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Review Article

BIOLOGICAL IMPORTANCE OF QUINAZOLIN-4-ONE SCAFFOLD AND ITS DERIVATIVES- A BRIEF UPDATE

B. HASEENA BANU*[1], K. V. S. R. G. PRASAD[2], K. BHARATHI[2]

[1]Krishna Teja Pharmacy College, Chadalawada Nagar, Renigunta Road, Tirupati-512506, Andhra Pradesh, India, [2]Institute of Pharmaceutical technology, Sri Padmavathi women's university, Tirupati-517502, Andhra Pradesh, India
Email: luckyaftab2002@gmail.com

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ABSTRACT

Heterocyclic compounds form the basis of many pharmaceutical, agrochemical and veterinary products. Among a wide variety of nitrogen heterocyclic moieties that have been explored for developing pharmaceutically useful molecules, quinazolinone plays an important role in medicinal chemistry and subsequently have emerged as a pharmacophore that possess a diversity of useful biological activities. The pharmacodynamic versatility of quinazolin-4-one moiety has been documented not only in many of its synthetic derivatives but also in several naturally occurring alkaloids isolated from animals, plants and microorganisms. This review gives an overview update on some biological activities of the promising synthesized quinazolinone molecules.

Keywords: Quinazolinone, Antimicrobial, Anticancer, Analgesic, Antioxidant, Anti-inflammatory.

INTRODUCTION

Among a wide variety of nitrogen heterocycles that have been explored for pharmaceutically important role, quinazolinones are one of the classes of fused heterocycles that are of considerable interest [1]. Construction of small molecule mimics of biological structures is a key contribution of organic chemistry to the discovery of new pharmaceuticals with the wide range of biological activities. There are two structural isomers, quinazolin-4-one (1) and quinazolin-2-one (2) with the 4-isomer being the more common (fig. 1). The stability of quinazolin-4-one nucleus has inspired medicinal chemists to introduce many bioactive moieties to this nucleus to synthesize new potential medicinal agents [2]. Quinazolinone nucleus is also considered as one of the well-established peptidomimetic scaffold [3]. The current review article will briefly outline an update on pharmacologically active compounds with 3-aminoquinazolinone template.

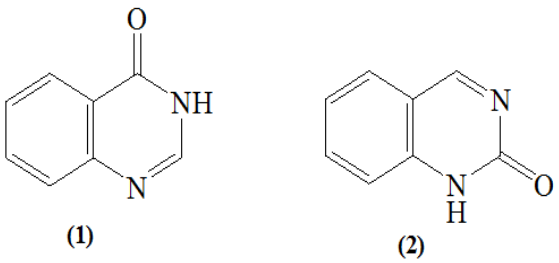

Fig. 1: Isomers of quinazolinone moiety (1) Quinazolin-4-one (2) Quinazolin-2-one

Biological importance of quinazolinon-4-one scaffold

Quinazolinones are fused heterocyclic compounds that constitute the building block of numerous natural products and synthetic analogs possessing an extensive array of biological activities.

Natural quinazolinone compounds (fig. 2)

Febrifugine (3) is well known antimalarial drug possessing quinazolinone in their structural framework [4]. Luotonine A (4), commonly found in traditional Chinese plant named *Peganum nigellastrum* (Luo-Tuo-Hao) is a human DNA topoisomerase I inhibitor and displays cytotoxicity towards the murine leukemia P388 cell line (IC50 = 1.8 µg/ml) by stabilizing the topoisomerase I/DNA complex [5, 6]. Rutaecarpine (5) is the major alkaloid component of a Chinese herbal drug, Wu-Chu-Yu, used extensively as a remedy for headache, cholera, and dysentery [7]. Benzomalvin A (6) is a human neurokinin (NK1) inhibitor and an indole amine 2, 3-dioxygenase inhibitor isolated from a fungal culture of *Penicillium sp* [8].

Quinozolin-4-one derivatives have been isolated from several fungi and originated via similar biosynthesis pathways. Aurantiomide C (7) was isolated from the marine-derived fungus, *Penicillium aurantio griseum* and was reported for its antibacterial, antifungal and antitumor activities [9].

Synthetic quinazolinone compounds

Antimicrobial Activities (fig. 3-5)

Abdul Jabar *et al.* reported the synthesis of 2-(2-methyl-4-oxoquinazolin-3(4H)-ylamino)-N'-(benzylidene) acetohydrazides. These synthesized compounds showed moderate to good antibacterial activity. Compounds (8a) and (8d) were found active against *E. Coli, S. Aureus, P. mirabilis* [10]. Some 3-amino quinazolinone derivatives were reported for their synthesis and antimicrobial activity and among them, compound (9) showed good activity against *C. albicans and A. niger* [11]. A series of 2-substituted-3H-quinazolin-4-one derivatives was synthesized, characterized and screened for antifungal activity against *Candida albicans* by cup plate method. Compounds (10a) and (10b) were found to exhibit good antifungal activity than the standard drug Voriconazole [12].

Ganguly and coworkers reported the synthesis of 3-(methylidene amino)-2-phenyl quinazolin-4(3H)-one (11) and 2-phenyl-3-{(E)-[(2E)-3-phenylprop-2-en-1-ylidene] amino} quinazolin-4(3H)-one (12). These compounds showed potent antibacterial activity against *S. aureus, B. subtilis and E. coli* [13]. A series of 2-benzyl-3-{4-[N-(3-substituted-1, 5-dihydro pyrazole-4-yliene) hydrazino] phenyl}-3H-quinazoline-4-one derivatives were synthesized and screened for their antibacterial and antifungal activity against pathogenic bacteria and pathogenic fungus. Antimicrobial results indicated that compound (13) showed significant activity [14].

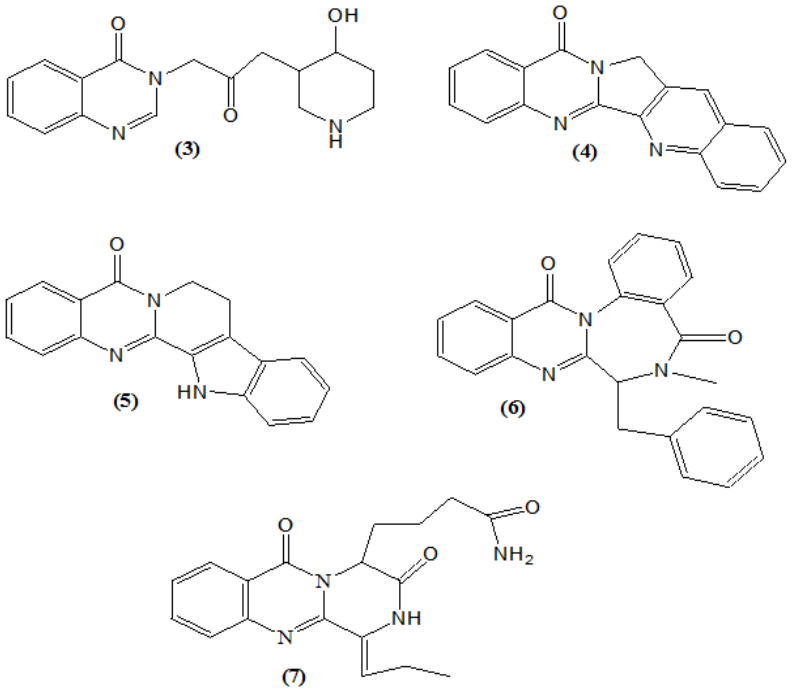

Fig. 2: Some naturally occurring quinazolin-4-one compounds

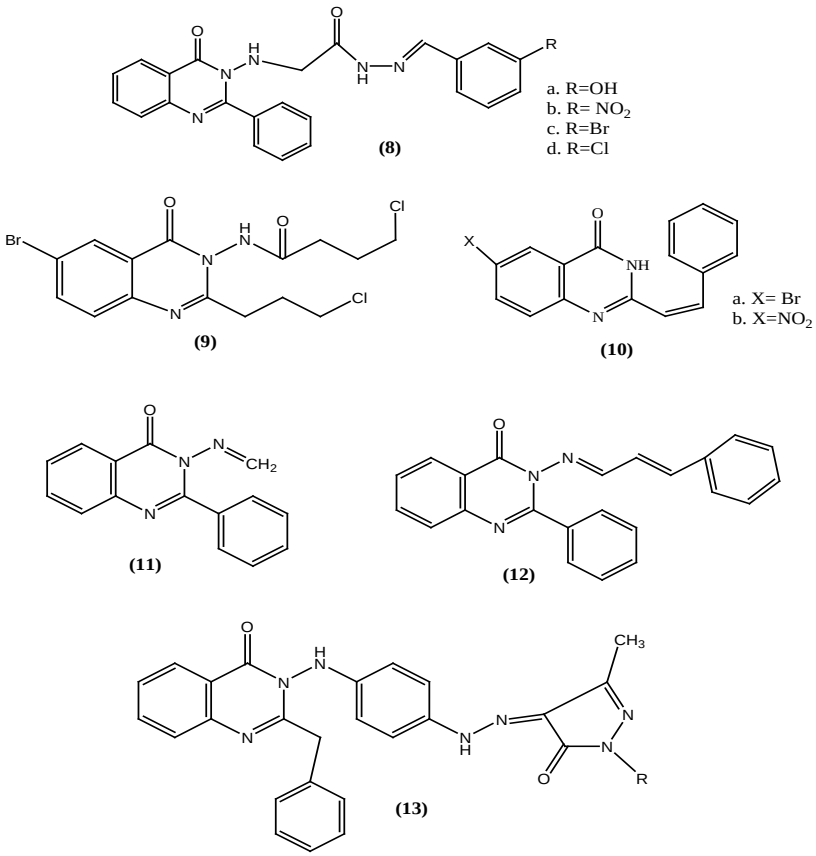

Fig. 3: Compounds with Quinazolin-4-one scaffold reported to possess antimicrobial activities

Siddappa *et al.* Reported the synthesis and antimicrobial activity of 3-[(2-hydroxy-6-methoxyquinolin-3-ylmethylene) amino]-2-methyl-3H-quinazoline-4-one (14) against selected fungi and bacteria [15]. N-(4-Oxo-2-substituted phenylquinazolin-3 (4H)-yl)-2-[(5-aryl-1, 3, 4-oxadiazol-2-yl) sulfanyl] acetamides were synthesized and antibacterial and antioxidant activities were performed by agar diffusion and DPPH method. Compounds (15a) and (15b) showed good antibacterial and moderate antioxidant activities [16].

Osman *et al.* reported the synthesis of 4-(4–oxo–3, 3–(dibenzamido)–3, 4–dihydroquinazolin–2–yl) phenyl–4–methyl benzenesulfonate [16] and 4-(3, 3–diacetamido–4–oxo–3, 4–dihydroquinazolin-2-yl) phenyl-4-methyl benzene sulfonate [17]. The prepared compounds exhibited good antimicrobial activities [17]. Ethyl-2-((2-methyl-4-oxoquinazolin-3(4H)-yl)diazenyl)-3-oxobutanoate [18] was synthesized and reported for *in vitro* antimicrobial activity against a number of microorganisms (*Staphylococcus aureus, E. coli, Proteus vulgaris, Pseudomonas*, and *Klebsiella*) and two fungal *Aspergillus niger* and *Candida albicans* [18]. Akhi *et al.* synthesized 2, 3-disubstituted quinazolin-4-(3H)-ones as one pot procedure from the reaction of anthranilic acid, acid chlorides and primary amines with the intermediate 4-(3H)-benzoxazinone at different microwave conditions. Compound (19) showed good activity against *E. coli* [19].

Novel 6, 8-dibromo-4(3H) quinazolinone derivatives have been synthesized and among them, compound 2-4-(2-phenyl-6, 8-dibromo-4-oxo(4H)quinazolinyl-N-ethyl amido benzoic acid hydrazide (20a) was found to exhibit the most potent *in vitro* antimicrobial activity against *E. coli, S. typhimurium, L. monocytogenes, S. aureus*, *P. aureginosa and B. cereus*. 2-4-(2-phenyl-6, 8-dibromo-4-oxo(4H) quinazolinyl-N-methylthioamido benzoic acid hydrazide (20b) was found to exhibit most potent *in vitro* antifungal activity against *C. albicans and A. flavus* [20]. Deepthi Kohli and coworkers synthesized N-(4-oxo-2-phenylquinazolinyl)-2-phenoxy acetamide derivatives and evaluated for their antibacterial activity by cup plate method by measuring inhibition zone. Compounds (21a) and (21b) showed more potent antibacterial activity than the standard drug Ampicillin [21].

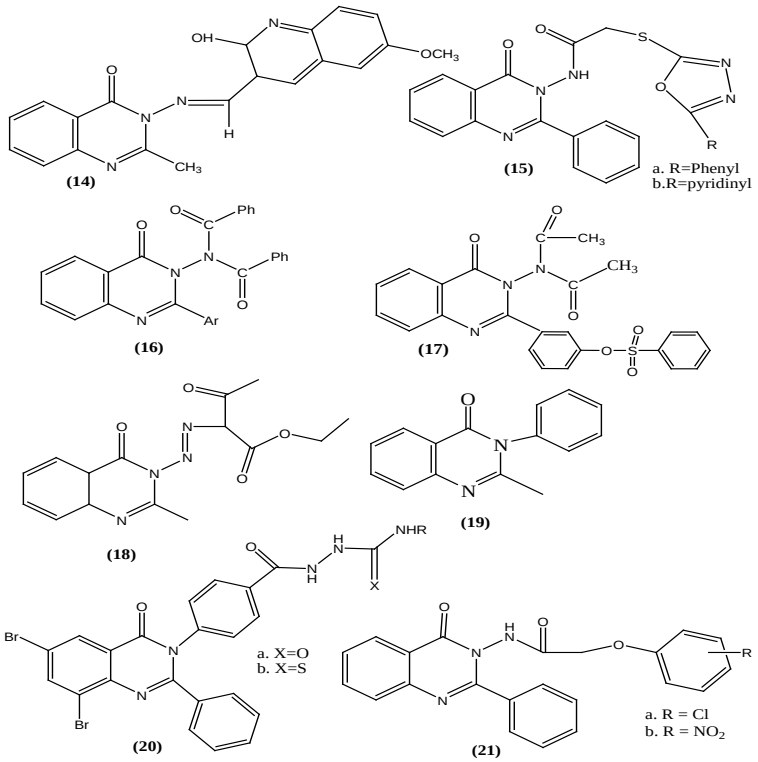

Fig. 4: Compounds with Quinazolin-4-one scaffold reported to possess antimicrobial activities

Antibacterial activities and antiradical activities against frequently used standards of free radicals 2, 2-diphenyl-1-picrylhidrazyl and galvinoxyl were found with compounds (22) and (23) comparable with those of well known antioxidant butylated hydroxytoluene [22]. 4, 6-disubstituted quinazoline derivatives were found with good antimicrobial and antifungal activities [23]. Various quinazolinone derivatives containing thiazole and thiazolidine moiety such as compounds (24a-e) exhibited potent antimicrobial activity against *S. aureus, E. Coli, B. subtilis, A. niger and C. albicans* [24].

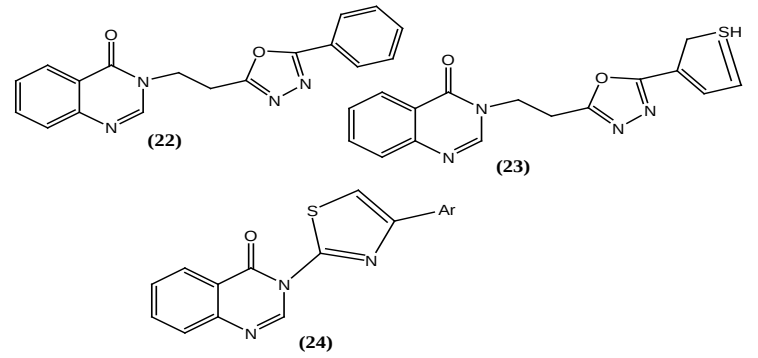

Fig. 5: Compounds with Quinazolin-4-one scaffold reported to possess antimicrobial activities

Anti-inflammatory and Analgesic activities (fig. 6)

A series of 3-(4-substituted phenyl or 4-fluorophenyl)-6-iodo-4-oxo-3, 4-dihydro-quinazoline derivatives was synthesized and screened for anti-inflammatory and analgesic activities and among them (25a) and (25b) were found to exhibit significant activities [25]. N-([1-(substitutedamino) methyl)-2-oxoindolin-3-ylidene)]4-(2-(methyl/ phenyl)-4-oxo-quinazolin-3-(4H)-yl) benzohydrazide derivatives were designed and synthesized from anthranilic acid. All the synthesized compounds (26a-c) exhibited good anti-inflammatory and analgesic activities compared to dicofenac and aspirin [26].

A series of 2-substituted-3H-quinazolin-4-one derivatives were designed and synthesized from anthranilic acid. All these compounds were characterized and screened for anti-inflammatory and antifungal activities. Compounds (27a) and (27b) exhibited significant anti-inflammatory activity after both 2 hrs and 4 hrs [12]. A series of 2-phenyl-4(3H) quinazolinone derivatives have been synthesized. Most of the tested quinazolinone derivatives showed considerable potent anti-inflammatory and analgesic activity of superior GIT safety profile in experimental rats in comparison to indomethacin as reference drug. Compounds (28a) and (28b) were found to be the most potent [27]. Mariappan *et al.* synthesized and reported anti-inflammatory activity of (29) 2-phenyl-3-(propylideneamino) quinazolin-4(3H)-one [28]. A series of novel 2-benzylamino-3-substituted quinazolin-4(3H)-ones have been synthesized by treating 3-amino-2-benzylamino quinazolin-4 (3H)-one, with different aldehydes and ketones. The title compounds were investigated for analgesic and anti-inflammatory activities. Compounds (30a-c) exhibited significant analgesic activity [29].

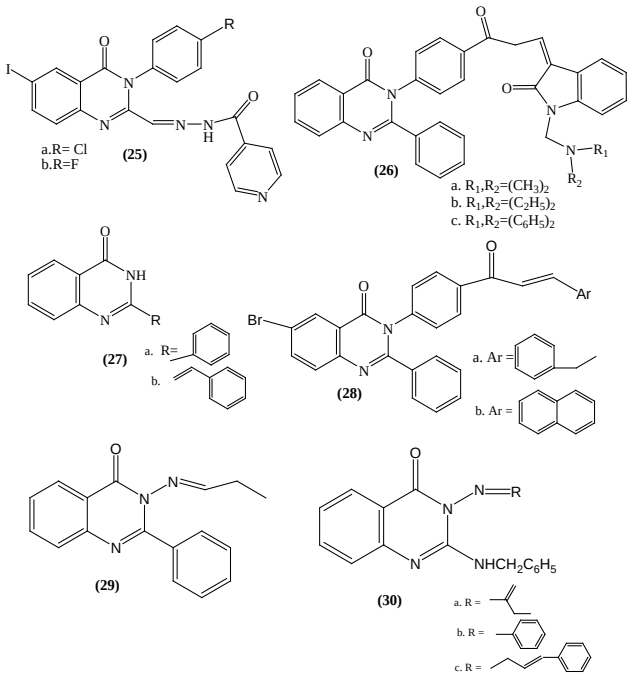

Fig. 6: Compounds with Quinazolin-4-one scaffold reported to possess analgesic and anti-inflammatory activities

Antioxidant activities (fig. 7& 8)

A series of 3-substituted schiff bases of quinazoline-2, 4-dione have been synthesized from the reactions of quinazoline-2, 4-dione with substituted aromatic aldehydes. DPPH inhibition potential and FRAP (Ferric reducing antioxidant power) assay were carried out using *in vitro* models. Compounds (31a-e) showed dose-dependent antioxidant activities [30]. A series of novel glutamine linked 2, 3-disubstituted quinazolinone conjugates was synthesized which showed potent radical scavenging activity against 2, 2-diphenyl-1-picrylhydrazyl, hydroxyl, nitric oxide, and superoxide radical scavenging assays [31].

Kiruthiga *et al.*, reported the synthesis and biological activity of 3-(4-benzoimidazolyl phenyl)-2(2-phenylamino) ethyl) quinazolin-4-one (32). The biological screening showed that, many of these synthesized compounds dispayed good antioxidant activity by hydrogen peroxide scavenging method and antimicrobial activity by turbidimetric method [32]. A study reported the successful synthesis and antioxidant activities of a series of 2, 3-disubstituted-quinazolin-4-ones (33). These compounds were further studied for cytotoxic activities [33]. Govindraj *et al.* reported the synthesis and anti-oxidant activity of 6, 8-Dibromo-2-phenyl-3-(4-phenylthiazol-2-yl)–quinazolin-4-one [34].

A series of new compounds were prepared by condensation reaction of 3-amino-2-methyl-4(3H) quinazolinone (34) with different substituted aromatic aldehydes in methanol. They were also evaluated for their antioxidant activities and the results suggest that few of the synthesized compounds showed better scavenging activity [35]. Al Omar reported the synthesis of quinazolinone derivative, 1-(6-iodo-4-oxo-2-propylquinazolin-3(4H)-yl) urea (35) and reported its antioxidant activity [36].

Novel quinazolinones functionalized with urea/thiourea/thiazole derivatives such as compounds (36), (37) and (38) were synthesized and evaluated for their antioxidant and 5-lipoxygenase (5-LOX) inhibition activities were found to be very effective[37].

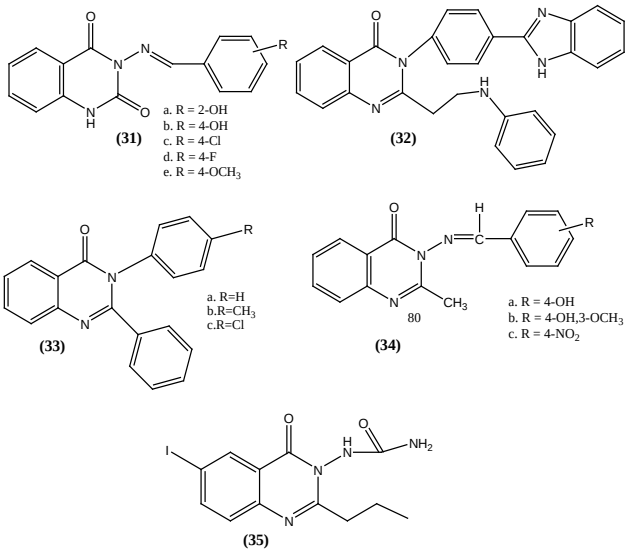

Fig. 7: Compounds with Quinazolin-4-one scaffold reported to possess antioxidant activities

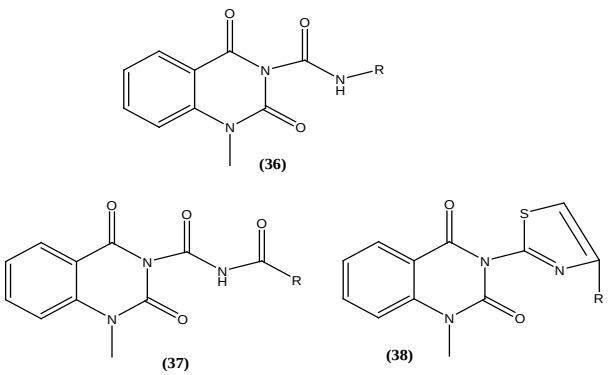

Fig. 8: Compounds with Quinazolin-4-one scaffold reported to possess antioxidant activities

Cytotoxic activities (fig. 9&10)

Therapeutic potential of novel nonclassical antifolate, 2-[N-(2′-Hydroxyethyl) amino] methyl-3H-quinazolin-4-one (HEAMQ) (39) towards human promonocytic U937 and murine lymphoblastic L1210 cell lines was studied. Results indicated that HEAMQ antineoplastic activity toward leukemia cells is associated with cell cycle arrest and apoptosis. The *in vivo* studies further confirmed the antitumor activity of HEAMQ and highlighted that this agent could be used to further increase therapeutic efficacies of traditional chemotherapeutic agents [38]. The cytotoxic effects of some new 2, 3-disubstituted-4(3H)-quinazolinone derivatives have been evaluated against HeLa cells (Human cervix carcinoma cell line) using the MTT (tetrazolium dye) colorimetric assay. Compounds (40a) and (40b) reduced cell viability to about 50% at 100 µM concentrations [39].

A series of some new 2, 3-disubstituted-6-iodo-3H-quinazolin-4-one derivatives was prepared and screened for their *in vitro* antitumor activity against the human breast cancer cell line (MCF-7), human cervix carcinoma cell line (HeLa), human liver cancer cell line (HepG2) and human colon cancer cell line HCT-8. Compound (41) exhibited potent activity [40]. 3-(2-chloro benzylidene amine)-2-(furan-2-yl) quinazoline-4(3H)-one (42) was found to be the most active candidate of the series at five dose level screening against Ovarian OVCAR-4 and Non-small cell lung cancer NCI-H522. Rational approach and QSAR techniques enabled the understanding of the pharmacophoric requirement [41].

The synthesis of some new 2-thieno-4(3H)-quinazolinone derivatives and their biological evaluation as antitumor agents using the National Cancer Institute disease oriented antitumor screen protocol was investigated. Compound 2-(2-thieno)-6-iodo-3-phenylamino-3, 4-dihydro quinazolin-4-one (43) was proved to be the most active members in this study [42].

Two new synthesized and characterized quinazoline Schiff bases (44) and (45) were found to be very active when investigated for anticancer activity against MCF-7 human breast cancer cell line [43]. Synthesis and *in vitro* evaluation of some quinazolinone derivatives (46) and (47) resulted in good Dihydro Folate Reductase (DHFR) activity compared to that of methotrexate. Some new Mannich bases of quinazolinone such as compounds (48a&b) exhibited possible good anti-prostate cancer activity during the docking studies [45].

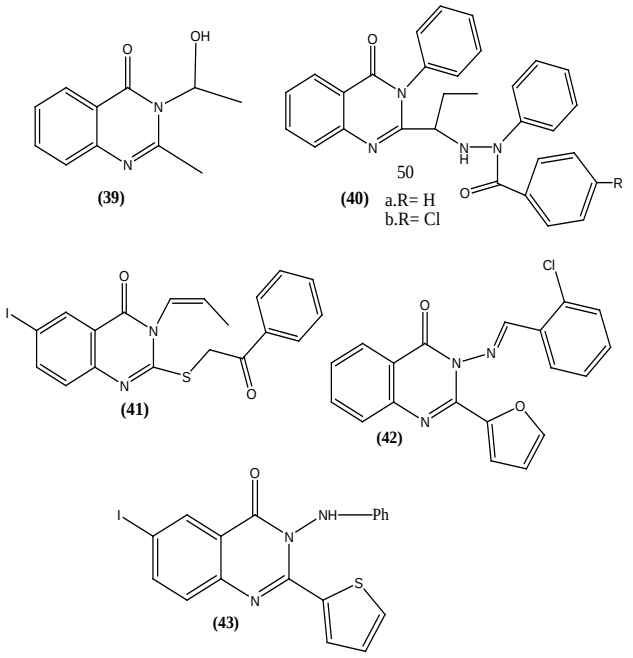

Fig. 9: Compounds with Quinazolin-4-one scaffold reported to possess cytotoxic activities

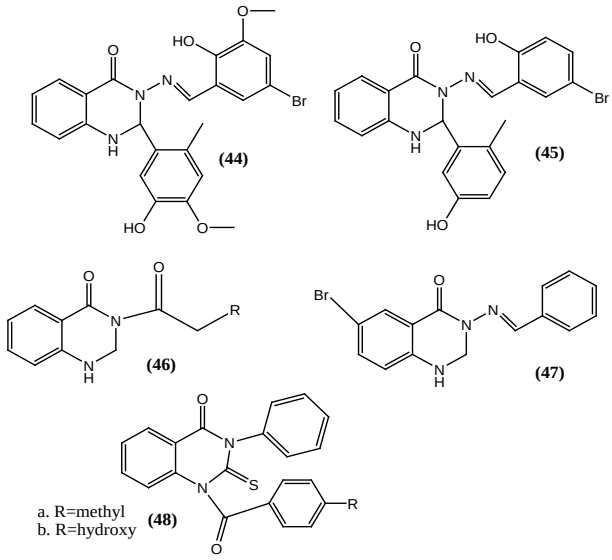

Fig. 10: Compounds with Quinazolin-4-one scaffold reported to possess anticancer activities

Anticonvulsant activities (fig. 11)

Novel 3-substituted-6-fluro-2-methyl-quinazolin-4(3H)-one derivatives were synthesized and tested for anticonvulsant activity. All the newly synthesized compounds had significant anticonvulsant activity. Three compounds showed promising activity, while the other five compounds had moderate activity. All compounds tested for neurotoxicity showed a good safety margin. In silico design, synthesis and pharmacological screening of novel mono bromo quinazolinone derivatives as NMDA receptor antagonists for anticonvulsant activity was reported. Compounds **(**49a &b**)** gave good results [46].

Ponnilavarasan ilangovan *et al.* synthesized a series of 3-N'(benzylidene semicarbazone)-2-phenyl 3H-quinazolin-4-one and evaluated for anticonvulsant and neurotoxicity. Compound (50) displayed potent activity [47]. Schiff bases of 3-amino-6, 8-dibromo-2-phenyl-quinazolin-4-(3H)-ones with various substituted aldehydes were synthesized and evaluated for their anticonvulsant activity on albino mice by maximal electroshock method using phenytoin as a standard. The compound (51) bearing a cinnamoyl functionality displayed a very high activity [48].

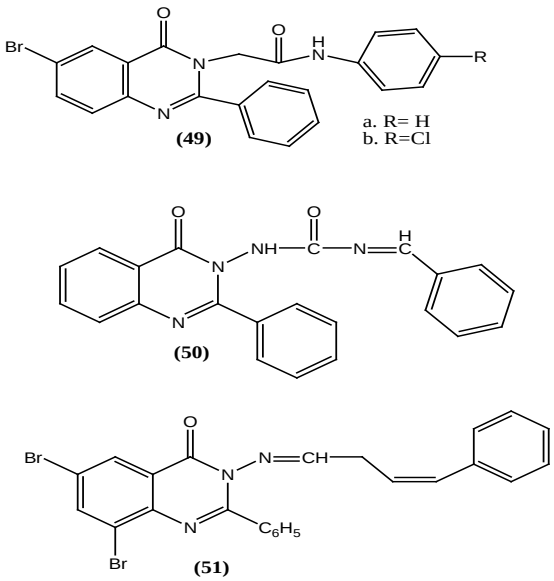

Fig. 11: Compounds with Quinazolin-4-one scaffold reported to possess anticonvulsant activities

Antiviral activities (fig. 12)

Among the synthesized 3-(benzylideneamino)-2-phenyl quinazoline-4(3H) ones, compound (52) was found to inhibit viral replication of para influenza-3virus, retrovirus-1, Coxsackie virus B4, Punta Toro virus *in vitro* cell cultures [49]. Saravanan *et al.* reported the synthesis and antiviral activity of a series of 2-phenyl 3-substituted quinazolin-4(3H) ones, among them compound (53) displayed potent antiviral activity [50].

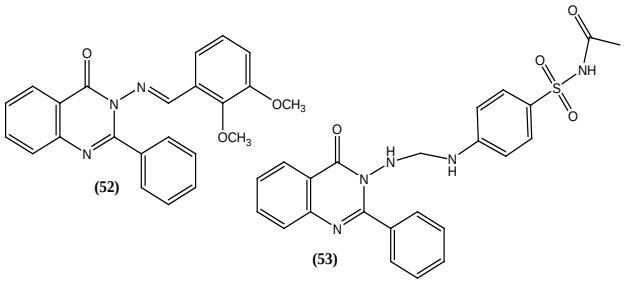

Fig. 12: Compounds with Quinazolin-4-one scaffold reported to possess antiviral activities

CONCLUSION

Quinazolinone nucleus has been gaining prominence due to the fact that its derivatives have been found to possess the wide spectrum of activities. This review is an effort to incorporate literature citations appeared during the past four years and considered as a potential moiety possessing myriad spectrum of antimicrobial, analgesic, anti-inflammatory, antioxidant, cytotoxic, antiviral etc. Its derivatives are central to the chemistry and biology of many therapeutically useful compounds and are also versatile synthetic building blocks and precursors for the generation of many biologically active molecules. Diversity of biological response profile of these moieties coupled with their applications in various active pharmaceutical ingredients has attracted considerable interest and demands the synthesis of highly substituted quinazolinone derivatives as promising future drugs.

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CONFLICT OF INTERESTS

Declared None

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