WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 13, 47-68. Review Article ISSN 2277– 7105

A REVIEW ON THE THERAPEUTIC POTENTIAL OF QUINOXALINE DERIVATIVES

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Article Received on
26 August 2017,

Revised on 17 Sep. 2017,
Accepted on 08 Oct. 2017

DOI: 10.20959/wjpr201713-9878

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ABSTRACT

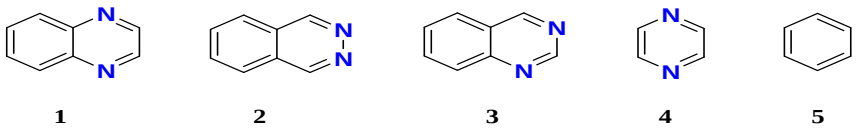
Quinoxaline nucleus based derivatives have attracted researcher's attention due to privileged and extensive applications in medicine, pharmaceuticals and pharmacological fields. Quinoxaline moiety is a part of various antibiotics such as echinomycine, levomycine, actinoleutine and also act as antiviral, anti-diabetic, anti-inflammatory, kinase inhibitors, anticancer, ion channel regulators and anti-protozoa agent. Various synthetic methodologies and strategies are developed to prepare quinoxaline compound libraries due to pivotal focal point of research activity in the field of pharmacology and medicine. In this review the substituted quinoxaline scaffolds synthetic chemistry, biological activities and applications are summarized.

KEYWORDS: Quinoxaline, pharmaceutical, antimicrobial, anticancer, anti-inflammatory, anti-diabetic.

1. INTRODUCTION

Quinoxaline **1** moiety belongs to the class of nitrogen containing benzoheterocycles having broad spectrum biological activities such as antitumor, antibacterial, antiviral, anticonvulsant, antifungal, antimicrobial, anticancer, anti-tubercular, antimalarial and anti-inflammatory etc.[1] Quinoxaline derivatives exhibit wide variety of applications in dyes, fluorescent materials, semiconductors in organic photo voltaic (OPV) cells, insecticides, fungicides, herbicides, anthelmintic etc.[2] Quinoxaline or benzopyazine is a fused heterocyclic compound made up of a benzene ring and pyrazine ring. Phthalazines **2**, quinoazoline **3**, and

cinnolenes are isomeric with quinoxline. Quinoxaline is formed by the fusion of diazine **4** with benzene **5** ring. [3]



1 **2** **3** **4** **5**

Figure. 1.0: Structures of quinoxaline and related heterocycles.

Benzopyrazine and diazanaphthalene are other names of quinoxaline. The number of resonance structures of quinoxaline are increased by the fusion of one or more benzene rings to quinoxaline and phenazine rings and the dipole moment of quinoxaline is zero.[4]

Literature survey reveals that different synthetic strategies and methodologies are applied to synthesize quinoxaline derivatives for their biological and pharmacological activities in medicine praxis. The present study shows advancement in synthesis and broad spectrum biological diversities of quinoxaline derivatives to develop new synthetic routes and pathways for the development of new therapeutic agents, drug design and future drug discovery.

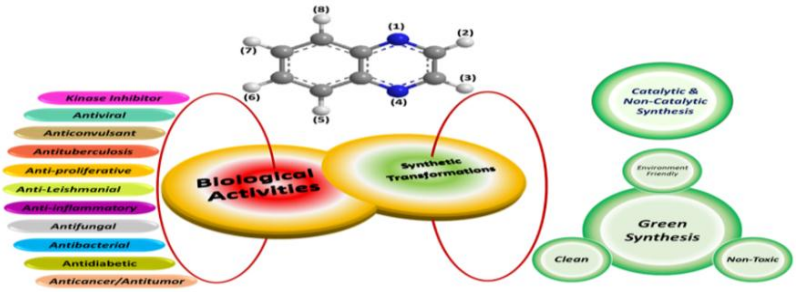
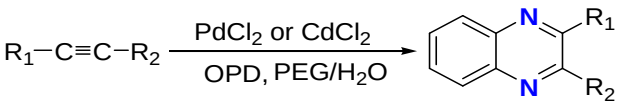


Fig. 1.1: Synthetic transformations and biological activities.

1.1. Synthesis of quinoxaline derivatives by catalytic strategies

Substituted quinoxaline di-ketones **7** can be prepared by oxidation of alkynes **6** with *o*-phenylene diamine (OPD) in the presence of catalyst.[5]

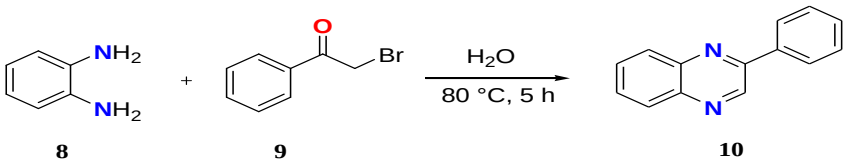


6 **7**

Where R_1 & R_2 alkyl or aryl

Scheme. 1.2: Synthesis of substituted quinoxaline derivatives 7.

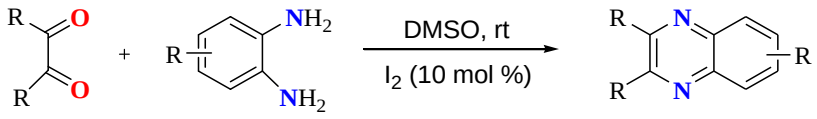
2-Bromo acetophenone **9** can react with OPD **8** in aqueous medium at 80 °C for 5 h to afford quinoxaline derivatives **10**.[6]



8 **9** **10**

Scheme 1.3: Synthesis of quinoxaline derivatives 10.

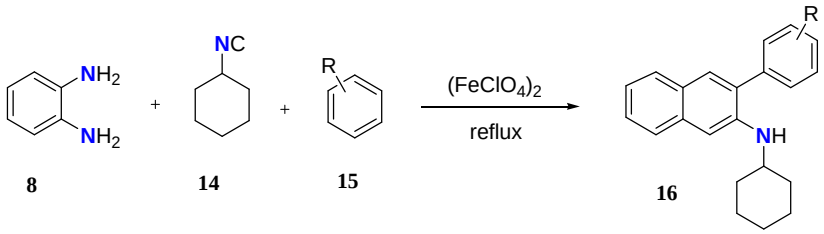
Another method to obtain substituted quinoxaline derivatives **13**, is to treat di-ketone **11** with substituted OPD **12** in the presence of catalyst and dimethyl sulfoxide (DMSO) solvent at rt.[7]



11 **12** **13**

Scheme 1.4: Synthesis of substituted quinoxaline derivatives 13.

N-Cyclohexyl-3-aryl-quinoxaline-2-amines **16** can be afforded in good yields by the condensation of aldehyde **15**, cyclohexyl isocyanide **14** and *o*-phenylene diamine **8.**[8]

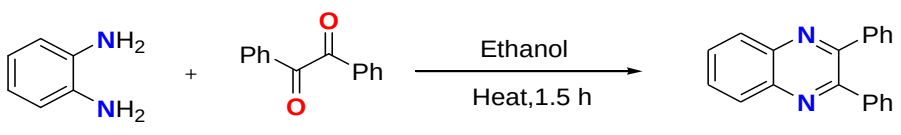


8 **14** **15** **16**

Scheme 1.5: Synthesis of *N*-cyclohexyl-3-aryl-quinoxaline-2-amines 16.

1.2. Synthesis of quinoxaline derivatives by non-catalytic strategies

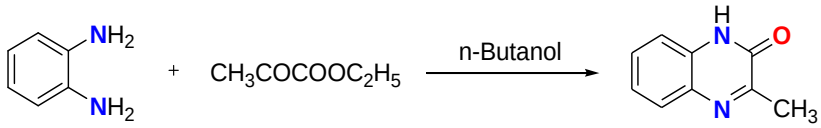
OPD **8** can be treated with benzil **17** in ethanol and heated for 1.5 h to yield 2,3-diphenyl quinoxaline (DPQ) **18**.[9]



8 **17** **18**

Scheme 1.6: Synthesis of quinoxaline derivative 18.

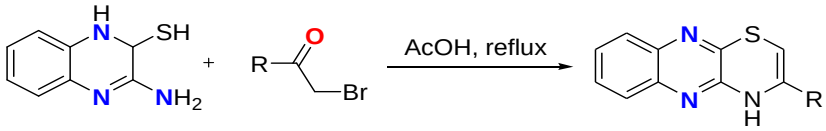
2-Hydroxy-3-methylquinoxaline **20** can be synthesized by the reaction of OPD **8** with ethyl pyruvate **19** in n-butanol.[10]



8 **19** **20**

Scheme 1.7: Synthesis of 2-hydroxy-3-methylquinoxaline derivative 20.

α-haloketones **22** can react with 2-amino-3-quinoxalinethiol **21** in glacial acetic acid to synthesize quinoxaline derivatives **23**. The reaction mixture was heated to reflux and product was obtained after recrystallization in ethanol.[11]



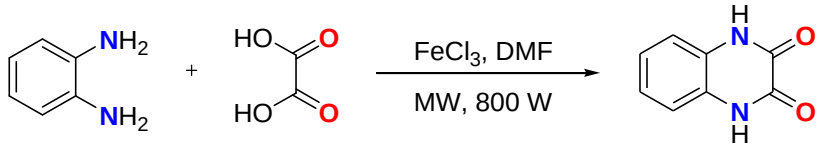
21 **22** **23**

Where R= CH_3, Ph, p -C_6H_4–Me, p -C_6H_4–OMe, p -C_6H_4–Ph, p -C_6H_4–Br, p - C_6H_4–NO_2

Scheme 1.8: Synthesis of quinoxaline derivative 23.

1.3. Synthesis of quinoxaline derivatives by green chemistry methodologies

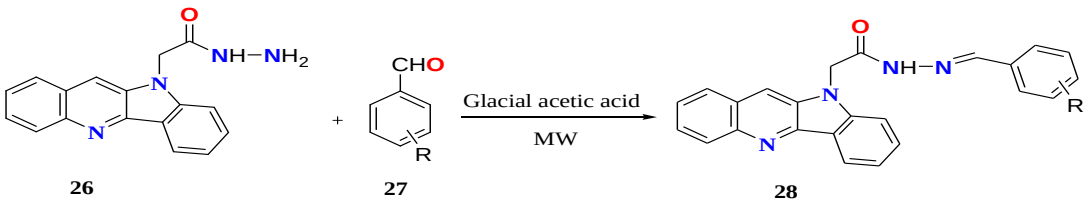
Quinoxaline derivative **25** can be prepared by reaction of OPD **8** with oxalic acid **24** in the presence of ferric chloride and dimethyl formamide (DMF). Reaction mixture was heated in microwave (MW) and compound **25** was obtained.[12]



8 **24** **25**

Scheme 1.9: Synthesis of quinoxaline derivative 25.

2-(5, 8-dihydro quinoxalino [2, 3-b] indol-5-yl) acetohydrazide **26** and substituted aromatic aldehyde **27** were reacted in presence glacial acetic acid to afford indolo [2,3-*b*]quinoxaline derivative **28** after exposing it to MW radiations.[13]

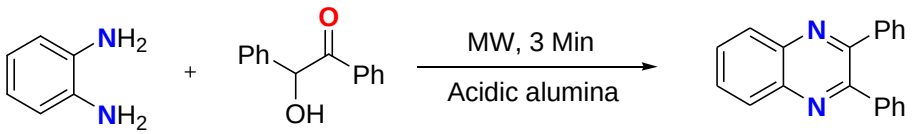


26 **27** **28**

Where R= H, 3-NO_2, Furfural, 4-CH_3, 4-OH, 4-$N(CH_3)_2$, 2-Cl, 4-OH, 3-OCH, 4-OCH_3, 2-OH

Scheme 1.10: Synthesis of indolo [2,3-*b*]quinoxaline derivative 28.

2-Hydroxy-1,2-diphenylethanone (Acyloin) **29** can be treated with OPD **8** in acidic alumina by exposing to MW radiation for 3 minutes to synthesize 2,3-diphenyl quinoxaline (DPQ) **18.**[14]



8 **29** **18**

Scheme 1.11: Synthesis of DPQ 18.

1.2. Biological and pharmacological applications of quinoxaline derivatives

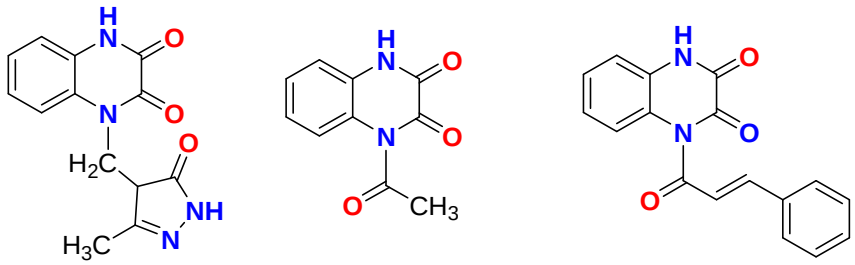
Quinoxaline derivatives have wide applications in biological, medicinal, insecticides, herbicides, fungicides, material chemistry like solar cells and pharmacological fields. Some novel condensed bridge head nitrogen heterocycles of quinoxaline exhibited antimicrobial activity against the gram positive and the fungi.[15] Quinoxaline derivatives act as antiprotozoal, antiviral, anti-inflammatory, and antibacterial and as a kinase inhibitor.

Quinoxaline derivatives also show anticancer, antimalarial, antimicrobial, anti-nociceptive, antiepileptic, anti-diabetic, anti-tubercular and anthelmintic characteristics.[16] Quinoxaline based antibiotics also inhibit the growth of gram-positive bacteria. Quinoxaline derivatives exhibit antifungal, anti HIV, anti-depressant and antineoplastic activities.[3]

1.2.1. Antimicrobial activities

Ramalingam and coworker synthesized 1-subtitued quinoxaline-2,3(1*H*,4*H*)-diones as the anti-microbial activity. The derivatives 1-((3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl) methyl)quinoxaline-2,3(1*H*,4*H*)-dione **30**, 1-acetylquinoxaline-2,3(1*H*,4*H*)-dione **31** and 1-cinnamyolquinoxaline-2,3(1*H*,4*H*)-dione **32** showed antibacterial activities against *S.aureus* with MIC = 26,20 and 20 µg/ml, E.coli with MIC = 30,24 and 26 µg/ml, P.vulgaris with MIC

= 30,26 and 30 µg/ml and *P.aeruginosa* with MIC = 35, 29 and 29 µg/ml and antifungal activities against A. Niger with MIC = 28, 20 and 24 µg/ml and C. albicans with MIC = 20, 00 and 18 µg/ml respectively. The standard used for these compounds are Nalidixic acid and clotrimazole for antibacterial and antifungal activities respectively.[17]



30 **31** **32**

Figure 1.2: Substituted 1,4-dihydroquinoxaline-2,3-dione antimicrobial derivatives.

Teja R. and coworkers afforded series of thiadiazolo[2`, 3`:2, 3]imidazo [4,5-b]quinoxalines from *o*-phenylenediamine and determined their antimicrobial potential through paper disc diffusion method, towards two strains of gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*), two strains of gram-positive bacteria (Bacillus cereus and Staphylococcus aureus) and two strains of fungi (*Aspergillus niger* and *Aspergillus fumigatus*). Solvent used was DMSO as a control, Ciprofloxacin and Fluconazole (100µg/ml/disc) were employed as standard against bacterial and fungal strains respectively. MIC values were confirmed by agar streak dilution method.

The derivatives 7,8-dinitro-2-phenyl-1,3,4]thiadiazolo[2 0,3 0:2,3]imidazo[4,5,b]quinoxaline **33**, 7,8-dinitro-2-(4-amino-phenyl)-[1,3,4]thiadiazol-o[20,3 0:2,3]imidazo[4,5-b] quinoxaline **34** and 7,8-dinitro-2-(2-hydroxy-phenyl)[1,3,4]thiadiazol-o[20,3 0:2,3]imidazo[4,5-b]quinoxaline **35** had good antibacterial and antifungal potential. Compound **33** had MIC values against *S. aureus* as 31.25µg/ml, *B. cereus* as 15.63µg/ml, *E. coli* as 31.25 µg/ml, P. aeruginosa as 15.63µg/ml, A. niger as 31.25µg/ml and A. fumigatus as 15.63µg/ml. Compound **34** had MIC values against *S. aureus* as 31.25µg/ml, *B. cereus* as 15.63µg/ml, *E. coli* as 31.25 µg/ml, *P. aeruginosa* as 31.25µg/ml, *A. niger* as 31.25µg/ml and *A. fumigatus* as 15.63µg/ml. Compound **35** had MIC values against *S. aureus* as 7.81µg/ml, *B. cereus* as 7.81µg/ml, *E. coli* as 31.25 µg/ml, *P. aeruginosa* as 7.81µg/ml, *A. niger* as 31.25µg/ml and *A. fumigatus* as 7.81µg/ml. Ciprofloxacin had MIC values against *S. aureus* as 15.63µg/ml, *B. cereus* as 7.81µg/ml, E. coli as 15.63µg/ml and P. aeruginosa as 7.81µg/ml. Fluconazole had MIC values against *A. niger* as 7.81µg/ml and *A. fumigatus* as 15.63µg/ml. Structure-

activity relationship (SAR) indicated the increased antimicrobial potential was due to presence of substitution of electron donating group on the compounds.[18]

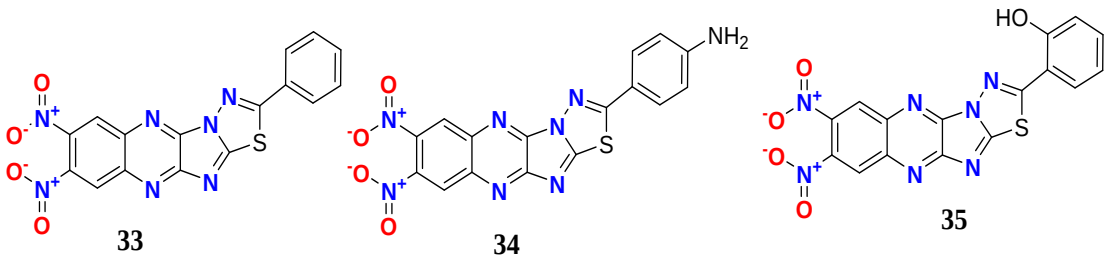


Figure 1.3: Substituted thiadiazolo based quinoxalines antimicrobial derivatives.

Yokoyama A. and coworkers synthesized 2,3-Bis(bromomethyl)quinoxaline derivatives by condensing 1,2-phenylene diamine derivatives with 1,4-dibromo-2,3-butanedione.The derivative 2,3-Bis(bromomethyl)-6-(trifluoromethyl) quinoxaline **36** had strong antibacterial activity against gram-positive bacteria Bacillus subtilis (MIC=12.5µg/ml) and Staphylococcus aureus (MIC=12.5 µg/ml). The scaffold 2,3-Bis(bromomethyl)-6-fluoroquinoxaline **37** was found to be most active against seven fungal strains as Aspergillus niger (MIC=50µg/ml), Penicillium citrinum (MIC= 25µg/ml), Cladosporium cladosporiodes (MIC=25µg/ml), Aureobasidium pullelans (MIC= 50µg/ml), Alternaria sp. (MIC=25 µg/ml), Mucor spinescens (MIC=25µg/ml), Gliocladium viren (MIC >100 µg/ml). Presence of trifluoromethyl group that is highly lipophilic at the 6-position and strong electron withdrawing group CF_3 was responsible for antibacterial activity of compound 36 and compound 37 had enhanced antifungal potential due to strong electron withdrawing group CN.[19]

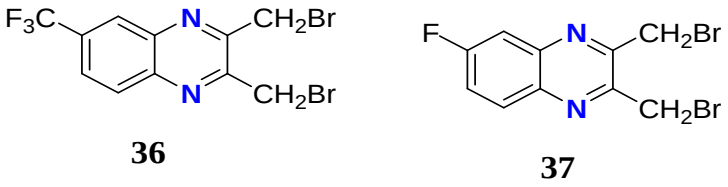
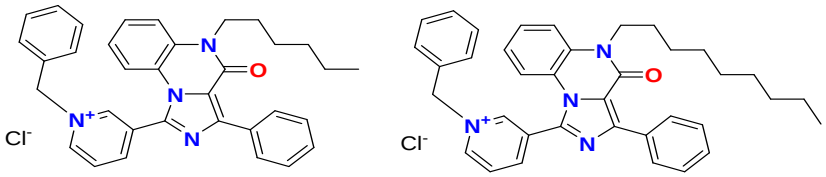


Figure 1.4: Substituted-2,3-Bis(bromomethyl)quinoxaline antimicrobial derivatives.

Mamedov V. A. and coworkers synthesized *N*-alkyl-pyridinium salts of 3-Phenyl(methyl)-5-alkyl-1-(pyridin-3-yl)imidazo[1,5-a]quinoxalin-4-ones and evaluated their activity against Gram-negative bacteria (*Pseudomonas aeruginosa* and *Escherichia coli*), Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus cereus*), and pathogenic fungi (*Aspergillus niger* and *Trichophyton mentagrophytes*) and yeast (*Candida albicans*). Standards used were

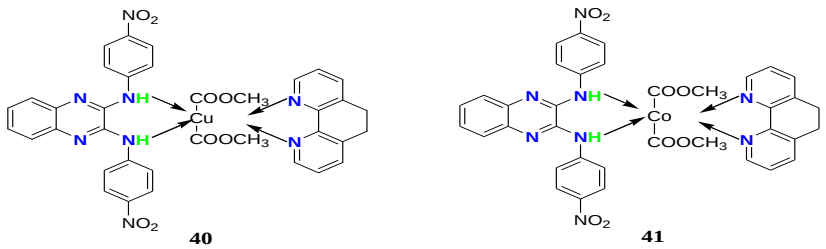
Ciprofloxacin, Ofloxacin and Norfloxacin for antibacterial activity and Clotrimazole and Amphotericin B were employed for antifungal activity. The derivatives 1-Benzyl-3-(5-hexyl-3-phenyl imidazo[1,5-a] quinoxalin-4-on-1-yl)pyridinium chloride **38** and compound 1-Benzyl-3-(5-nonyl-3-phenyl imidazo[1,5-a]quinoxalin-4-on-1-yl)pyridinium chloride **39** had good antibacterial and antifungal activity when compared to reference. MIC values of **38** against *S.aureus* as 0.97, *B.cereus* as 6.3, E.coli as >500, *P.aeruginosa* as >500, *A.niger* as >500, *T.mentagrophytes* as 500 and *C.albicans* as 7.8 µg/ml. MIC values of **39** against *S.aureus* as 1.95, *B.cereus* as 12.5, *E.coli* as >500, *P.aeruginosa* as >500, *A.niger* as >500, *T.mentagrophytes* as 500 and *C. albicans* as 3.9µg/ml.[20]



38 **39**

Figure. 1.5: Substituted quinoxalin-4-ones antimicrobial derivatives.

Dhanaraj C. J. and coworker reacted N_2, N_3-bis(4-nitrophenyl)quinoxaline-2,3-diamine with 1,10-phenanthroline to afford Co(II), Ni(II), Cu(II) and Zn(II) mixed ligand complexes. The synthesized compounds were evaluated against bacterial strains as *S. aureus*, *E. coli*, *P. aeruginosa* using Chloramphenicol as standard and fungal strains as *C. albicans*, *A. flavus* and *A. niger* using Nystatin as standard through disc diffusion method. Cu (II) mixed ligand **40** had strong antibacterial activity and Co (II) mixed ligand **41** had strong antifungal potential.[21]



40 **41**

Figure. 1.6: Substituted quinoxalin-4-ones antimicrobial derivatives.

Patel N. B. and coworkers synthesized novel *N*-(substituted phenyl)-2-[5-(quinoxalin-2-yloxymethyl)-[1,3,4]oxadiazol-2-ylsulfanyl]-acetamides from 2-hydroxy quinoxaline and evaluated their antibacterial activity against gram positive bacteria *S. aureus* and *S. pyogenes*, gram negative bacteria *E. coli* and *P. aeruginosa* and antifungal activity against *C. albicans*,

A clavatus and *A. niger*. The scaffolds 5-(quinoxalin-2yl-oxymethyl)-2-[N-(2-methylphenyl)acetamide-2-thio]-1,3,4-oxadiazole **42** and 5-(quinoxalin-2yl-oxymethyl)-2-[*N*-(3,4-dichlorophenyl)-acetamide-2-thio]-1,3,4-oxadiazole **43** having CH_3 group at 2-position Cl at 3,4-position, showed increased activity MIC values of 12.5 for **42** and 50µM for **43** against *P. aeruginosa* when compared to chloramphenicol and ciprofloxacin used as reference drugs. Compound **42** had good activity against *S. pyogenes* with MIC value as 25µM when compared to ciprofloxacin. Compound **43** had also significant potential against fungus *C. albicans* showing MIC as 250 µM.[22]

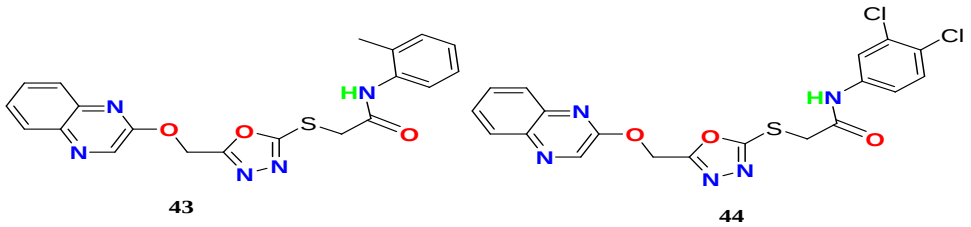


Figure. 1.7: Quinoxalin-oxadiazol moiety based antimicrobial derivatives.

1.2.2. Antibacterial activities

Galil AE et al reported that 2-Substituted(1,4-dioxo-3,4,4e,5,10,10a,hexahydro-1*H*-5,10-benzenobenzo[*g*]phthalazine derivatives **45** established as potent antibacterial agent.[23] 2-Methylquinoline-3(4*H*)-thione **46** showed less antibacterial activities than 4-ethyl-2-methylquinoline-3(4*H*)-thione **47** as compared to the standard references of clotrimazole and tetracycline.[24]

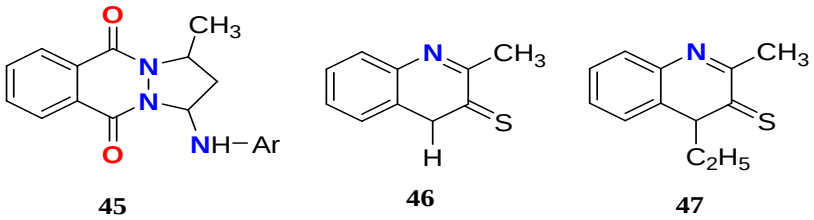


Figure. 1.8: Quinoxalin antibacterial derivatives.

Dhanaraju M.D. and coworkers synthesized (E)-3-(4-or3-Amino phenylimino)quinoxaline-2(3*H*)-one oxime Schiff base derivatives and determined their anti-leptospiral activity. The (E)-3-(3-(3-nitrobenzylideneamino)phenylimino)quinoxaline-2(3H)-one oxime **50** had prominent activity as compared to standard drug Pencilin G. Percentage motility inhibition value for spirochete bacteria for the compound 12 as 91.2% and for standard it was 94.1%.[25]

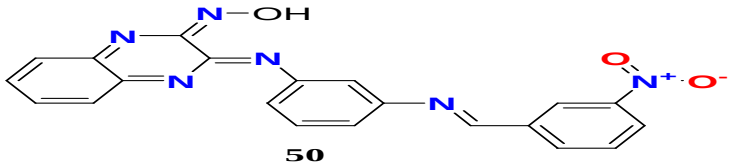


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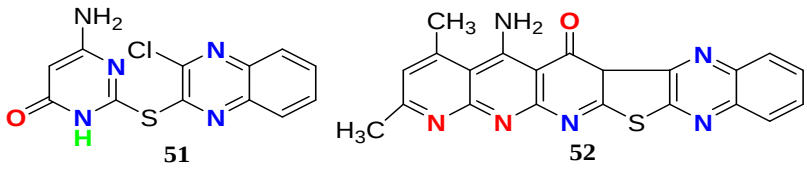
Figure. 1.9: Anti-leptospiral activity of quinoxalin derivatives.

1.2.3. Anti-inflammatory activities

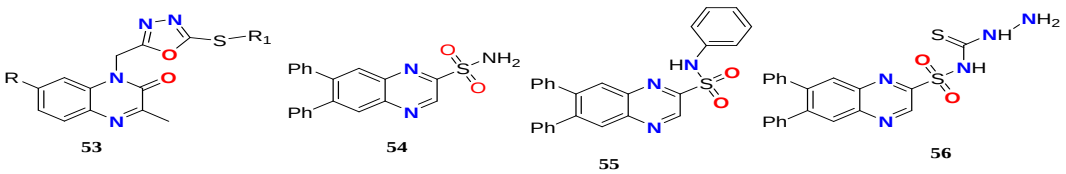
Abu Hashem et. al. synthesized 6- amino-2-(3-chloroquinoxalin-2-ylthio)pyrimidin-4(3*H*)-one by reacting 6-aminothiouracil and 2,3-dichloroquinoxaline in ethanol and evaluated their anti-inflammatory activity against carrageenan-induced paw edema. Diclofenac sodium was used as standard. The derivatives 6-amino-2-(3-chloroquinoxalin-2-ylthio)pyrimidin-4(3H)-one **51** and 7-Amino-4,6-dimethyl-1,8-naphthyridino-[2,3:4,5]pyrimido[2`,1`:2,3]thiazolo [4,5-b]-quinoxaline-8-one **52** had more significant anti-inflammatory potential with percentage protection as 41.3±1.25 and 45.5±1.25 respectively as compared to standard 42.0±1.36. SAR indicated that presence of pyrimidine ring might be responsible for the anti-inflammatory activity of derivatives **51** and **52**.[26]



51 52

Figure. 2.0: Anti-inflammatory activity of quinoxalin derivatives.

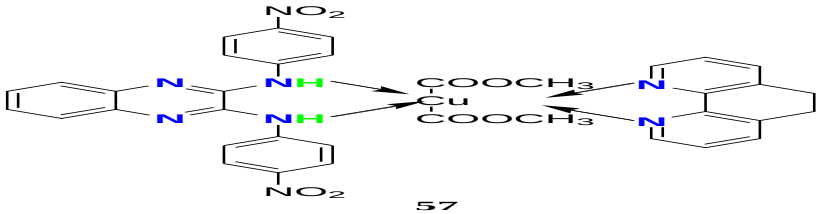
Wagle et al reported that 3-Methyl-7-substituted-1{[5-(aryl)-1,3,4-oxadiazoles-2-yl]-methyl}-quinoxaline-2(1*H*)-ones **53** are best anti-inflammatory compound. Non-steroidal anti-inflammatory drugs (NASID) were used for inflammation, arthritis, margarine, fever or for acute and chronic pains.[27] Rahul & Rajendra afforded sulfonamide quinoxaline derivatives such as 6,7-diphenylquinoxaline-2-sulfonamide **54,** *N*-6,7-triphenylquinoxaline-2-sulfonamide **55** and *N*-((6,7-diphenylquinoxalin-2-yl)sulfonyl)hydrazinecarbothioamide **56** showed anti-inflammatory characteristics and properties.[28]



53 54 55 56

Figure. 2.1: Anti-inflammatory oxadiazole and sulfonamide based quinoxalin derivatives

1.2.4. Antioxidant Activities: Dhanaraj C. J. and coworker reacted N^2, N^3-bis(4-nitrophenyl)quinoxaline-2,3-diamine with 1,10-phenanthroline to afford Co(II), Ni(II), Cu(II) and Zn(II) mixed ligand complexes. Ascorbic acid was used as control. Cu (II) complex **57** had enhanced antioxidant activity when the concentration of the compound increased. Hence the activity was dose dependent.[21]

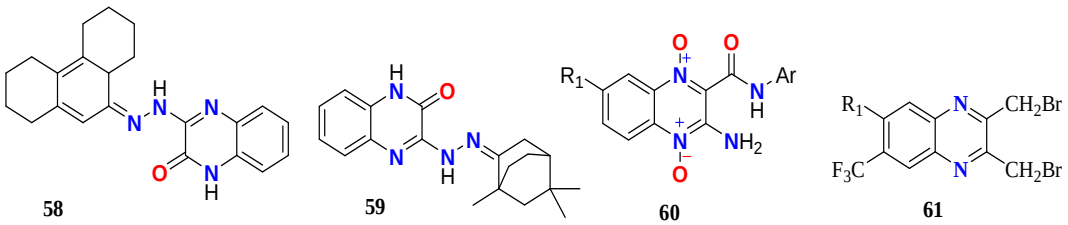


57

Figure. 2.2: Quinoxalin Cu (II) complex antioxidant derivative.

1.2.5. Antifungal activities

Olayinka et al., 2010 reported that (*Z*)-3-{2-[1-(6-Chloro-2-oxo-2*H*-chromen-3-yl) ethylidene] hydrazinyl}quinoxalin-2(1*H*)-one **58**, and (*Z*)-3-[2-(propan-2-ylidene)hydrazinyl]quinoxalin-2(1*H*)-one **59** were proved be potent antifungal agents.[29] Soliman prepared quinoxaline-1,4-di-*N*-oxide compounds by the Beirut reaction between the phenazine derivative and the indenoquinoxaline and reported that the derivative (3-Amino-*N*-(4-methoxyphenyl)-2-quinoxaline carboxamide-1,4-di-*N*-oxide **60** showed antifungal properties.[30] Hisato et al reported that the derivatives of 2,3-bis(bromo methyl)quinoxaline **61** with different substituents at the 6- and 7-positions. The tri flouro methyl group at position-6 showed highest antibacterial as well as broad spectrum antifungal properties.[31]



58 59 60 61

Figure. 2.3: Anti-fungal activities of quinoxaline derivatives.

1.2.4. Anti-Protozoal activities: Kaplum et al synthesized the 2,3-diarylsubstituted quinoxalines which were screened for promastigotes and intracellular amastigotes of L. amazonensis. The derivatives 6,7-dichloro-2,3-diphenylquinoxaline **62** and 3-(3-methoxyphenyl)-2-(4-methoxyphenyl)quinoxaline **63** antiprotozoal activities proved as therapeutic agents for treatment of leishmaniasis.[32]

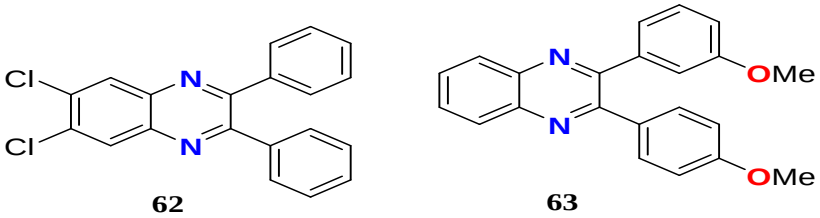


Figure 2.4: Anti-fungal activities of substituted 2,3-diphenylquinoxaline derivatives.

Nakamura C. V. and coworkers synthesized 2, 3-disubstituted quinoxaline compounds and evaluated their antileishmanial and antitrypanosomal activity. Compound 2-chloro-6-methoxy-3-(methylsulfinyl)quinoxaline **64** and 2,7-dichloro-3-(methylsulfinyl)quinoxaline **65** were prepared by oxidation of 3-chloro-2-methylthioquinoxalines. Compound **64** was found highly active against promatigotes and epimastigotes with IC_{50} value as 0.8±0.2µM and 0.5±0.1µM respectively and for Trypomastigotes EC_{50} as 4.2±1.2µM. Compound **65** was demonstrated good activity against promatigotes and epimastigotes with IC_{50} value as 0.1±0.0µM and 0.1±0.0µM respectively and for Trypomastigotes EC_{50} as 1.7±0.1µM. **64** had one chlorine with one methoxy group and **65** had two chlorine atoms responsible for enhanced antiprotozoan activity.[33]

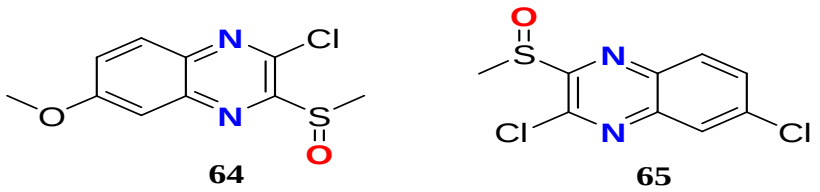


Figure. 2.5: Quinoxalin methylsulfinyl moiety based anti-protozoal derivatives.

1.2.5. Anticonvulsant activities

Eslam et al., synthesized different quinoxaline-2,3-diones scaffolds such as 6-isocyano-7-nitroquinoxaline-2,3(1*H*,4*H*)-dione **65,** 6,7-dinitroquinoxaline-2,3(1*H*,4*H*)-dione **66** & 6-(1*H*-imidazol-1-yl)-7-nitroquinoxaline-2,3(1*H*,4*H*)-dione **67** which showed excellent anticonvulsant activities.[34] Alswah, M. et al reported that 1-(2-([1,2,4]triazolo[4,3-a]quinoxalin-4-ylthio)acetyl)-4-cyclohexylsemicarbazide **68** and 1-(2-([1,2,4]triazolo[4,3-a]quinoxalin-4-ylthio)acetyl)-4-phenyl semicarbazide **69** exhibited excellent and remarkable anticonvulsant activities which were due to the presence of substituents at position 4 of condensed heterocyclic system of quinoxaline.[35]

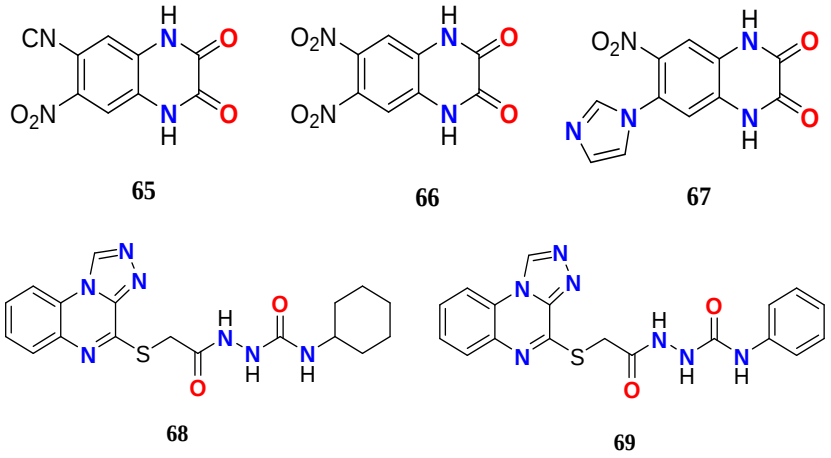


Figure. 2.6:Anti-convulsant quinoxaline derivatives.

1.2.6. Anti-tuberculosis activities

Xiaoka synthesized the quinoxaline derivatives **70, 71 & 72** which have antibacterial activity and showed activity against *Mycobacterium tuberculosis*.[36] 7-Methyl-3-(4'-fluoro)-phenyl quinoxaline-2-carbonitrile-1,4-di-*N*-oxide quinoxaline derivative **73** exhibited selective activity against *Mycobacterium tuberculosis*.[37]

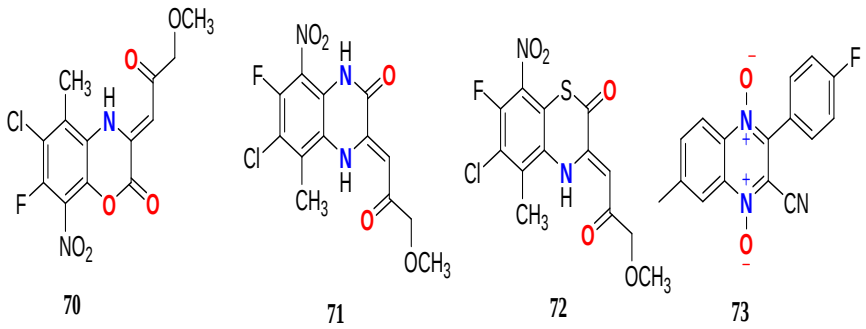


Figure. 2.7: Anti-tuberculosis quinoxaline derivatives.

Yuan and coworkers in 2016 synthesized a series of quinoxalin 1, 4-di-*N*-oxide derivatives and demonstrated their anti-tuberculosis activities. Among the series the compounds the quinoxalin 1,4-di-*N*-oxide derivative **74** and **75** showed potent anti-tuberculosis activities having MIC value 50 and 0.39 µg/ml and CC_{50} value >100 and 50 µg/ml.[38]

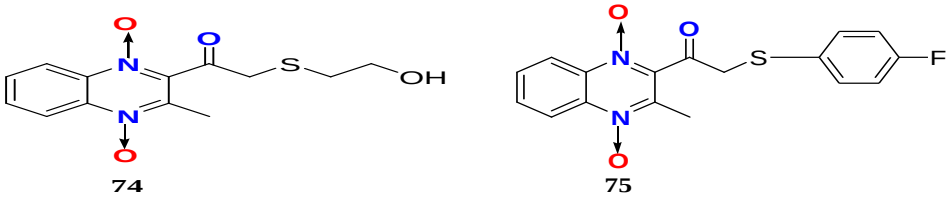


Figure. 2.8: Anti-tuberculosis quinoxalin 1,4-di-*N*-oxide derivatives.

Santivañez-Veliz, M. and coworkers synthesized quinoxaline derivatives and studied them for anti-tuberculosis activity. The scaffolds **76** and **77** proved as best anti-tubercular agents against non-replicating Mycobacterium tuberculosis with IC_{50} value of 1.2 µm and 0.5 µm respectively.[39]

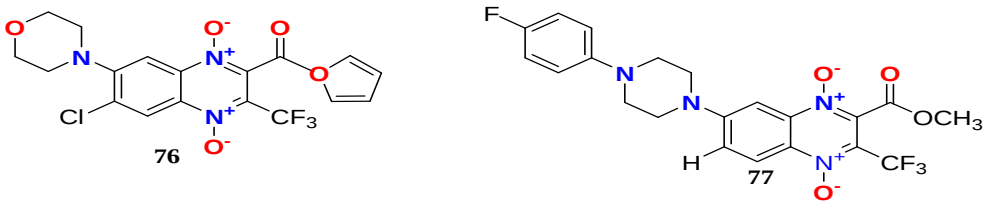


Figure 2.9: Anti-tuberculosis quinoxalin 1,4-di-*N*-oxide derivatives.

1.2.7. Anti-diabetic activities

Eissa IH and coworkers in 2017 prepared quinoxaline derivatives as anti-hyperglycemic activity. The derivative 1-cyclohexyl-3-(4-(2-(3-methyl-2-oxoquinoxalin-1(2*H*)-yl) acetamido)phenyl- sulfonyl) urea **78** exhibited best anti-hyperglycemic activity with decrease of blood glucose level is 50.58 % and bind to PPARɣ with IC_{50} = 0.482 µM and showed good insulin secreting activity having EC_{50} = 0.92 µM.[40]

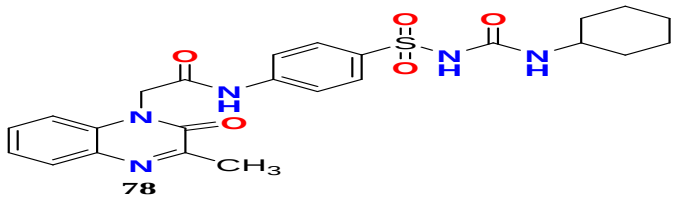


Figure 2.10: Anti-diabetic quinoxalin-dione derivative.

1.2.9. Anti-cancer and anti-proliferative activities

Deleuze et al. afforded Imidazo[1,2-*a*]quinoxaline analogues **79** and **80** were synthesized by condensation of 2-imidazole carboxylic acid, followed by a coupling with *ortho*-fluoroaniline. These quinoxaline derivatives showed prominent antitumor activities against a human amelanotic melanoma cell line (A 375 cells). These analogues were used in cytokine research in outside of living organism or *in vitro* but not *in vivo*.[41]

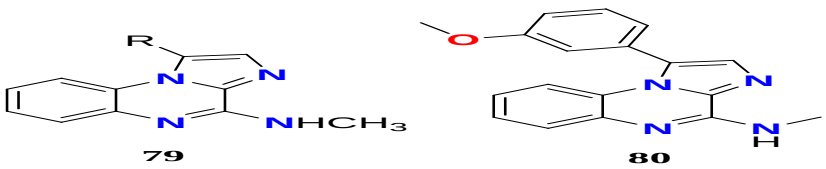


Figure. 2.11: Anti-tumor Imidazole based quinoxalin derivative.

Paola et al prepared 5,7-Diamino-3-phenyl-2-benzylamino, 2-phenoxy **81** and 2-thiophenyl **82** substituted novel quinoxalines derivatives exhibited antitumor activity in nine different cell lines of human cancers.[42] Quinoxaline-6-carbaldehyde such as (*Z*)-5-(quinoxalin-2-ylmethylene) thiazolidine-2,4-dione **83** (*E*)-1-(2,5-dimethoxyphenyl)-3-(quinoxalin-2-yl)prop-2-en-1-one **84** derivatives were derived from chalcones which demonstrated highly effective impact and activities against brain tumor cell lines (glioma) from human and rat origin.[43]

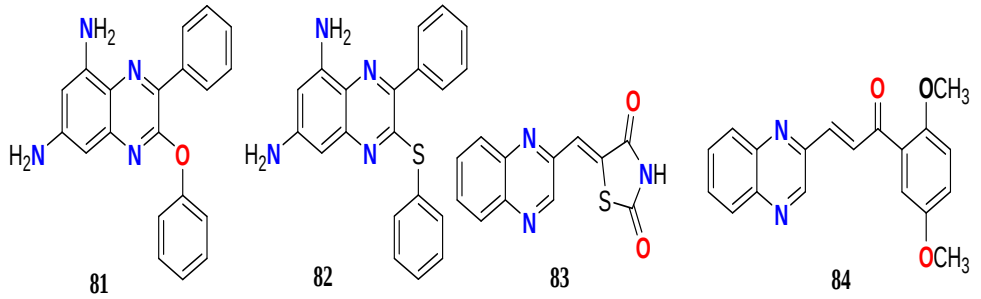


Figure. 2.12: Anti-tumor quinoxalin derivatives.

Zhang and coworkers in 2017 reported *N*-substitued-3-oxo-1,2,3,4-tetrahydro-quinoxaline-6-carboxylic acid derivative and studied their anti-proliferative activity. The saffold methyl 3-oxo-1-(2-(3,4,5-trimethoxyphenyl)acetyl)-1,2,3,4-tetrahydroquinoxaline-6-carboxylate **85** showed best anti-proliferative activity against HeLa with IC_{50} = 0.126 µM, SMMC-7721 with IC_{50} = 0.071 µM and K562 cell line with IC_{50} = 0.164 µM.[44] Patinote and coworkers studied imidazo[1,5-a]quinoxaline and pyrazolo[1,5-a]quinoxaline derivatives for their anti-proliferative activity. The imidazoquinoxaline derivative named 1-bromo-N,8-dimethylimidazo[1,2-a]quinoxalin-4-amine **86** proved as best anti-proliferative agent for human melanoma cell line A375 and its 66% inhibition rate was observed.[45]

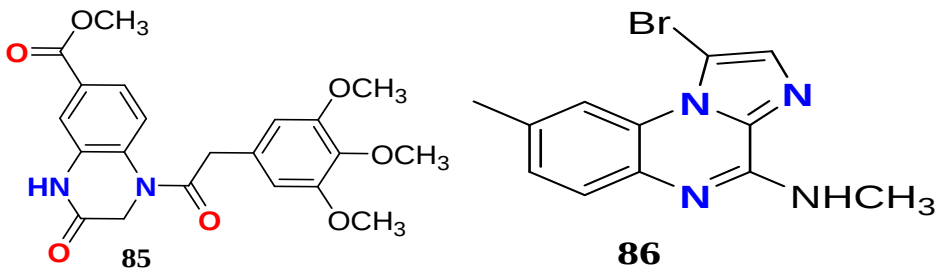
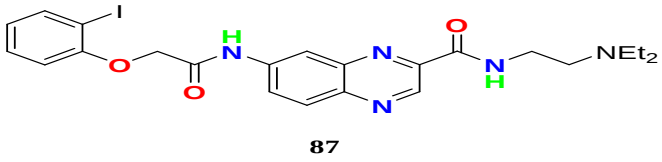


Figure. 2.13: Anti-proliferative quinoxalin derivatives.

M. Emmanuel and coworkers (2014) synthesized novel quinoxaline derivatives by reacting 4-nitro phenyl(2-((2-(diethylamino)ethyl)carbomoyl)quinoxalin-6-yl)-carbamate with *N*,*N*-

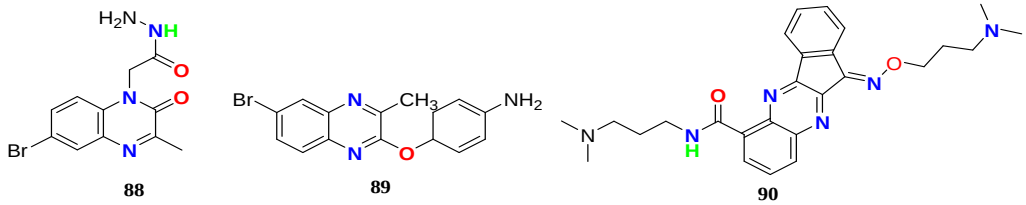
Diisopropyl ethylamine, in dry tetra hydrofuran. These compounds were evaluated for anti-tumor activity against melanoma cells line and compound **87** exhibited high anticancer activity with 3.30 ± 0.75% ID/g.[46]



87

Figure. 2.14: Anti-cancer quinoxalin derivatives.

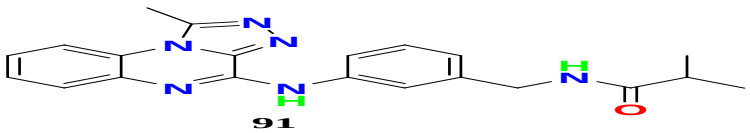
Abbas SH. and co-workers prepared substituted quinoxaline then analyzed for anticancer activity against breast cancer cell line (MCF-7), Non-small cell lung cancer cells line (NCI-H460) and CNS cancer cells line (SF-268). Doxorubicin was used as a standard drug. Compounds 2-(6-Bromo-3-methyl-2-(1H)quinoxalinon-1-yl)acetohydrazide **88** and 4-(6-bromo-3-methyl quinoxalin-2-yloxy)cyclohexa-1,5-dienamine **89** were the most potent derivatives than all other tested compounds. The IC_{50} values of compound **88** were 0.01 ± 0.001µg/L for MCF-7, 0.02 ± 0.004 µg/L for NCI-H460 and 0.06 ± 0.002 µg/L for SF-268. The scaffold **89** have IC_{50} 0.02 ± 0.001 µg/L, 0.03 ± 0.006 µg/L and 0.06 ± 0.008 µg/L for MCF-7, NCI-H460 and SF-268 cells lines respectively.[47] Tseng and coworkers afforded indeno[1,2-*b*] quinoxaline derivatives by refluxing *N*-[3-(Dimethylamino)propyl]-11-oxo-11*H*-indeno[1,2-*b*]quinoxaline-6-carboxamide hydrochloride and 3-(dimethylamino)propoxyamine hydrochloride in ethanol. The compounds were evaluated for anticancer activity against MDA-MB231, PC-3, Huh-7 and human fetal lung fibroblast cell line (MRC-5). Among all the tested compounds, 11-{[3-(dimethylamino)propoxy]imino}-*N*-[3-(dimethylamino) propyl]-11*H*-indeno[1,2-*b*]quinoxaline-6-carboxamide **90** exhibited more potency against MDA-MB231, PC-3, and Huh-7 with IC_{50} values of 0.87 µM, 0.82 µM and 0.64 µM respectively. It showed inactivity against MRC-5 cells line with an IC_{50} value of 31.51 µM. Substitution of methyl group did not influence the activity while substitution of amino alkoxyimino groups increase the anti-cancer activity.[48]



88 **89** **90**

Figure 2.15: Anti-cancer quinoxalin derivatives.

Ali I. and coworkers reported to synthesize quinoxaline derivatives by reacting N-(3-(aminomethyl)phenyl)-1-methyl-[1,2,4]triazolo[4,3-a]quinoxalin-4-amine with acetyl chloride in presence of *N*,*N*-Diisopropylethylamine. These compounds were screened for anticancer activity against luckemia cell lines Ty-82 and THP-1. The derivative **91** was the most potent anticancer agent than all other synthesized compounds with IC_{50} value 2.50µM and 1.60 µM against Ty-82 and THP-1 cell lines, respectively. Substitution of isobutyl amide group enhance the anti-cancer activity while removal of tertiary butyl carbamate group lessen the activity.[49]



91

Figure. 2.16: Quinoxalin-triazol based anti-cancer derivative.

CONCLUSION

The review article reveals that quinoxalines derivatives are benzoheterocyclic which have wide spectrum and diversified potential pharmaceutical and pharmacologically activities such as anti-tubercular, anti-leishmanial, anticancer, anticonvulsant, antiviral, anti-depressant, anti-proliferative, antifungal, anti-inflammatory and antibacterial. The plethora of research mentioned in this review article is help for researchers in the synthesis of new quinoxaline derivatives and also aid the scientists in the development of quinoxaline nucleus based new medicines, therapeutic agents, analogues and drugs with greater bio absorption as well as having no cytotoxicity for the treatment of various diseases to serve the humanity.

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