogs. SAR consideration revealed the importance of phenyl substituent in comparison with other heterocycle compounds at the 4th position of triazine. Especially, structures 13a and 13b have shown the highest cytotoxic activity with an IC_{50} = 2.52 ± 0.69 µM and 1.57 ± 0.06 µM against HEP-G2 and HCT116 cell lines, respectively [Figure 2].[53]

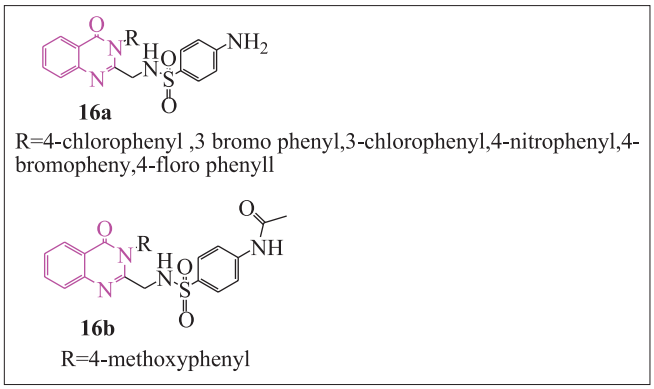

Figure 4: Quinazolinone-sulfonamide hybrids

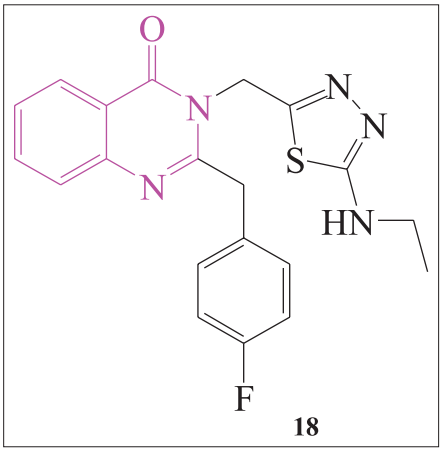

Figure 6: Thiadiazole-linked quinazolinone hybrid

Oxadiazole is a pharmacologically active backbone that appears in famous pharmaceutical drugs such as oxolamine (cough suppressant), butalamine (vasodilator), fasiplon (anxiolytic), and pleconaril (antiviral).[54,55] Hence, Srinivas *et al*. have synthesized hybrid compounds based on oxadiazole-Isoxazole and quinazoline. All derivatives exhibited good anticancer activity against four cancer cell lines (A549, MCF-7, MDA MB-231, and DU-145). Significantly compounds 14a and 14b showed potent activity on the DU-145 cell line with an IC_{50} of 0.011 ± 0.001 µM and on A549 cell line with an IC_{50} of 0.014 ± 0.0061, respectively [Figure 2]. SAR analysis showed that methoxy substituted derivatives have shown promising activity on four cancer cell lines.[56]

ANTIBACTERIAL ACTIVITIES

Sulfonamide analogs had shown antibacterial activity.[57] On the other hand, 4-amino and its *N*-anilinoquinazolines derivatives were famous for being as selective inhibitors of tyrosine kinase.[58] Because of such points, Kumar *et al*. reported two new hybrids of quinazoline and benzenesulfonamide derivatives by connecting the benzene sulfonamide moiety on 4-amino quinazolinone scaffold. Among the hybrid

analogs, compound 15b has shown more potent antimicrobial activity than 15a [Figure 3]. However, these molecules have not shown reasonable anticancer activity against two breast adenocarcinoma cell lines, MDA-MB-231 and MCF 7, maybe, because of the presence of oxazole ring.[59]

Some derivatives of quinazolinone-sulfonamide hybrids (16a and 16b) were designed using glycine amino acid as a precursor through an efficient multistep synthetic procedure. Synthesized compounds were assayed by the microdilution method against bacterial and fungal strains. In general, the compounds had a greater effect on gram-positive bacteria. The most active scaffolds belong to category 16a, containing 4-chloro-phenyl and 3-bromophenyl substitutions at position N-3 of quinazolinone scaffold, respectively. SAR analysis showed that halogenated phenyl substituents (bromo, chloro, and fluoro) have a more significant effect on activity than nonhalogenated phenyl substituents (nitro, methoxy, and methyl). Compounds with substitutions mentioned in Figure 4 indicated good activity against both the fungal species, including *Aspergillus niger* than *Candida albicans* [Figure 4].[60]

Azetidinone ring is found as the primary fragments in many of natural and synthetic compounds.[61] The presence azetidinone ring in essential antibiotics such as cephalosporins, thienamycins, and penicillins highlighted the importance of this ring in medicinal chemistry research. Myangar and Raval have designed and synthesized azetidinyl quinazolinone hybrid derivatives. Then, these molecules were checked for *in vitro* antibacterial and antifungal screening. Molecule 17 [Figure 5] demonstrates potent antitubercular activity. The antibacterial activity data exhibit that the derivatives with electron-withdrawing substituents (halogen and nitro) showed better to moderate activity. In contrast, analogs containing chloro and methoxyl substituent indicated better antifungal activities.[62]

OTHER PHARMACOLOGICAL ACTIVITIES

Urease is a metalloenzyme that plays a valuable role in the hydrolysis of urea. This reaction occurs in two steps and produces ammonia and carbamate. Spontaneously carbamate hydrolyzes to carbonic acid and ammonia.[63] This hydrolysis phenomena increase pH, which causes *Helicobacter pylori* to survive.[64] As mentioned in the articles, triazole, thiadiazole, and semicarbazones have shown urease inhibition.[65,66] Hence, in the search for potent urease inhibitors, Menteşe

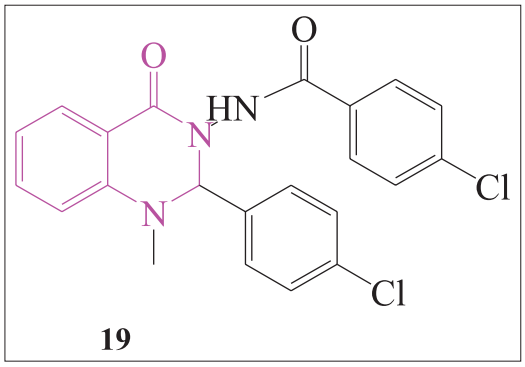

Figure 7: Dihydroquinazoline-benzamide hybrid

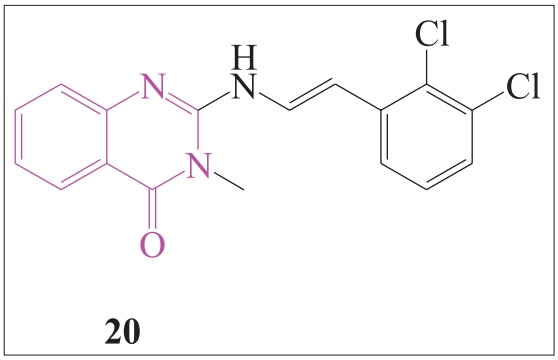

Figure 8: Hydrazine-linked quinazolinone hybrid

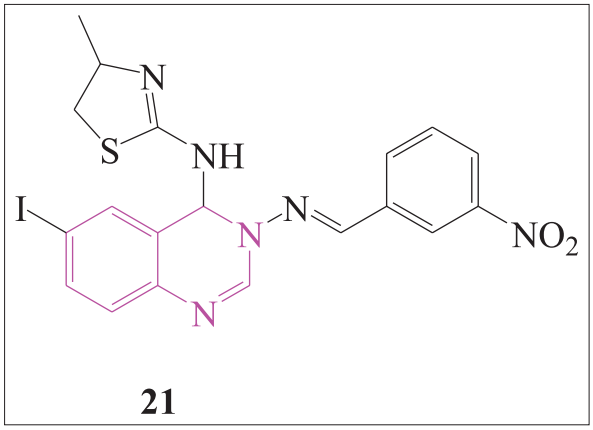

Figure 9: Quinazoline-thiazoline hybrid

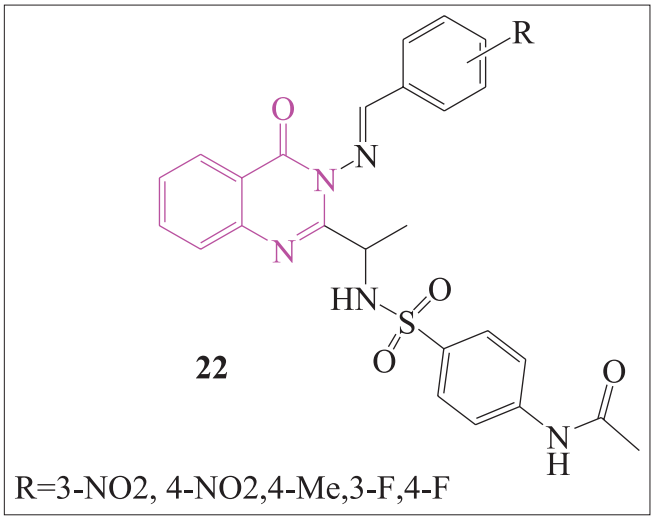

Figure 10: Sulfonamide-linked quinazolinones

et al. synthesized five series hybrid compounds by the connecting of quinazolinone with thiadiazole, triazole, and thiosemicarbazide. Then, these compounds evaluated their *in vitro* urease inhibition characteristics. Among five series of hybrids, thiadiazole derivatives exhibited for their more potent activity than other analogs. SAR analysis showed that halogenated phenyl substituents (fluoro) at position-2 had more potent inhibitor activity than other substituents, and compound 18 has especially shown the most activity with an IC_{50} value of 1.88 ± 0.17 μg/mL [Figure 6]. Furthermore, docking simulation results of these compounds with *Jack bean* urease (PDB ID: 3 LA4) have shown a good correlation of *Jack bean* urease inhibition with the experimental results.[67]

Inhibition of COX enzyme (which plays a significant role in prostaglandin biosynthesis) can cause analgesic effects.[68] Proquazone and fluproquazone are two well-known nonsteroidal anti-inflammatory drug (NSAIDs) that contain a quinazolinone scaffold.[69,70] Due to the anti-inflammatory and analgesic activities of quinazolinone and in the search for effective COX-1/2 inhibitors, Sakr *et al*. have synthesized a unique series of dihydro quinazoline-benzamide hybrids. These molecules have been assayed for their anti-inflammatory, analgesic, gastric ulcerogenic, and COX-1/2 inhibitory activity. For this purpose, two neighboring phenyl rings are linked to a primary heterocyclic moiety (quinazolinone) at 2 and 3 positions (V-shape). Furthermore, a linker (ester or amide) between one of the phenyl rings and the primary heterocycle (quinazolinone) can improve COX-2 selectivity. Otherwise, carboxylic acid, sulfonyl, and sulfonamide groups were seen in traditional NSAIDs which were removed. Among all the synthesized hybrids, compound 19 exhibited the most excellently biological activity in all the tests [Figure 7]. SAR consideration indicated the critical role of the substitution (nitro, chloride, methoxy, and fluoride groups) in both phenyl rings. Furthermore, the results of the docking analysis were compared with the results of the experimental study (PDB ID: 1CX2).[70]

Alzheimer's disease (AD) is a modern neurodegenerative disease that causes dementia. BACE1 plays a vital role in AD.[71,72] Hence, in the explore for AD therapy, Haghighijoo *et al*. synthesized hybrid compounds containing quinazolinone and hydrazone moieties as BACE1 inhibitors. Among the synthesized analogs, compound 20 has shown promising activity against BACE1 (IC50 = 3.7 μM) [Figure 8]. SAR consideration exhibited that the small H-bond donors (OH group) in phenyl ring improve the inhibitory activity. Furthermore, the addition of two chlorine atoms on the phenyl moiety improves the inhibitory activity. Furthermore, the results of the docking analysis with BACE1 (PDB code: 4B70) exhibited the lowest binding energy and high docking score.[73]

DPP-4 is a protease enzyme that inactivates glucose-dependent insulin tropic polypeptide and glucagon-like peptide 1. DPP-4 inhibitors play vital roles in maintaining glucose homeostasis.[74] By considering the antidiabetic activities of quinazoline and thiazoline scaffolds, Ali *et al*. synthesized some of the thiazoline-linked quinazolinones hybrids by multistep reactions starting from anthranilic acid. Target compounds were assayed for their *in vitro* DPP-4 inhibitory activity, *in vivo* antidiabetic activity, and (1,1-diphenyl-2-picrylhydrazyl) radical scavenging properties. Due to the great activity of compound 21 [Figure 9] in DPP-4 enzyme inhibition (IC_{50} = 0.76 nM), it could be used as a lead compound for developing new antidiabetic agents. Compound 21 with score value-6.27 displayed better binding interaction to DPP-IV (PDB Code: 2RGU).[75]

Some derivatives of sulfonamide-linked quinazolinones were prepared by ionic liquid-mediated stereoselective synthesis. These compounds were evaluated for their antimalarial potency. Compound 22, shown in Figure 10, was determined to be active antimalarial agents (IC_{50} = 0.068 μg/mL) as compared to standard drugs. Docking results against the enzymes human DHFR and *Plasmodium falciparum* DHFR confirmed *in vitro* evaluations.[76]

CONCLUSION

Due to biologically activities of hybrid compounds of quinazolinones/quinazoline, these heterocycles are an essential backbone in the range of synthetic compounds. Molecular hybridization is a new technique for combining one or more small molecules in one molecule to introduce new pharmacologically active lead compounds. This review covered important diseases, such as diabetes, Alzheimer, microbial infections, and cancer. The purpose of this review is to illustrate the biological activity of quinazolinone and quinazoline-based hybrids for the development of new therapeutic agents.

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Conflicts of interest
There are no conflicts of interest.

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