IJBPAS, August, 2023, 12(8): 3565-3578

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

REVIEW ON SYNTHESIS AND BIOLOGICAL EVALUATION OF QUINAZOLINES DERIVATIVES

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Received 16th Sept. 2022; Revised 25th Oct. 2022; Accepted 15th Nov. 2022; Available online 1st Aug. 2023

https://doi.org/10.31032/IJBPAS/2023/12.8.7335

ABSTRACT

The heterocyclic compounds have great importance in medicinal chemistry. One of the most important heterocyclic compounds in medicinal chemistry are quinazoline derivatives they have wide variety of pharmacological activity are anti-microbial, anti-cancer analgesic, anti-HIV, anti-convulsion activity. In this review we are highlighting the recent marketed released drugs, preparation methods and biolocial activities.

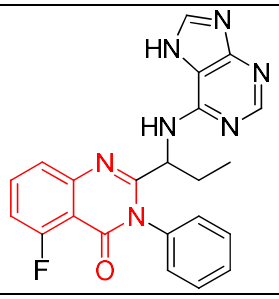
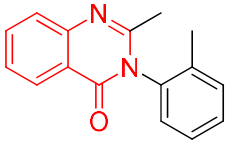
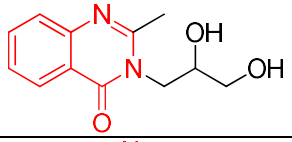
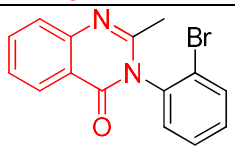
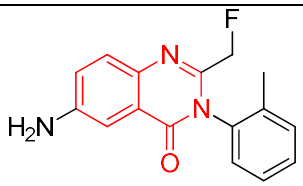
Keywords: Quinazoline, Antimicrobial, Cytotoxic, antioxidant

1. INTRODUCTION

The name of quinazoline was first given by Weddige as he observed that it is isomeric with two compounds i.e cinnoline and quinoxaline. Chemically, quinazoline constitutes an important class of fused heterocycles six membered (benzene and pyrimidine) rings **[1]**. It is having a molar mass of 146.149gms/mole. It has numerous different names like 4(3H)- Quinazolinone; 4(1H)- Quinazolinone; 3,4-Dihydroquinazolin-4-one; 4(3H)-Quinazolone;4-Hydroxyquinazoline; 4-oxo-3,4 dihydroquinoline.

1.1. Marketing drugs:

1.1.General properties of quinazolines:

Brand name	Drug name	Structure
Zydelig	**Idelalisib**	
Quaalude	**Methaqulone**	
Zaleplan	**Diproqualone**	
Mandrax	**Mebroqualone**	
Arofuto	**Afloqualone**	

1.2. General formula: $C_8H_6N_2O$

Quinazolinones are generally hetero cyclic compounds contain oxygen attached to quinoline at 4th position.

Other names of quinazolinones are 4-oxoquinazoline, 4-quinazolinol, 4-quinazolinone.

State: Solid

Melting point: 217.5ºC

Boiling point: 303.5ºC

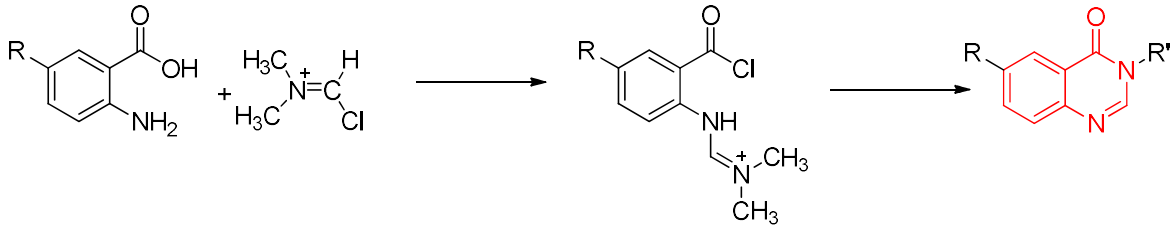
Refractive index: 1.666

Colour: Blue

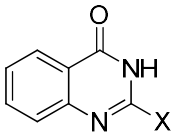
Solubility: Soluble in cold dil. acid and alkaline solution and destroyed when heated with the acid or alkaline solutions.

2.0. Preperation of quinazoline:

2.1 General procedure for synthesis of quinazolinone derivatives:

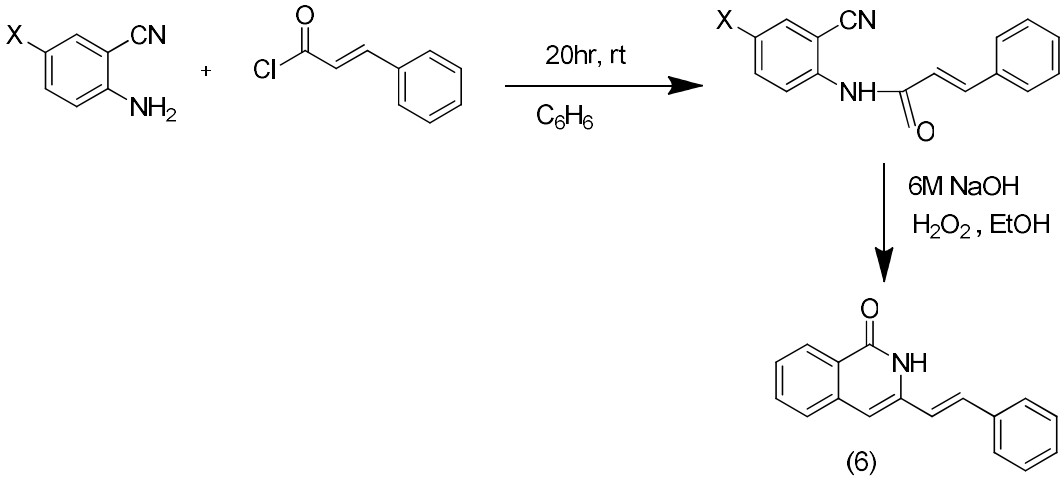


2.2. 2-Substituted-4(3H)-quinazolinones and -quinazolines:



2.2.1. Amidation and cyclisation of 2-aminobenzoic acid derivatives:

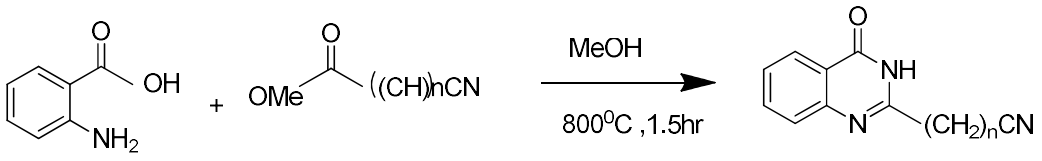
The most well-known methodology includes amidation of 2aminobenzonitrile, 2-aminobenzoic corrosive and 2-aminobenzamide. For instance, the response of 2-aminobenzonitrile with 3-phenylacryloyl chloride followed by oxidative ring conclusion under essential conditions delivered 2styryl-4(3H)-quinazolinone (6) in 29% yield **[2-5]**.



(6)

2.2.2. Condensation of imidates with 2-aminobenzoic acid:

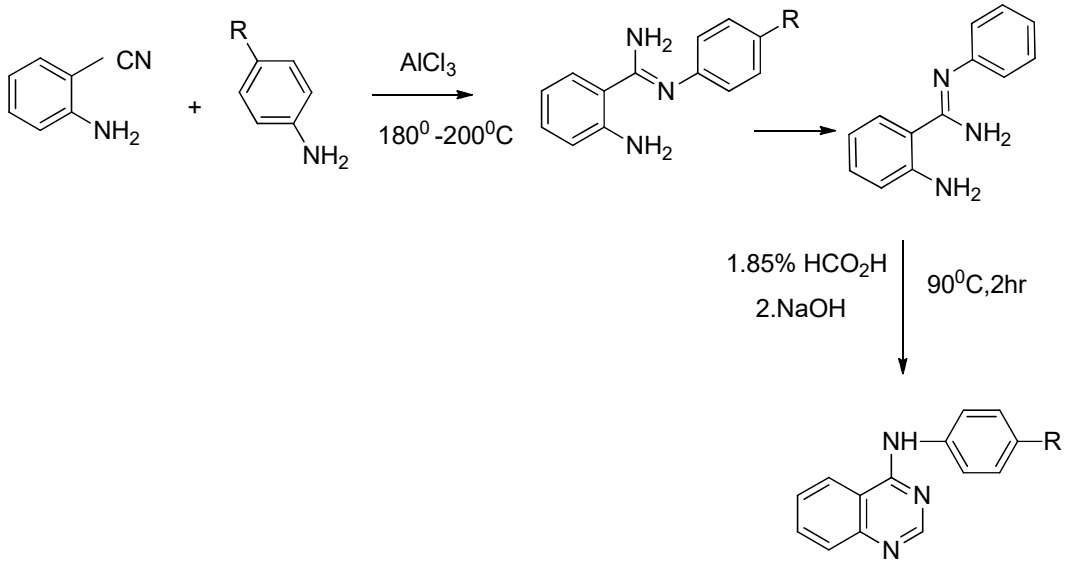
The response of anthranilic corrosive with imidates in methanol at 800^0C bears the ideal quinazolinones (7) in great yields **[6-14]**.



(7)

2.2.3. Reaction of anilines with 2-aminobenzonitrile:

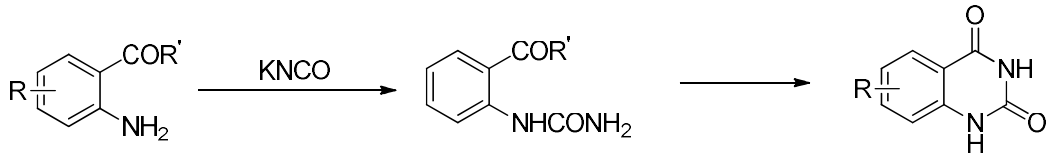
The 2-amino-N-arylbenzamides outfitted the 4-arylaminoquinazolines (14) in great yields (70–92%) when warmed with 85% formic corrosive. This course was later adjusted to empower the planning of 2-aryl-4-aminoquinazolines **[15-16]**.



(14)

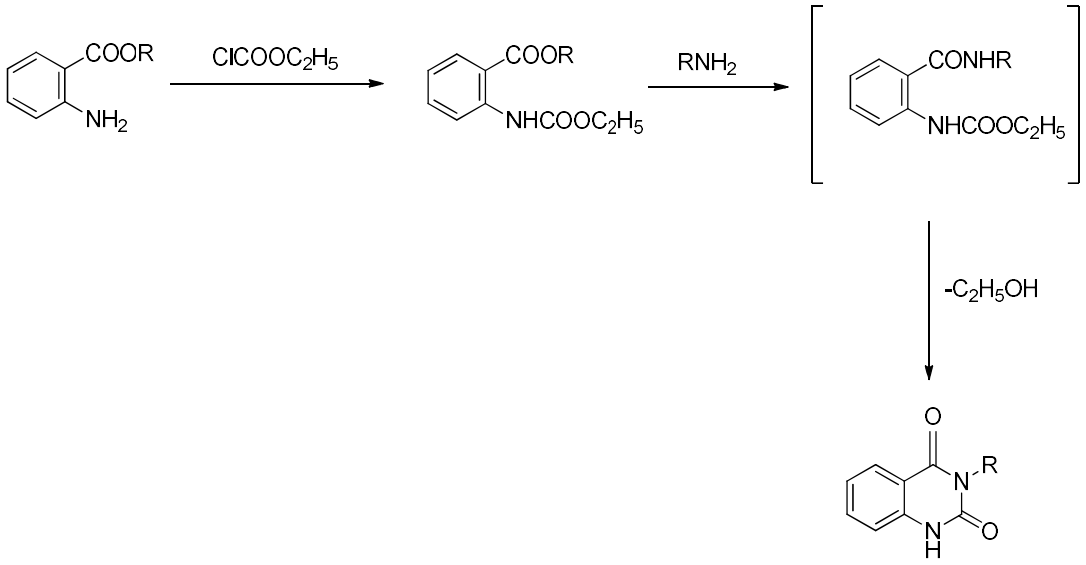
2.3. O-Substituted Quinazolinones:

2.3.1. From O-Ureidobenzoic Acid: Theo-ureidobenzoic acids are prepared from the corresponding anthranilic acid and potassium cyanate. The ureido acids are then easily cyclized totherespective1,2,3,4-tetrahydro-2,4-dioxoquinazolines by heating with acid or alkali.



scheme 15

2.4. From O-Ethoxy Carbonylamino benzoic Esters or Amides: When o-ethoxycarbonylamino benzamide and its 4-methyl derivatives are heated over the irmelting points, then they lose water and form 1,2,3,4-tetrahydro-2,4-dioxoquinazoline.



3.0. Spectral data

3.1. UV Visible Spectroscopy:

The wavelength ranges from 260nm to 270nm.

3.2. IR Spectroscopy:

Prominent band is between 1000cm^{-1} to 3500cm^{-1}.

3.3. NMR Spectroscopy:

Chemical shift value of quinazolinones by H^{1}NMR is 8.0(d-1NH-Quinazolinone) 7.89(d C=N, N_2-Quinazolinone) 7.63-8.03(M 4H Aromatic).

Chemical shift value of quinazolinones by 13C NMR is 161.0(C=O C_4 Quinazolinones), 145.7(C=N C_2 Quinazolinones), 120.8-148.2(C_5-C_{10} aromatic methyl groups).

3.4. Mass Spectroscopy:

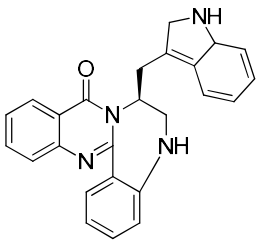
LCMS: for Quinazolinones m/z value is 146(M+1=99.09).

3.5. Elemental Analysis:

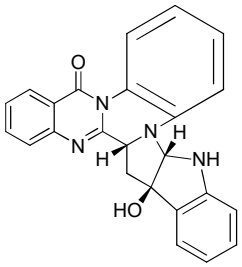
C- 65.75%, H- 4.14%, N- 19.17%, O- 10.95%.

4.0. Biolocial evaluation of quinazoline derivatives

4.1. Antimicrobial activity: G. P. Suresha *et al* **[17]** revealed a novel arrangement of urea/thioureas of quinazolinones conjugated lysine 13 and screened for their in vitro antimicrobial action. The action results indicated that the mixes containing urea and thiourea subsidiaries applied exceptionally intense action contrasted with measures.

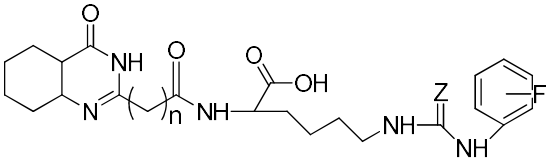


Asperlicin D

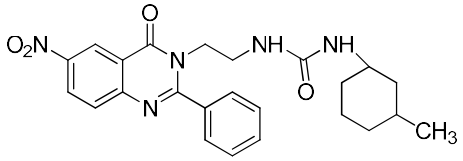


Asperlicin E

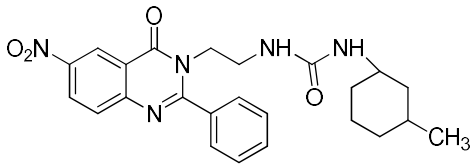
M. Rana *et al* **[12]** detailed a progression of 1-[2-(6-nitro-4oxo-2-phenyl-4H-quinazolin-3-yl)- ethyl]3-phenyl ureas. The blended mixes were measured for antimicrobial movement by sequential soup weakening procedure. A portion of the mixes indicated great movement against various bacterial strains. Great restraint was watched for compound 14 against strain E. coli at 40 μg/mL of MIC.



R. Dahiya *et al* **[13]** have integrated two subbed quinazoline/imidazolyl-salicylic corrosive conjugated with amino corrosive/peptides and were tested for antimicrobial and anthelmintic exercises against eight pathogenic microorganisms and three-night crawler species. Among the tried mixes, 15 and 16 showed higher antimicrobial movement against Pseudomonas aeruginosa, Klebsiella pneumoniae and Candida albicans and 17 showed better antifungal action against the dermatophytes Trichophyton mentagrophytes and Microsporum audouinii.

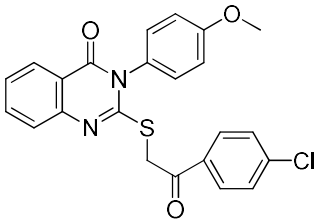


4.2. Anti-inflammatory activity: E. Manivannan and S. C. Chaturvedi **[14]** have blended a progression of methyl sulfinyl/methyl sulfonyl subbed 2,3-diaryl quinazolinone subordinates. These mixes were assessed for both non-ulcerogenic and anti-inflammatory exercises. The compound 19 rose as the most dynamic compound right now. Halogen iotas or methoxy bunches at R1 and R3 position of 2,3-diaryl-3H-quinazolin-4-ones seems to positively affect the non-ulcerogenic and anti-inflammatory intensity.



19

4.3. Anti-tumour activity: [15] orchestrated some new 3-subbed quinazolin-4(3H)- ones and 3, 4-dihydro-quinazolin-2(1H)- one subordinates and detailed that mixes 20 and 21 as wide range anti tumours indicating viability toward various cell lines that has a place with various tumour sub planes.



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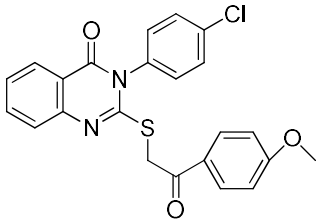
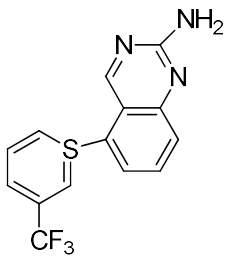


21

4.4. Anti-malarial activity: L. M. Werbel *et al* **[16]** orch estrated an assortment of analogs of 2,4-diamino-6-[(aryl)thio] quinazolines with known antimalarial properties wherein the 4-amino gathering was supplanted by hydrazine and hydroxyamino moieties and they found that such changes decrease particularly the antimalarial properties of this arrangement. The compound 22 was tried against an ordinary drug sensitive strain of Plasmodium berghei in mice by the parenteral course.



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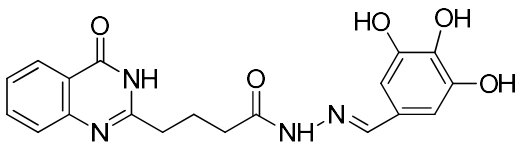
4.5. Anti-oxidant activity: Rakesh planned and combined a progression of quinazolinone inferred Schiff's bases and screened for their cell reinforcement action. Mixes 23 and 24 with OH and OCH3 bunches in benzene ring (electron giving) displayed more grounded radical rummaging exercises than the benchmarks.



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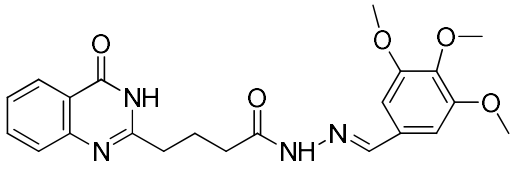
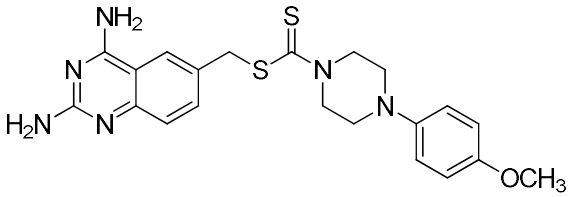


24

4.6. Anti-proliferative activity: S. L. Cao announced a novel arrangement of 4-subbed piperazine-1-carbodithioate subordinates of 2, 4-diaminoquinazoline were tried for their antiproliferative exercises against five human disease cell lines including A549 (lung malignant growth), MCF-7 (bosom adenocarcinoma), HeLa (cervical carcinoma), HT29 and HCT-116 (colorectal disease). Among the combined mixes 25-27 were the most dynamic individuals with IC50 values in the range 1.58-2.27, 1.84-3.27 and 1.47-4.68 μM against five disease cell lines analysed, separately.



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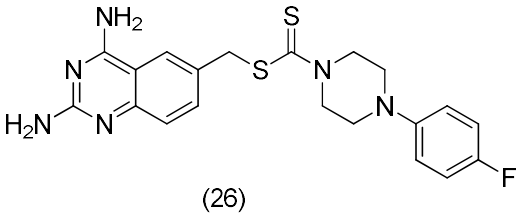

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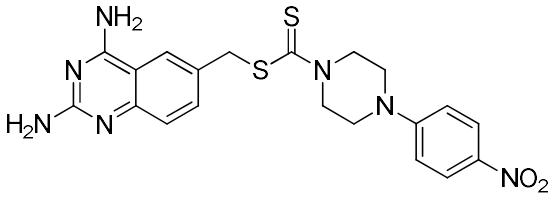
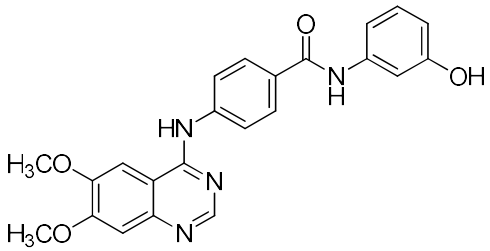
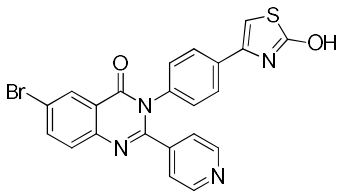


(27)

4.7. Anti-tuberculosis activity: A. T. Tran blended a progression of quinazoline subsidiaries and assessed against M. tuberculosis as GlmU uridyl transferase inhibitors. The most intense inhibitor 28 right now an IC50 of 74 μM against GlmU uridyl transferase action and fills in as a promising beginning stage for the revelation for progressively strong inhibitors.



4.8. Analgesic activity: F. Eweas planned and incorporated some novel 2-pyridyl(3H) quinazolin-4-one subsidiaries and assessed for their pain-relieving action. All the tried mixes indicated great pain-relieving action in contrast with the reference standard indomethacin. The rates of maximal security were noted with the tried mixes 29 and 30 by 75.67 and 75.40 %, individually.



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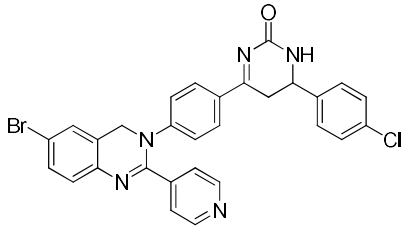

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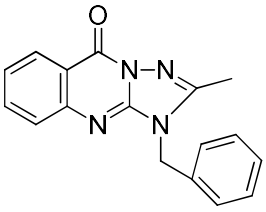
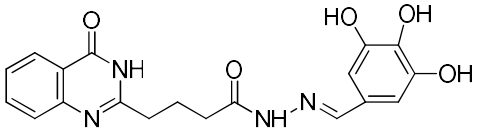
4.9. Anti-hypertensive activity: V. Alagarsamy and U. S. Pathak44 orchestrated a progression of 3-benzyl-2-subbed 3H-[1,2,4] triazolo[5,1-b]quinazolin-9ones and assessed for their in vivo antihypertensive movement utilizing unexpectedly hypertensive rodents (SHR). While all the test mixes showed huge antihypertensive movement, compound 31 was seen as the most dynamic antihypertensive specialist than the reference standard prazosin.



4.10. Anti-ulcer activity: Rakesh planned and incorporated a progression of quinazolinone inferred Schiff's bases and screened for their in vitro antiulcer movement. Mixes 32 and 33 with OH and OCH3 bunches in benzene ring (electron giving) indicated brilliant antiulcer action than the standards.



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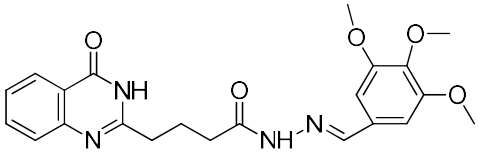

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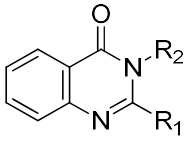
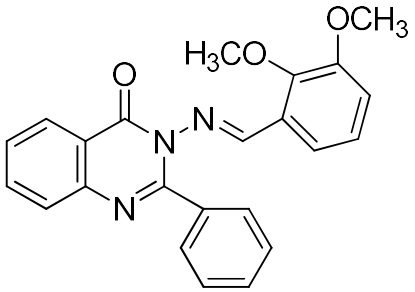
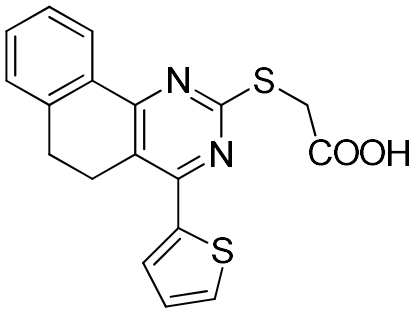
4.11. Anti-bacterial activity: Nagar combined and discovered enemy of bacterial movement of quinazoline-(3H) one. The action of certain subsidiaries were practically identical with fluconazole.



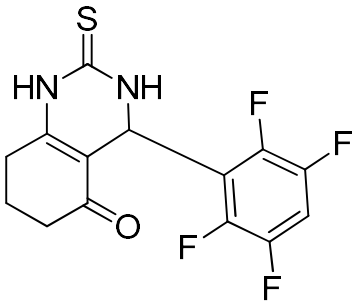
4.12. Cytotoxic activity: Krishnan blended arrangement of 3-(benzylidene amino)- 2-phenyl quinazoline-4(3H)- ones was incorporated by response of 3-amino-2-phenyl-3H-quinazoline-4-one with different carbonyl mixes and investigated cytotoxic movement.



4.13. Anti-HIV activity: Yahia blended a progression of dihydrobenzo[h]quinazoline subsidiaries utilizing aryl methylene thiopyrimidine and 2-(4-(thiophen-2-yl)-5,6-dihydrobenzo[h]quinazolin-2-ylthio) acidic corrosive (4) as a beginning materials. The natural screening indicated that a significant number of these mixes have great anticancer and antiviral exercises.

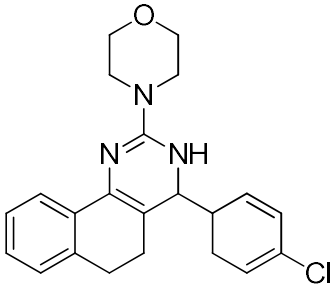


4.14. Anti-fungal activity: Octa hydro quinazoline was acquired by a change of the Biginelli response with phenacyl bromide and bromo malononitrile to outfit thiazolo [2,3-b] quinazoline and they found the association of compound with formamide, formic corrosive, and phenyl isothiocyanate yielded the comparing pyrimidinothiazolo[2,3 b] quinazolines and showed antifungal activity against Candidaalbicans.

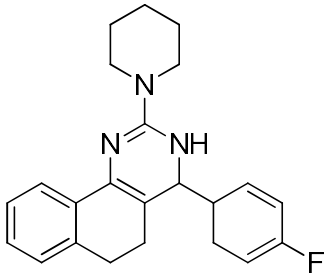


4.15. Antileishmanial activity: Compounds of both manufactured and characteristic starting point including an assorted gathering of synthetic structure have been accounted for as antileishmanial operators. These incorporate generally nitrogen heterocyclic, for example, quinolines, purine, pyrimidine, acidine,

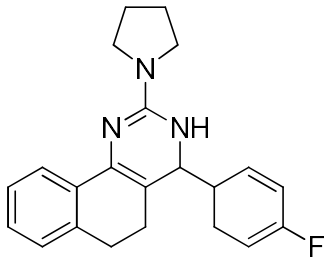
phenothiazines, bisbenzamides, pyrazolol, pyridine, benzothiazole, and imidazolines. The 4-(subbed benzylidine)- 2-subbed 5,6-dihydrobenzo[h]quinazolineand4-(substituted benzylidene)- 2-subbed 3,4,5,6-tetrahydrobenzo[h]quinazolinefrom2-(subbed benzylidene) tetralone-1 and a few subbed guanidine sulphates are assessed for their in vitro antileishmanial movement and they detailed that mixes (100–102) show promising antileishmanial action against Leishmaniadonovani.



100

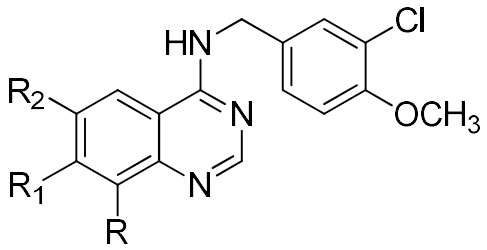


101



102

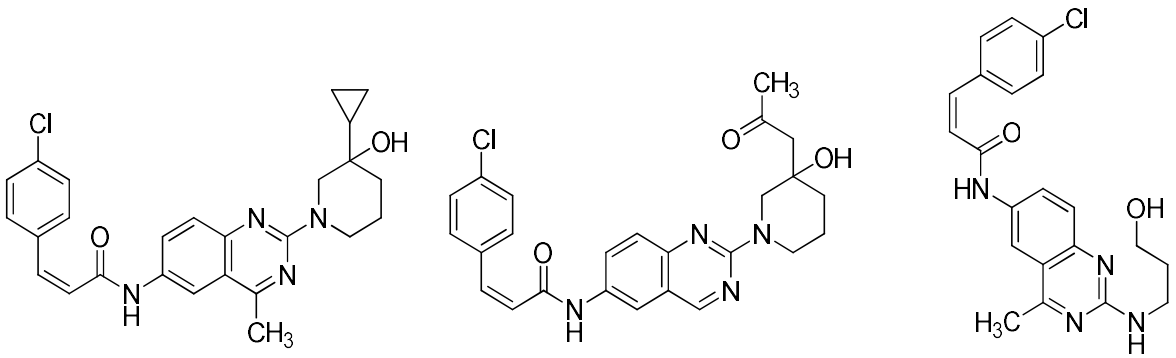
4.16. Neuroprotective activity: Few quinazoline subordinates (103a–c) were assessed for their movement as strong and exceptionally particular PDE5 inhibitors to be utilized for male erectile dysfunction.



(103 a-c)

	R	R_1	R_2
103a	C_3H_7	OCH_3	$NHCOCF_3$
103b	CH_2CH_2OH	OCH_3	$NHCOCH_3$
103c	CH_2CH_2OH	OCH_3	$NHCOCH_3$

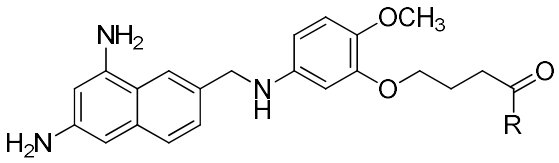
4.17. Anti-obesity activity: A progression of quinazoline subordinates (104–106) are to be considered as an adversary for melanin concentrating hormone receptor 1 (MCHR1)



104 105 106

SCHEME 71

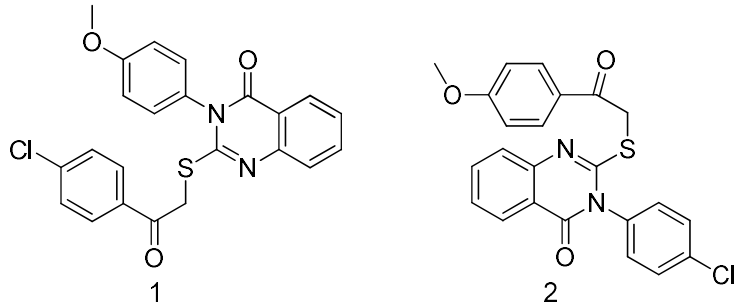
4.18. Anti-protozoan activity: A series of quinazoline subordinates (107a-b) were assessed for their action as a strong inhibitor of trypanosoma cruzi dihydrofolate reductase.



107a R= OC_2H_5

107b R= OCH_3

4.19. Quinazolinones as Anticancer Activity: Some new 3substituted quinazolin-4(3H)-ones and 3,4-dihydro-quinazolin-2(1H)-one derivatives are reported that compounds 2-[2-(4-chlorophenyl)-2-oxo-ethylthio]-3-(4-methoxyphenyl) quinazolin-4(3H) one (1) and 3-(4-chlorophenyl)-2-[2(4-methoxyphenyl)-2-oxo-ethylthio] quinazolin-4(3H)-one (2) as broad-spectrum antitumor show effectiveness toward numerous cell lines that belong to different tumour subpanels **[17]**.



1 2

Scheme 21

5.0. CONCLUSION:

Quinazolines are most potent compounds which have wide variety of biological activities. In theses arical to describe the methods of preparation and impotant activities which have been done recently on theses compounds. Finally it is concluded that these compound majorly have chemotherapeutic activity.

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