RECENT ADVANCES OF QUINAZOLINONE DERIVATIVES AS MARKER FOR VARIOUS BIOLOGICAL ACTIVITIES

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ABSTRACT

Heterocyclic chemistry comprises at least half of all organic chemistry research worldwide. Quinazolinone and its derivatives constitute an important class of heterocyclic compounds. The chemistry of quinazoline compounds has more than centuries old history; however the intense search for biologically active substances in this series began only in the last few decades. In this present communication an attempt is made to cover the medicinally active compounds, along with the recent discoveries, which were reported to possess various biological activities.

Keywords: Quinazolinone, pharmacological activity, Heterocyclic, Quinazoline

INTRODUCTION

An introduction to Medicinal Chemistry gives us a very detailed look at the world of medicine¹. Principles of medicinal chemistry is necessary to consider physicochemical properties, used to develop new pharmacologically active constituents and their mechanism of action and many of them are entered to pharmacological screening for determining their biological activity. This random screening process has been inefficient, but it has resulted in identification of new lead compounds whose structures have been optimized to produce clinical agents². A rich tradition of analog design strategies has evolved for creating new compounds within medicinal chemistry research for biological evaluation³.

Heterocyclic chemistry is a chemistry involving the heterocyclic compounds, which has atoms of at least two different elements as number of ring. The heterocyclic atoms may be inorganic, though the compound contains carbon atoms in the ring. The word hetero means “different from carbon and hydrogen”². Heterocyclic chemistry comprises at least half of all organic chemistry research worldwide. In particular, heterocyclic structures form the basis of many pharmaceutical, agrochemical and veterinary products⁴. Heterocyclic chemistry is a potential part of the synthetic organic chemistry, covering a wide variety of bioactive molecules. Among six-membered heterocycles, quinazoline occupies significant position and is commonly found in a wide variety of natural products, synthetic pharmaceutical molecules, and other functional materials⁵. The critical role played by heterocycles in drug design cannot be denied. Even where the natural substrate or ligand for a biological target does not contain a heterocycle, drugs whether of natural or man-made origin that act on that target frequently contain heterocyclic groups⁶. The aim of this review is to highlight the wide range of developments displayed by Quinazolinone Derivatives which have been found to possess wide spectrum of activities such as anti-inflammatory, antioxidant, antimicrobial, antipsychotic, antihypertensive⁷⁻¹¹. Quinazolinone (Figure 1) is a building block for approximately 150 naturally occurring alkaloids isolated to date from a number of families of the plant kingdom, from animals and from microorganisms such as *Bacillus cereus*,

Bouchardatia neurococca, *Dichroa febrifuga*, and *Peganum nigellastrum*¹²⁻¹⁵.

Structure and Chemical Reactivity

The first quinazolinones (1) was synthesized in the late 1860s from anthranilic acid and cyanogens to give 2-cyanoquinazolinone (2) Methaqualone (3) was synthesized for the first time in 1951 and it is the most well known synthetic quinazolinone drug, famous for its sedative-hypnotic effects¹⁶. Proquazone a derivative of quinazoline-2-one exhibits potential NSAID potential which has been used in the disease conditions like rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, musculoskeletal disorders, acute inflammatory conditions and acute pain states such as dysmenorrhoea, postoperative pain and headache⁵³.

Quinazolinone is heterocyclic chemical compound with two conjoined aromatic rings incorporating with two nitrogen atoms and one of the carbons oxidized with keto oxygen. It is also called as quinazolinones, chemically known as Quinazolin-4(3H)-one¹⁷. There are two structural isomers, 2-quinazolinone (4) and 4-quinazolinone (5), with the 4-isomer being the more common.

Isomers of quinazolinones

The name quinazoline (German: Chinazolin) was first proposed for this compound by **Weddige**, on observing that this was isomeric with the compounds cinnoline and

quinoxaline. and many derivatives of quinazoline system known so far, keto-quinazolines also called as quinazolinones, are the most important compounds¹⁸. Depending upon the position of the keto or oxo group, these compounds may be classified into two types:

1. 2-(1*H*) quinazolinones (or) 1, 2-dihydro-2-oxo quinazolines and
2. 4(3*H*)-quinazolines or 3, 4-dihydro-oxoquinazolines

These systems 1 & 2 exhibit lactam-lactam tautomerism and undergo hydroxyl group replacement reactions. 2-cyano-

4(3*H*)-quinazolinone was the first quinazolinone derivative to be synthesized¹⁹.

3*H*,1*H* and OH tautomers of 4-quinazolinone

Nucleophilic reaction²⁰

Amidation and cyclization

The most common approach involves amidation of 2-aminobenzonitrile with 3-phenylacryloyl chloride followed by oxidative ring closure under basic conditions produced 2-styryl-4(3*H*)quinazolinone²¹.

General methods of Synthesis

Synthesis of 1*H*-quinazolinone 2,4 dione from 2-aminobenzonitrile with 3.0 equivalent of DBU in DMF was performed at room temperature 20°C for 24 hrs²².

Quinazolin-4(3*H*)-one was prepared by heating 2-aminobenzoic acid with formamide at 125-130°C and cyclization takes place as described²³.

Synthetic efforts started from *o*-chlorobenzoic acid, amination, esterification followed by reaction with isocyanates resulted in 1,3-disubstituted quinazolin-2,4-diones²⁴.

Biological activities of Quinazolinone derivatives

Anti inflammatory

Spiro [(2*H*, 3*H*) quinazoline-2, 10-cyclohexan]-4(1*H*)-one

A series of Spiro [(2*H*,3*H*) quinazoline-2,10-cyclohexan]-4(1*H*)-one derivatives have been synthesized in which some novel quinazolinone derivatives showed considerable potent anti-inflammatory and analgesic activity of superior GIT safety profile in experimental rats in comparing to Indomethacin (10mg/kg) and Tramadol (20mg/kg) as reference drugs⁷.

2-Phenyl-4(3*H*) quinazolinones

Derivatives of 2-phenyl-4(3*H*) quinazolinone have been synthesized and most of the tested quinazolinone derivatives showed considerable potent anti-inflammatory and analgesic activity of superior GIT safety profile in experimental rats in comparing to indomethacin as reference drug²⁵.

N- (Pyrimidin-2-yl-benzenesulfonamide) quinazolin-4(3*H*)-one

A series of quinazolinones derivatives exhibited potent anti inflammatory and analgesic activities at dose 50mg/kg *p.o* with the objective of discovering novel and potent anti-inflammatory agent²⁶.

3-(*p*-Substituted phenyl)-6-bromo-4(3*H*)-quinazolinone

Besides the diverse biological activities ascribed to quinazolinones derivatives and enzyme inhibitory effect of several 6-bromoquinazolinones and based on continuation of our drug research program on the development of safe quinazolinones anti inflammatory agents, it was of interest to synthesize a novel series of 6-bromoquinazolin-4(3*H*)-ones incorporated into other heterocyclic moieties such as pyran, pyridine and other ring system to be evaluated for their analgesic and anti-inflammatory activity²⁷.

Antimicrobial activity

2-Oxo-azetidinyl-quinazolin-4(3*H*)-ones

Quinazolinones derivatives are considered as good antimicrobial agents. Most of derivatives were synthesized from schiff bases showing antibacterial activity for example derivatives of 2-oxo-azetidinyl-quinazolin-4(3*H*)-ones. Some possess antibacterial activity against *S. aureus*, *B. subtilis* and *E. coli*. They were also screened for antifungal activity showing maximal activity against *C. albicans* was compared with Amphotericin B as standard drug⁹.

screened for their antibacterial activity against Gram-negative bacteria, *Escherichia coli*, *Pseudomonas aeruginosa* and gram-positive bacteria *Streptococcus pneumoniae*, *Bacillus subtilis*, as well as demonstrated significant antifungal activity against fungi viz. *Candida albicans*, *Aspergillus fumigatus*, *Aspergillus flavus* and *Aspergillus niger*²⁸.

Triazolo[4,3-a]-quinazolin-7-ones

The newly synthesized derivatives triazolo[4,3-a]-quinazolin-7-ones, [1,2,4,5]-tetrazino[4,3-a]-quinazolin-8-ones and indolo[2,3-c][1,2,4]-triazino[4,3-a]-quinazolin-8-ones were

2-Mercapto-3-(4-chlorophenyl)-6-iodo-3H-quinazolin-4-ones

Substituted derivatives was prepared and screened for antimicrobial activity in which various compounds like 30, 31, 32, and 33 showed a remarkably antimicrobial activity and could be useful as templates for further development through modification or derivatization to design more potent antimicrobial agents²⁹.

Antibacterial activity

(4-Oxo-2-phenylquinazolin-3(4H)-yl-amino) derivatives

The newly synthesized quinazolinone derivatives were evaluated for their antibacterial activity by cup plate method against bacterial strains *Staphylococcus aureus* and *Escherichia coli*. Ampicillin was used as standard drug at a concentration 100 µg/ml³⁰.

2-(Substituted styryl)-quinazolin-4(3H)-ones

Among the new derivatives 3-(5-phenyl-1,3,4-oxadiazole-2-yl)-2-(substituted styryl)-quinazolin-4(3H)-ones derivatives evaluated, specific antibacterial activity was performed by cup plate method against bacterial strains *Bacillus subtilis*, *Staphylococcus aureus* (gram-positive), *Escherichia coli* and

Proteus vulgaris (gram-negative) at a concentration of 100 µg/ml. Streptomycin and penicillin were used as standard drugs at a concentration of 100 µg/ml³¹.

4-Oxoquinazolin-3(4H)-yl-N-substituted

Antibacterial evaluation of these compounds was done and synthesized compounds were tested against gram-positive bacteria *Staphylococcus aureus* and *Bacillus cereus*, gram-negative bacteria *E. coli*, *Candida albicans* and *Pseudomonas aeruginosa*. A solution of the standard drug Ampicillin was prepared at the same concentration³².

Antibacterial and Antifungal

6,7-Bis-(arylthio)-quinazolin-5,8-dione and fluoro[2,3-f]quinazolin-5-ol

Derivatives were synthesized and tested for *in vitro* antifungal activity against *Candida*, *Aspergillus* species, and *Cryptococcus neoformans*. Among them tested many of fluoro[2,3-f]quinazolin-5-ols and 6,7-bis(arylthio)-quinazolin-5,8-diones showed good antifungal activity. The compounds (37) completely inhibited the growth of all against *Candida* and *Aspergillus* species tested at the MIC level of 12.5 lg/mL. The results suggest that fluoro [2, 3- f]quinazolin-5-ols and 6,7-bis(arylthio)-quinazolin-5,8-diones would be promising antifungal agents³³.

R1=H, Cl, CH₃, C₂H₅, EtOH

R2=CH₃

R3=F, CH₃O, H, OH

2, 3-Disubstituted quinazolinone derivatives

In vitro antimicrobial activities of synthesized compounds were carried out against two gram-positive bacteria *S. aureus* and *B. cereus* and two gram-negative bacterias *S. marcescens* and *P. merabitis* by using disc diffusion method. Antibacterial activity was screened by measuring the zone inhibition on agar plates using standard Ampicillin whereas antifungal activity was tested by measuring the zone of inhibition on agar plates with two fungal species *A. chraceus* Wilhelm and *P. chrysogenum* Thom and compared with Mycostatin as standard³⁴.

Piperazinyl-Quinazolin-4-one Analogs

The newly synthesized quinazolinones analogs were evaluated for *in vitro* antibacterial and antifungal activity by using broth dilution method against gram negative strains and gram positive strains respectively *E. coli*, *P. aeruginosa*, *Kl.p*= *Kl. pneumoniae*, *S. typhi*, *S. aureus*, *S. pyogenus*, *B. subtilis*. The compounds displayed comparable activity against all standard antibiotics like Gentamycin, Ampicillin, Chloramphenicol³⁵.

Antioxidant

6-Iodo-2-propyl-4(3H)-quinazolinone

A new series of 6-iodo-2-propyl-4(3H)-quinazolinone and its fused heterocyclic were prepared and evaluated that various derivatives inhibit aldehyde oxidase exclusively by more than 98% for their antioxidant activity. This type of inhibition was found to be competitive with Ki value ranging from 50-400 mM with respect to aldehyde oxidase⁸.

Antipsychotic

Quinazolidin-4(3H)-one & 2-phenyl-2,3-dihydrophthalazine-1,4-dione or 1-phenyl-1,2-dihydropyridazine- 3,6-dione

On the basis of systematic studies on the structure-activity relationships in aryl piperazine group of serotonin ligands,

various new derivatives containing quinazolidin-4(3H)-one and 2-phenyl-2,3-dihydrophthalazine-1,4-dione or 1-phenyl-1,2-dihydropyridazine- 3,6-dione fragments were synthesized and the dual 5-HT1A/5-HT2A receptor ligand was further tested for its potential psychotropic activity which showed a distinct anxiolytic-like activity in a conflict drinking test in

rats and the observed effect was more potent in terms of the active dose, than that produced by diazepam used as a reference drug¹⁰.

(42)

Thiadiazole-2-styryl quinazoline-4(3H)-ones

A series of novel 3-[5-substituted phenyl-1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones were synthesized and evaluated for anticonvulsant, sedative-hypnotic and CNS depressant activities at doses of 30, 100, and 300 mg/kg body weight and examined that 2-styrylquinazolin-4(3H)-one derivatives were the most potent were examined in the maximal electroshock induced seizures (MES) and subcutaneous pentylenetetrazole induced seizure models in mice. The neurotoxicity was assessed using the rotorod method and few compounds exhibited anticonvulsant activity and sedative-hypnotic activity respectively and from the experimental observation it was concluded that synthesized compounds exhibited relatively better sedative-hypnotic and CNS depressant activities³⁶.

(43)

2-(Substituted)-3-[[substituted]amino}quinazolin-4(3H)-one

Thirty new 2-(substituted)-3-[[substituted]amino}quinazolin-4(3H)-one were designed and synthesized keeping in view the structural requirement of pharmacophore and evaluated for anticonvulsant activity and neurotoxicity and the most active compound of the series was 3-((E)-[3-(4-chloro-3-methylphenoxy)phenyl]methylidene)amino)-2-phenylquinazolin-4(3H)-one, which showed 100% protection (4/4, 0.5 h) and 75% protection (3/4, 0.25 h) at a dose of 100 mg/kg in mice³⁷.

(44)

Ar=2-ClC₆H₅
2-NO₂C₆H₅

R=H, CH₃

(45)

R=H, CH₃, C₂H₅

3-[5-Substituted phenyl-1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones

A series of new 3-[5-substituted phenyl-1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones were synthesized and evaluated for anticonvulsant, sedative hypnotic and CNS depression activities. After *i.p.* injection to mice or rat at doses of 30, 100, and 300 mg/kg body weight. 2-styryl quinazolin-4(3H)-ones derivatives were examined in the maximal electroshock induced seizures and subcutaneous pentylenetetrazole induced seizure models in mice and only few of compounds showed anticonvulsant activity in one or more test models. Amongst all compounds some exhibited significant sedative hypnotic activity via actophotometer screen. Therefore it was concluded that synthesized compounds exhibited better sedative-hypnotic and CNS depressant activities than anticonvulsant activity³⁸.

(46)

Ar= *p*-ClC₆H₄

m-C₆H₄

R= C₆H₅
p-OCH₃C₆H₄
m-ClC₆H₄
-C₆H₄

1-(4-Substituted-phenyl)-3-(4-oxo-2-phenyl/ethyl-4H-quinazolin-3-yl)-urea

Several new 1-(4-substituted-phenyl)-3-(4-oxo-2-phenyl/ethyl-(4H)-quinazolin-3-yl) urea were synthesized and

screened for anticonvulsant, CNS depressant and sedative-hypnotic activity in the mice. After *i.p.* injection to mice at doses of 30, 100, and 300 mg/kg body weight and synthesized compounds were examined in the maximal electroshock induced seizures (MES) and subcutaneous pentylenetetrazole (induced seizure models in mice. All the compounds were found to exhibit potent CNS depressants activity as indicated by increased immobility time. It was concluded that newly synthesized compounds possessed promising CNS activities³⁹.

3-(Substitutedbenzo[d]thiazol-2-yl)quinazolin-4(3H)-one

A series of 6-bromo-2-ethyl-3-(substituted benzo [d] thiazol-2-yl)quinazolin-4(3H)-one were synthesized using appropriate synthetic route and evaluated experimentally by the Maximal Electro Shock and the PTZ-induced seizure methods. Among the tested compounds, 3-(benzo[d]thiazol-2-yl)-6-bromo-2-ethylquinazolin-4(3H)-one has shown significant activity against tonic seizure and 6-bromo-2-ethyl-3-(6-methoxybenzo [d] thiazol-2-yl)quinazolin-4(3H)-one against clonic seizure without any sign of neurotoxicity and hepatotoxicity by PTZ-induced seizure model⁴⁰.

Anticonvulsant

Thiadiazolyl and Thiazolidinonyl quinazolin-4(3H)-ones

A series of 3-{[5-(alkylbenzylideneamino)-1,3,4-thiadiazol-2-yl]methylamino}-2-methyl-6-monosubstituted quinazolin-4(3H)-one have been synthesized and examined by Supra maximal electroshock seizure pattern test by using test drugs or phenytoin sodium 30 mg/kg *i.p.* and Pentylenetetrazole seizure pattern test with pentylenetetrazol in dose of 70 mg/kg *s.c.* in scruff of neck. The compounds were screened for their anticonvulsant activity and were compared with the standard drugs, phenytoin sodium, lamotrigine and sodium valproate standard drug used in this model was sodium valproate (74 mg/kg *i.p.*)⁴¹.

Substituted quinazolinones semicarbazones

The search for new anticonvulsant drugs continues to be an active area of investigation in medicinal chemistry. The present study describes the synthesis of newer quinazolinone derivatives and their anticonvulsant activities. The newly synthesized compounds were evaluated *i.p.* into the mice in the maximal electro shock, subcutaneous strychnine threshold test, using doses 30, 100, 300 mg/kg, and neurotoxicity screens, observation was carried out at two different time intervals by using phenytoin as standard drug⁴².

3H-Quinazolin-4-one

A new series of 3-substituted (methyl, ethyl or phenyl)-3H-quinazolin-4-one derivatives were synthesized and evaluated for anticonvulsant activity and are shown to possess highest anticonvulsant activity at low doses (50–100 mg/Kg), whereas at doses over 100 mg/Kg and they showed a stimulant effect on the central nervous. A series of halogenated derivatives, 3-methyl, 3-ethyl and 3-phenyl-6-mono and 6,8-disubstituted-3H-quinazolin-4-one derivatives was also synthesized and evaluated for anticonvulsant activity and reduced anticonvulsant activity was recorded. Phenobarbitone sodium was used as a reference drug⁴³.

Substituted 2-mercapto-4-(3H)-quinazolinone analogs

A new series of 2-mercapto-3-(4-chlorophenyl)-4-oxo-6-iodoquinazolinone was synthesized and their anticonvulsant activities have been examined using the PTZ-seizure threshold test at 200 mg/kg dose/level by using pentylenetetrazole as reference drugs⁴⁴.

53a: X=H
53b: X=tetrabromo
53c: X=tetrachloro

Antihypertensive

3-Substituted quinazoline 2,4-dione

Quinazolinone and quinazolinone derivatives are of considerable interest due to their wide array of pharmacological properties. The previous isolation of two of these compounds, namely 1-methyl-3-(2'-phenylethyl)-1*H*,3*H*-quinazoline-2,4-dione and 1-methyl-3-[2'-(4'-methoxyphenyl)ethyl]-1*H*,3*H*-quinazoline-2,4-dione, from the seed husks of Mexican *Zanthoxylum* species has been reported¹¹.

Quinazoline-2,4-dione

This wide range of biological activities has stimulated interest in new approaches for the synthesis of quinazoline-2,4-dione derivatives⁴⁵.

(55)

(56)
R=H, OCH₃

Quinazoline-2,4-diones

One of the important heterocycles and have been shown to possess pharmacologically interesting properties such as anti-hypertensive, antidiabetic, and immunosuppressive activities. Among these, synthetic pelanserine is a well established potent anti-hypertensive, having activity comparable to ketanserine⁴⁶.

(57)
R=H, OCH₃

Quinazoline-4(3*H*)-ones

Derivatives are considered showed good cytotoxicity and antiviral activity and most of derivatives showing cytotoxicity and antiviral activity for example derivatives of 3-(benzylideneamino)-2-phenylquinazoline-4(3*H*)-ones were evaluated against *herpes simplex* viruses-1, *herpes simplex virus*-2, *vaccinia virus*, *vesicular stomatitis virus*, *herpes simplex virus*-1 TK- KOS ACVr, *para influenza*-3 virus, *reovirus*-1, *Sindbis virus*, *Coxsackie virus* B4, *Punta Toro virus*, *feline corona virus* (FIPV), *feline herpes virus*, *respiratory syncytial virus*, *influenza A H1N1* subtype, *influenza A H3N2* subtype, and *influenza B virus* and Compound 2a showed better antiviral activity against the entire tested virus⁴⁷.

(58)

Quinazolinone derivatives

Newly synthesized quinazolinones derivatives (59) with various substitution like with piperazine on acylation gave 2-(piperazin-1-yl-methyl)quinazolin-4(3*H*)-one (59) and further alkylation and acylation of 59a resulted in the formation of compounds (59b-f) which were evaluated for their anti-cancer activity by MTT assay method and compounds 59b, 59c and 59f showed more potent anti-cancer activity⁴⁸.

R
a=H,
b=Acetyl,
c=Propionyl,
d=Isobutryl,
e=Heptanoyl,
f=Ethyl

2-Furano-4(3*H*)-quinazolinones

It was of interest to synthesize 4(3*H*)-quinazolinones incorporated into another heterocyclic moiety such as furan ring system i.e 2-furano-4(3*H*)-quinazolinones to be evaluated as antitumour activity and synthesis of diamides (open ring quinazolinones), quinoxalines and their biological evaluation as antitumor agents among the various compounds the anticancer activity at single high dose was selected for compound 3-(2-chloro benzylidinamine)-2-(furan-2-yl)quinazoline-4(3*H*)-one was found to be the most active candidate of the series at five dose level screening against Ovarian and Non-small cell lung cancer respectively⁴⁹.

2-Chloromethyl-4(3H)-quinazolinones

A series of novel 2-chloromethyl-4(3H)-quinazolinones were needed as key intermediates based on it, 2-hydroxymethyl-4(3H)-quinazolinones were conveniently prepared in one pot moreover, two novel 4-anilinoquinazoline derivatives substituted with chloromethyl groups at the 2-position were synthesized and showed promising anticancer activity⁵⁰.

4-Quinazolinone

2-(3-methoxyphenyl)-6-pyrrolidinyl-4-quinazolinone was selected as the lead compound. In our continuing search for potential anticancer candidates. These target compounds were assayed for their cytotoxicity *in vitro* against six cancer cell lines, including human monocytic leukemia cells, mouse monocytic leukemia cells, human hepatoma cells and human lung carcinoma cells. Most of them exhibited significant cytotoxic effect, with EC₅₀ values ranging from 0.30 to 10.10 M. Preliminary findings indicated that compound 68 induced G₂/M arrest and apoptosis on cells⁵¹.

3-(Substituted benzylideneamino)-7-chloro-2-phenyl quinazoline-4(3H)-one

A series of novel 3-(substituted benzylideneamino)-7-chloro-2-phenyl quinazoline-4(3H)-one derivatives has been synthesized and observed that 3-amino 7-chloro-2-phenyl quinazolin-4(3H)-one and 7-chloro-3-[(4-chlorophenyl)methylidene] amino]-2-phenylquinazolin-4(3H)-one, showed remarkable activity against CNS Cancer cell line⁵².

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