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REVIEW

Comprehensive Review on Versatile Pharmacology of Quinoxaline Derivative

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Abstract—Quinoxaline is a nitrogen-containing heterocyclic compound having many pharmaceutical and industrial purposes. It can be synthesized by adopting green chemistry principles. The quinoxaline containing drugs such as Olaquindox, Echinomycin, Atinoleutin, Levomycin, and Carbadox are currently used as an antibiotic in the market. The objective of this review is to enumerate the various multifunctional property of the quinoxaline moiety. This present review contains the newer quinoxaline derivatives against many targets, receptors, or microorganisms. This work comprises the study on quinoxaline as a core unit from the year 2002 to 2020. All the collected literature has been combined and highlighted for the effective use of that particular derivative. Various potent quinoxaline compounds have been analyzed in the literature. About 50 papers have been reviewed for the novel quinoxaline compounds, the potent derivatives have been reported, and structures were given. The critical role of the quinoxaline on the various heterocyclic moieties has been given more attention in this review. This review paves the way as a source of references for the further development of drug discovery in the wide spectrum of its biological importance.

Keywords: quinoxaline, biological activity, IC_{50} value, anti-microbial, anti-cancer, anti-malarial

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Abbreviations: RNA, ribonucleic acid; DNA, deoxyribonucleic acid; BET, bromodomain and extra-terminal; *t*-BOC, tertiary butyl carbamate; ADMET, absorption distribution metabolism excretion and toxicity; IC_{50}, inhibition constant; PDB, protein data bank; CNS, central nervous system; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; TPZ, tirapazamine; MIC, minimum inhibitory concentration; 3D-QSAR, three-dimensional quantitative structure–activity relationship; PTZ, pentylenetetrazol; PAMPA, parallel artificial membrane permeation assay; BBB, blood–brain barrier; MABA assay, microplate alamar blue assay; SDRMIC, single drug-resistant minimum inhibitory concentration; Mtb, Mycobacterium tuberculosis; UPLC-MS, ultra-pressure liquid chromatography-mass spectroscopy; EEFs, exo-erythrocytic forms; DMF, dimethylformamide; HIV-RT, human immunodeficiency virus reverse transcriptase; CPE, cytopathogenic effect; DPPH assay, 2,2-diphenyl-1-picrylhydrazyl assay; FRET, fluorescence resonance energy transfer; PPARγ, peroxisome proliferator-activated receptor gamma; SURs, sulfonylurea receptor; qRT-PCR, quantitative reverse transcription-polymerase chain reaction; COX-2, cyclooxygenase-2; HPLC-MS, high-performance liquid chromatography-mass spectroscopy; MALDI-TOF, matrix-assisted laser desorption/ionization-time of flight; ABTS, 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid; SAR, structure–activity relationship.

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INTRODUCTION

In 1884, Korner [1] and Hinsberg [2] first discovered the reaction of spontaneous condensation between *o*-phenylene diamines and 1,2-dicarbonyl compounds to give the product as quinoxaline (C8H6N2). A white crystalline powder occurs widely in natural products and many pharmaceuticals ingre-

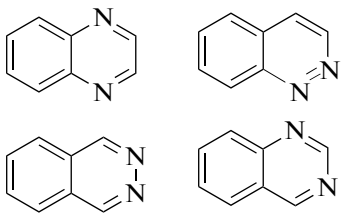
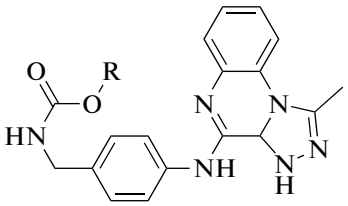


Fig. 1. Quinoxaline and its isomers.



1 = R–O–C(CH_3)

2 = R–C_2H_5

Fig. 2. Chemical structure of [1,2,4]triazolo(4,3-*a*)quinoxaline-amino-phenyl derivatives.

dients. They were also called 1,4-diazanapthalene,1, 4-naphthyridine, etc. Structurally quinoxaline is isomeric (Fig. 1) to other Naphthyridines like Quinazoline, Cinnoline, Phthalazine [3].

Several decades before quinoxaline derivatives were first synthesized and tested for antimalarial activity [4, 5]. In 1965, the synthesis of quinoxaline-bearing sulfonamide with their physicochemical properties was reported [6]. Besides, indolo-(2,3-*b*)quinoxaline derivatives and 3,4-dihydro quinoxaline-2(1*H*)-thiones derivatives were reported for their anti-viral activity [7, 8]. As a veterinary medicine [9], quinoxaline with sulfonamide derivatives was used in the treatment of bacterial infections such as coccidiosis.

The existing antibiotics in market based on quinoxaline nucleus are Quinomycin or Echinomycin [10], Levomycin [11] and Quinacillin [12] that are active against Gram-positive bacteria. Echinomycin (*N*-[2,4,12,15,17,25-hexamethyl-27-methylsulfanyl-3,6,10,13,16,19,23,26-octaoxo-11,24-di(propan-2-yl)-20-(quinoxaline-2-carbonylamino)-9,22-dioxa-28-thia-2,5,12,15,18,25-hexazabicyclo[12.12.3]nonacosan-7-yl]quinoxaline-2-carboxamide) was a naturally occurring antibiotic which is used in treating cancer patients [13]. It also used as an anti-bacterial, antiviral and a strong RNA synthesis inhibitor. It was isolated from *Streptomyces echinatus* bacterium and from *Streptomyces lasalienis*. Varenicline [14] (7,8,9,10-tetrahydro-6*H*-6,10-methanoazepino[4,5-*g*]quinoxaline) was used for recovery of patients from nicotine addiction (Nicotine receptor agonist). Brimonidine was (5-bromo-*N*-(4,5-dihydro-1*H*-imidazol-2-yl)-quinoxalin-6-amine) used in treatment of glaucoma [15, 16] and ocular hypertension [17, 18].

Later on, it was found to be a potential lead compound in various fields of medicine and pharmacy. By conducting various research on this lead compound, the substituted quinoxaline along with their derivatives possess a wide range of applications in treating many diseases such as anti-cancer [19], anti-Alzheimer's [20], anti-inflammatory [21], anti-convulsion [22], anti-microbial [23], anti-mycobacterium [24], anti-protozoal [25], antihypertensive agents [26], anti-oxidant [27], etc.

In continuation of our research on quinoxaline [28–32], herein we report the complete review for the versatile pharmacological action of the same heterocycle.

1. ANTI-CANCER AND ANTI-PROLIFERATIVE ACTIVITY

A novel series of [1, 2, 4]triazolo(4,3-*a*)quinoxaline-amino-phenyl derivatives as bromodomain and extra-terminal (BET) protein inhibitors were designed by Imran Ali et al. An emerging BET protein was identified as a target for a new small molecule treatment as an anti-cancer. In vitro biological inhibition activity for all the synthesized compounds was done using BRD4 binding assay. A compound (1) (Fig. 2). With tertiary butyl carbamate (BOC) substituted triazole-quinoxaline shows better cellular potency when compared with standard I-BET762 (Molibresib) and OTX-015 (Birabresib). Further replacing BOC with iso-butyryl amide (2) (Fig. 2) gives a more potent compound with improved ADME parameters [33].

Ibrahim H. Eissa et al. designed and synthesized a series of quinoxaline moiety by the fusion of DNA pairs using hydrophobic interactions. In silico studies like Docking, ADMET parameters, and characterization for all the synthesized compounds were carried out. All the compounds were evaluated for their anti-proliferative activity against HePG-2, MCF-7 and HCT-116 cell lines via Sulforhodamine B colorimetric assay. The DNA-topoisomerase-II activity was measured to find the mode of action. About four compounds namely, 1-(2-bromoethyl)-1,4-dihydro quinoxaline-2,3-dione (3), 4-amino-*N*′(3-chloroquinoxalin-2-yl) benzohydrazide (4), *N*′-(3-chloroquinoxalin-2-yl)isonicotinohydrazide (5), and 3-mercaptoquinoxalin-2-yl carbamimidothioate (6) (Fig. 3) showed better inhibition activity with the IC_{50} value between 7.6 ± 0.4 and 11.9 ± 0.2 μM in human cell lines compared with doxorubicin as a reference agent (IC_{50} = 9.8 μM) [34].

Derivatives of dehydroabietic acid (DAA) and quinoxaline were designed and synthesized by Wen Gu et al. The designed compounds were evaluated their anticancer activity against three human cell line namely MCF-7 (breast cancer cell line), SMMC-

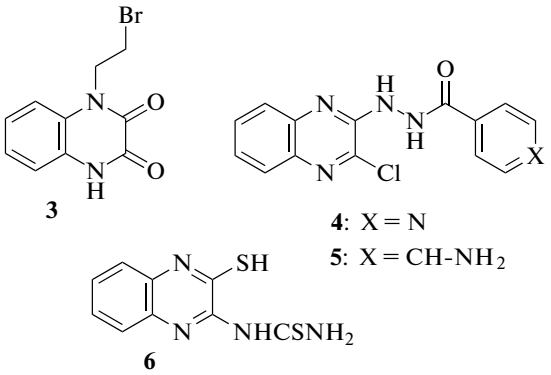


Fig. 3. Chemical structure of quinoxaline moiety.

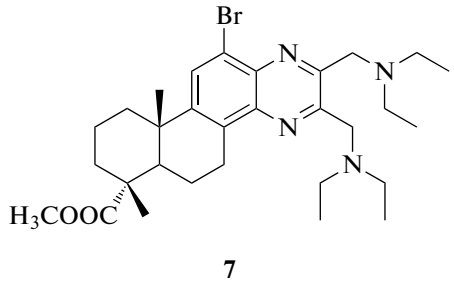


Fig. 4. Chemical structure of dehydroabietic acid (DAA) quinoxaline derivative.

7721(hepatocarcinoma cell line) and HeLa (cervical carcinoma cell line) by MTT assay (using Etoposide as reference drug). The compound methyl 12-bromo-2',3'-bis((diethylamino)methyl)-13,14-pyrazinyl deisopropyldehydroabietate **(7)** (Fig. 4) exhibited more activity in all three cell lines. The compound also showed G0/G1 phase cell cycle arrest and induces apoptosis in a dose-dependent manner on the SMMC-7721 cell line [35].

Hebat-Allah S. Abbas et al. discovered a new series of substituted quinoxaline derivatives and evaluated the *c*-Met kinase inhibitor activity. CDOCKER was used to find the binding affinity of all the designed compounds with protein c-Met kinase 3f66 (PDB ID). In vitro cytotoxicity in MCF-7 (breast adenocarcinoma), NCI-H460 (lung cancer cell line) and SF-268 (CNS cancer cell line) were examined. Compounds 6-bromo-3-(4-methoxystyryl)quinoxaline-2(1*H*)-one (8), 2-(6-bromo-3-methyl-2-(1*H*)quinoxalinon-1-l)acetohydrazide (9), 6-bromo-3-methyl-*N*-[4-(piperidin-1-ylsulfonyl)phenyl] quinoxalin-2-amine (10), 2-[6(7)-bromo-2-methyl quinoxalin-3-yloxy]aniline (11), 4-[6(7)-bromo-2-methylquinoxalin-3-yloxy]aniline (12) and 4-(6-Bromo-3-methylquinoxalin-2-yloxy)-*N*-(4-chlorobenzylidine)aniline (13) (Fig. 5) showed the highest activity against the cancer cell line and compared with doxorubicin as a standard drug [36].

Zahra Ghanbarimasir et al. developed a new hybrid of 2-aminoimidazole-quinoxaline. The structures of compounds were spectrally analyzed. An MTT assay was carried out in two concentrations (50 and 10 μg/mL) against colon cancer cells (HCT-116) and breast cancer cells (MCF-7) with Doxorubicin and Imatinib as a reference agent. In this series, three compounds (*E*)-4-phenyl-1-((quinoxalin-2-ylmethylene)amino)-1*H*-imidazol-2-amine (14), (*E*)-1-(((6-chloroquinoxalin-2-yl)methylene)amino)-4-(4-methoxy phenyl)-1*H*-imidazol-2-amine (15), (*E*)-1-(((7-chloroquinoxalin-2-yl)methylene)amino)-4-(4-methoxy phenyl)-1*H*-imidazol-2-amine (16) (Fig. 6) showed 70% inhibition at 50 μg/mL and 40% against inhibition at 10μg/mL concentrations. Especially compound (14) showed induced apoptosis in both the cancer cell lines [37].

Scherbakov A.M. et al. reported a novel series of quinoxaline-2-carbonitrile-1,4-dioxide. The research reported potency especially against breast cancer under hypoxia and normoxia conditions. A modified

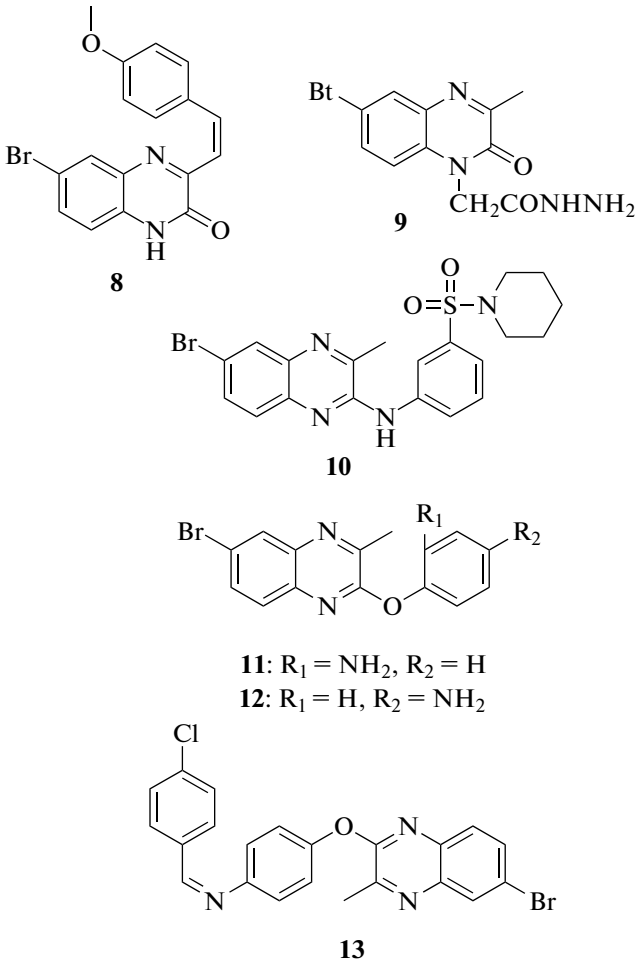
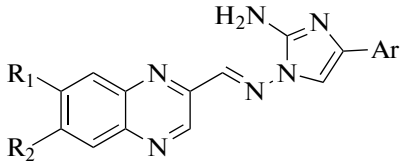
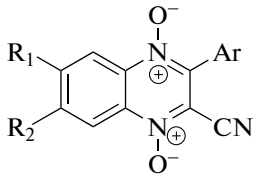


Fig. 5. Chemical structure of substituted quinoxaline derivative as a c-MET kinase inhibitor.



14: R_1, R_2= H, Ar = phenol
15: R_1 = Cl, R_2 = H, Ar = *p*-OMe-phenol
16: R_1 = H, R_2 = Cl, Ar = *p*-OMe-phenol

Fig. 6. Chemical structure of 2-aminoimidazole-quinoxaline derivative.



17: R_1, R_2= F, Ar = phenol
18: R_1 = Cl, R_2 = F, Ar = phenol
19: R_1, R_2= F, Ar = 4-OMe-C_6H_4
20: R_1, R_2 = F, Ar = 3-FC_6H_4

Fig. 7. Chemical structure of quinoxaline-2-carbonitrile-1,4-dioxide.

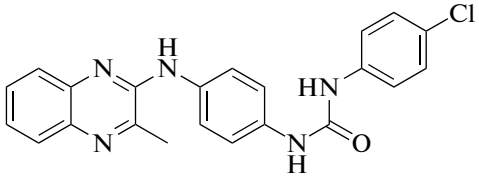


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Fig. 8. Chemical structure of quinoxaline derivative as anti-cancer.

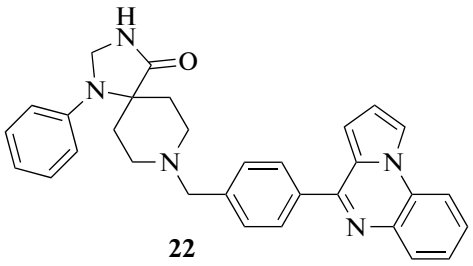

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Fig. 9. Chemical structure of pyrrolo[1,2-*a*]quinoxaline derivative.

MTT assay was done against MCF-7, MDA-MB-231 human breast cancer cell lines under certain conditions. Cytotoxicity against HCT-116 human colon cancer cell line and K562 human hematopoietic cell line were also reported. TPZ (tirapazamine) and doxorubicin were selected as standard drugs respectively. All the synthesized compounds showed 3 to 40 fold more potent than the standard drugs. Thus di-substituted derivatives (17, 18, 19, and 20) (Fig. 7) like halogen increases the antiproliferative activity and cytotoxicity but mono substitution lowers the activity [38].

Aliya M.S. El Newahie et al. synthesized a series of quinoxaline derivatives as potent anti-cancer agents. The designed compounds were based on amide, urea, thiourea, and sulphonamide moieties. The synthesis was done by reacting o-phenylenediamine and α-keto carboxylic acids. An in-vitro assay was carried out against three cancer cell lines–HCT116 (colon cancer), MCF-7 (breast cancer), and HepG2 (hepatocellular carcinoma) by MTT assay. Doxorubicin was used as a reference agent. The compound 1-(4-chlorophenyl)-3-(4-((3-methyl quinoxalin-2-yl)amino)phenyl)urea (21) (Fig. 8) Showed a promising activity against the HCT116 cell line with an IC_{50} value of 2.5 μM and produced disruption in the G2/M phase cell cycle [39].

A new series of pyrrolo[1,2-a] quinoxaline-based compounds were designed and reported by Jean Guillon et al. An MTT assay against three human leukemia cell lines – K562, HL60, and U937 were performed. The compound 1-phenyl-8-[[4-(pyrrolo[1,2-a]quinoxalin-4-yl) phenyl] methyl]-1,3,8-triazaspiro[4.5]decan-4-one (22) (Fig. 9) showed the highest activity with MIC value of 3.5 ± 0.2 μM in K562, 15 ± 0.4 μM in HL60 and greater than 20 μM in U937 cell line [40].

2. ANTI-MICROBIAL ACTIVITY

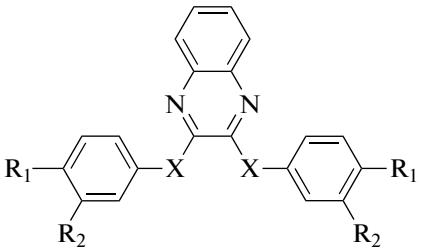
El-Atawy M.A. et al. designed a new series of substituted quinoxaline, which were expected to inhibit anti-bacterial and anti-fungal agents. This type of dual-acting compound was synthesized by two methods. One method was by cyclo-condensation of benzyl derivatives with *o*-phenylenediamine and the other method was 2,3-disubstituted quinoxaline by nucleophilic replacement reactions. In vitro screening of antibacterial activity against gram-positive bacteria such as *Bacillus subtilis* (RCMB 015), *Staphylococcus aureus* (RCMB 010010) and gram-negative bacteria such as *Escherichia coli* (ATCC 25955) and *Proteus vulgaris* (ATCC 13315) and anti-fungal activity *Candida albicans* (ATCC 10231) and *Aspergillus flavus* (RCMB 002002) were reported. Gentamycin and Ketoconazole were taken as a standard drug respectively. The compounds 2,3-di(thio-4-chlorophenyl)quinoxaline (23) and *N2*,*N3*-bis(3-chlorophenyl)quinoxaline-2,3-diamine (24) (Fig. 10) showed highest inhibition activity on Gram-negative bacte-

rium (*E. coli*) at a concentration of 8 μg/mL and the pentacyclic compound (25) (Fig. 10) Benzimidazo[2',1':2,3]thiazolo[4,5-*b*]quinoxaline showed highest anti-fungal inhibition activity on both the species at 16 μg/mL. This reveals that the aromatic amine and sulfur functionality of quinoxaline-bearing compounds enhances the anti-bacterial and anti-fungal activity respectively [41].

A series of new Schiff bases of quinoxaline derivatives were designed, synthesized, and evaluated by Govindaraj Saravanan et al. Docking score of the compounds against the *Mycobacterium tuberculosis* receptor (PDB ID: 2PZI) were reported. The paper disc diffusion technique was used to find the MIC values of the synthesized compounds. Anti-bacterial activity against, Gram-positive bacteria *Bacillus subtilis* (ATCC 6633), Gram-negative bacteria *Pseudomonas aeruginosa* (ATCC 27853) and *Klebsiella pneumonia* (ATCC 13883) and for anti-fungal activity *Aspergillus niger* (ATCC 9029) and *Aspergillus flavus* (ATCC 10124) were reported. Ciprofloxacin and Ketoconazole as standard drugs, respectively. Among all the synthesized compounds, only compound 2-(2-(4-nitrobenzylidene)hydrazinyl)-*N*-(4-((3-(phenylimino)-3,4-dihydro quinoxalin-2(1*H*)-ylidene)amino)-phenyl)acetamide (26) (Fig. 11) shows most potent inhibition activity when compared to the standard drugs [42].

Heying Zhang et al. achieved a goal of discovering a new anti-fungal agent by molecular hybridization of thiazolidiones and quinoxaline ring fusion. A novel 26 quinoxalin-1,4-di-*N*-oxides with thiazolidione moiety were prepared. An in-vitro broth microdilution assay against four fungi strains such as *C. albicans* (ATCC 90028), *C. tropicalis* (ATCC 7349), *A. fumigatus* (3.5352), and *C. neoformans* (2.3201). Amphotericin b and Ketoconazole were used as standard drugs. The derivatives of 7-*F*-2-(3'-*P*-fluorophenyl-4'(5*H*)-thiazolidinone)-quinoxaline-1,4-di-*N*-oxide (27), 7-*F*-2-(3'-*P*-chlorophenyl-4'(5*H*)-thiazolidinone)-quinoxaline-1,4-di-*N*-oxide (28), 7-*Cl*-2-(3'-*P*-fluorophenyl-4'(5*H*)-thiazolidinone)-quinoxaline-1,4-di-*N*-oxide (29), 7-*Cl*-2-(3'-*P*-chlorophenyl-4'(5*H*)-thiazolidinone)-quinoxaline-1,4-di-*N*-oxide (30) (Fig. 12) showed more potent inhibitory actions with the MIC values ranges from 2–4 μg/mL. further studies like 3D-QSAR analysis and contour analysis showed better activity of about $Q_2 = 0.914$, $r_2 = 0.967$ and $Q_2 = 0.918$, $r_2 = 0.968$ respectively. Thus, electron-withdrawing groups possess good anti-fungal activity [43].

Ammar Y.A. et al. discovered a novel fragment-based drug design of disubstituted sulfonyl quinoxaline compounds. The novel 2,3-quinoxalinedione-6-sulfonyl chloride was synthesized by the reaction of 2,3-(1*H*,4*H*)-quinoxalinedione with chloro-sulphonic acid. Followed by the reaction of chloro-sulfonic acid gives a new molecule. All the compounds were evaluated for their anti-microbial activity using



23: X = S, R_1 = Cl, R_2 = H
24: X = NH, R_1 = H, R_2 = Cl

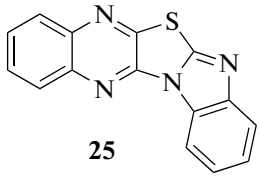


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Fig. 10. Chemical structure of 2,3-disubstituted quinoxaline derivative.

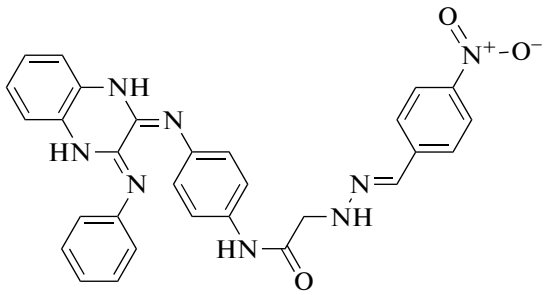

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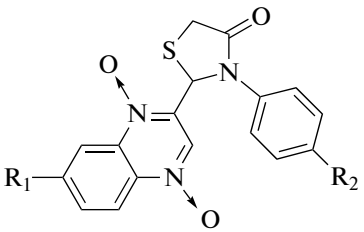
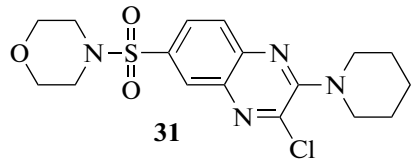
Fig. 11. Chemical structure of Schiff bases quinoxaline derivative.



27: R_1 = –F, R_2 = –F
28: R_1 = –F, R_2 = –Cl
29: R_1 = –Cl, R_2 = –F
30: R_1 = –Cl, R_2 = –Cl

Fig. 12. Chemical structure of quinoxalin-1,4-di-*N*-oxides with thiazolidione moiety.



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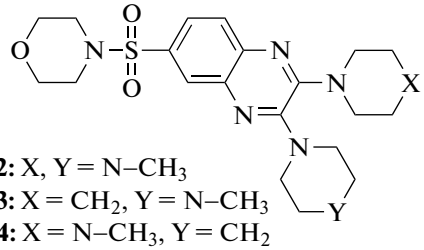
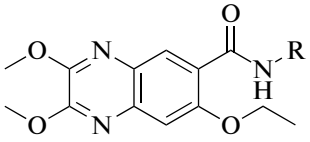


32: X, Y = N–CH_3
33: X = CH_2, Y = N–CH_3
34: X = N–CH_3, Y = CH_2
35: X = O, Y = N–CH_3
36: X, Y = O

Fig. 13. Chemical structure of substituted sulfonyl quinoxaline derivatives.



37: R = 3-chloro-4-fluorophenol
38: R = 2-iodo-3-trifluoromethylphenyl
39: R = 2-hydroxyethyl
40: R = 2-ethynylphenyl

Fig. 14. Chemical structure of quinoxaline-6-carboxamide derivatives.

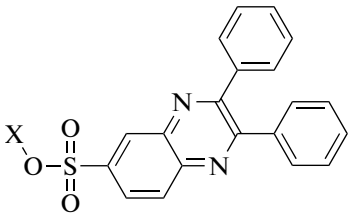
conventional paper disc diffusion method against six anti-bacterial strains namely *Bacillus subtilis* (ATCC 6633), *S. aureus* (ATCC 29213), *E. faecalis* (ATCC 29212) as gram-positive bacteria, and *E. coli* (ATCC 25922), *P. aeruginosa* (ATCC 27853), *S. typhi* (ATCC 6539) as gram-negative bacteria and also against two anti-fungal strains, *C. albicans* (ATCC 10231), *F. oxysporum* (RCMB 008002). Tetracycline and amphotericin B used as the standard drug. Among the synthesized compounds, six compounds 3-chloro-6-morpholinosulfonyl-2-(piperidin-1-yl) quinoxaline (31), 2,3-bis (4-methyl piperazine-1-yl)-6-morpholino sulfonyl quinoxaline (32), 3-(4-methylpiperazin-1-yl)-2-(piperidin-1-yl)-6-morpholinosulfonyl quinoxaline (33), 2-(4-methylpiperazin-1-yl)-3-(piperidin-1-yl)-6-morpholino sulfonyl quinoxaline (34), 3-(4-methylpiperazin-1-yl)-2-morpholino-6-morpholinosulfonylquinoxaline (35), 3-hydrazino-2-(morpholino)-6-morpholino sulfonyl quinoxaline (36) (Fig. 13) showed promising antibacterial activity with the MIC values ranging from 2.44–180.14 μM and the compounds (31) and (36) showed higher antifungal activity than the standard drug with the MIC value ranging from 19.79 to 39.59 μM. Further docking studies revealed that these compounds possess a good binding affinity towards DNA gyrase in comparison with ciprofloxacin [44].

Keesari Srinivas et al. synthesized a series of novel quinoxaline-6-carboxamide derivatives. The compounds were estimated for the activity using the agar gel diffusion method against four bacterial strains namely, *Staphylococcus aureus* (MTCC 96), *Streptococcus pyogenes* (MTCC 442), *Escherichia coli* (MTCC 443), *Pseudomonas aeruginosa* (MTCC 424) by taking norfloxacin as a standard drug. The compounds *N*-(3-chloro-4-fluorophenyl)-7-ethoxy-2,3-dimethoxyquinoxaline-6-carboxamide (37), 7-ethoxy-*N*-(2-iodo-3-(trifluoromethyl) phenyl)-2,3-dimethoxyquinoxaline-6-carboxamide (38), 7-ethoxy-*N*-(2-hydroxyethyl)-2,3-dimethoxyquinoxaline-6-carboxamide (39), 7-ethoxy-*N*-(2-ethynyl phenyl)-2,3-dimethoxyquinoxaline-6-carboxamide (40) (Fig. 14) showed highest antibacterial activity [45].

Goyal Rakesh et al. designed and synthesized a new series of 2,3-diphenylquinoxaline-7-sulphonyl chloride using an elimination-addition reaction. In silico studies revealed a good binding affinity for the compounds towards gamma-glutamyl transpeptidase enzyme. The compounds were subjected to the diffusion method for their microbial screening in two different concentrations (200 and 400 μg) against *S. aureus* (2079) and *E. coli* (2685). Zone of inhibition was determined. Azithromycin was taken as a reference drug. The compound naphthalene-2-yl-2,3-diphenylquinoxaline-7-sulphonate (41) showed good sensitivity in both the strains of organisms. In 400 μg, the compounds 4-hydroxyphenyl-2,3-diphenylquinoxaline-7-sulphonate (42) and naphthalene-1-yl-2,3-diphenylquinoxaline-7-sulphonate (43) (Fig. 15) also showed sensitivity in both the strains [46].

Rahul Ingle et al. reported the synthesis of 2,3-diphenylquinoxaline derivatives by Nucleophilic substitution reaction. The reactants were refluxed with primary aromatic amines with 10% aqueous sodium hydroxide to give the novel quinoxaline derivatives. All the synthesized compounds were evaluated through the disk diffusion method using the tube dilution technique against *S. aureus* and *E. coli.* (ATCC 2079 and ATCC 2685 respectively). Azithromycin was used as a reference drug. In this series, three compounds N-(2-nitrophenyl)-2,3-diphenylquinoxaline-6-sulfonamide (44), N-(4-chlorophenyl)-2,3-diphenylquinoxaline-6-sulfonamide (45), *N*-(3-chlorophenyl)-2,3-diphenylquinoxaline-6-sulfonamide (**46**) (Fig. 16) showed potent inhibition activity against the strains. Substitution of the electron-withdrawing group on the 2,3-diphenylquinoxaline had strong inhibition activity against the bacterial strains [47].

An intermediate cyclization of the Pictet–Spengler reaction involved the synthesis of 5,6-dihydroindolo[1,2-α] quinoxaline derivatives by Hui Xu, et al.



41: X = C_6H_5OH
42: X = 1-napthalene
43: X = 2-napthalene

Fig. 15. Chemical structure of 2,3-diphenylquinoxaline-7-sulphonyl chloride derivatives.

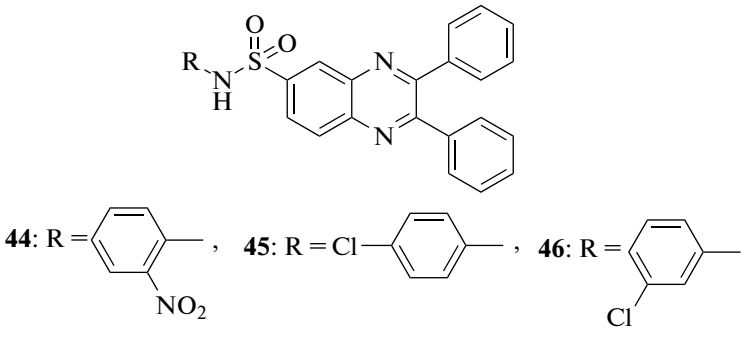
The resultant structure was confirmed by spectral data. Using the Potato dextrose agar method, all the compounds were evaluated for their antifungal activity against five phytopathogenic species i.e., *Fusarium graminearum, Pyricularia oryzae, Fusarium oxysporum* f. sp. *vasinfectum, Alternaria alternata, and Alternaria brassicae.* Hymexazol was the standard (an agricultural fungicide). Among the series of synthesized compounds, five compounds 6-(*p*-hydroxyphenyl)-5,6-dihydro-indolo[1,2-*a*]quinoxaline (47), 6-(*p*-Hydroxyphenyl) -5,6-dihydro-7-methylindolo[1,2-*a*]quinoxaline (48), 6-(*p*-hydroxy phenyl)-5,6-dihydro-8-methyl indolo[1,2-*a*]quinoxaline (49), 6-(*p*-Hydroxyphenyl)-5,6-dihydro-10-methindolo[1,2-*a*]quinoxaline (50), 6-(4-nitrophenyl)-5,6-dihydro-9-cyanoindolo[1,2-*a*]quinoxaline (51) (Fig. 17) showed a promising antifungal activity against various fungal strains. The compounds with the presence of cyano group at the A-ring and hydroxyl groups at the fourth position on the E-ring of 5,6-dihydro-indolo[1,2-*a*]quinoxalines play a prominent role in the action [48].

Dalia Hussein Soliman et al. synthesized a novel quinoxaline-1,4-di-*N*-oxide by Beirut reaction which includes the formation of an intermediate β-ketoamide or β-cyanamide in the presence of an inorganic catalyst (anhydrous potassium carbonate). Agar well diffusion assay was done against various bacterial and fungal strains in different concentrations. For anti-bacterial activity, gram-positive bacteria such as *Streptococcus pneumonia* (RCMB010010), *Bacillus subtilis* (RCMB 010067), and gram-negative bacteria like *Pseudomonas aeruginosa* (RCMB 010046), *Escherichia coli* (RCMB 010052) were used in comparison with standard drug ampicillin. For anti-fungal activity, strains like *Aspergillus fumigatus* (RCMB 02568), *Syncephalastrum racemosum* (RCMB 05922), *Geotrichum candidum* (RCMB 05097), and *Candida albicans* (RCMB05036) were used and compared with amphotericin B. The compound 3-amino-*N*-(4-methoxyphenyl)-2-quinoxaline carboxamide 1,4-di-*N*-oxide (52) (Fig. 18) showed the best inhibition activity with the MIC value of 0.12 μg/mL in *S. pneumonia* (bacterial strain) and 0.24 μg/mL in *Aspergillus fumigatus* (fungal strain) [49].

Henen M.A. et al. reported a new series of [1, 2, 4]-triazolo(4,3-*a*)quinoxaline derivatives by incorporating various [1, 3, 4]-oxidiazole, [1, 2, 4]-triazole, piperazine, piperidine, and thioamide. Using agar disk diffusion method, the compounds were checked for its anti-bacterial activity against *B. subtilis* and *S. aureus* (gram-positive), *E. coli* (gram-negative) and *C. albicans* for anti-fungal activity. Ciprofloxacin and Clotrimazole as a standard agent. The compounds *N*-[8-methyl-4-(piperidin-1-yl) [1, 2, 4]triazolo [4,3-*a*]quinoxalin-1-yl]benzamide (53), 8-methyl-4-[(4-phenyl-5-(thien-2-yl)-4*H*-1,2,4-triazol-3-yl)thio] [1, 2, 4] triazolo[4,3-a] quinoxaline-1-amine (54), 8-methyl-4-{[3-(3,4-dimethoxy)benzylideneamino]-1H- [1, 2, 4]-triazolo-5-yl)thio]- [1, 2, 4]-triazolo[4,3-a]quinoxaline-1-amine (55), 1-(4-chloro-8-methyl [1, 2, 4]triazolo[4,3-a]quinoxalin-1-yl)-3-ethyl thiourea (56) (Fig. 19) showed more potent antimicrobial activity [50].

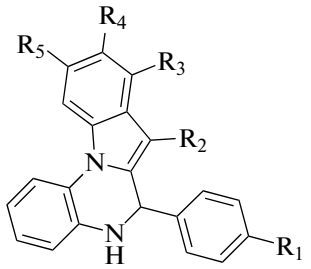
3. ANTI-CONVULSANT ACTIVITY

Abdelghany Aly Elhelby et al. designed and synthesized novel series of arylidene-quinoxaline derivatives as an anti-convulsant activity. All the compounds structure was confirmed by spectral analysis. In-vivo studies were done for the synthesized compounds



44: R = NO_2, **45**: R = Cl, **46**: R = Cl

Fig. 16. Chemical structure of 2,3-diphenylquinoxaline-6-sulfonamide derivatives.



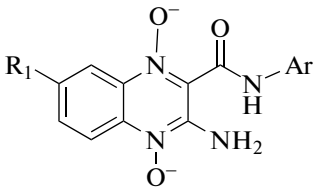
47: R_1 = OH, R_2 = H, R_3 = H, R_4 = H, R_5 = H
48: R_1 = OH, R_2 = Me, R_3 = H, R_4 = H, R_5 = H
49: R_1 = OH, R_2 = H, R_3 = Me, R_4 = H, R_5 = H
50: R_1 = OH, R_2 = H, R_3 = H, R_4 = H, R_5 =Me
51: R_1 = NO_2, R_2 = H, R_3 = H, R_4 =CN, R_5 = H

Fig. 17. Chemical structure of 5,6-dihydro-indolo[1,2-*a*] quinoxaline derivatives.

using adult Albino male mice with the weight of 20–25 g. Phenobarbital sodium was taken as a reference agent. The compound with a 4-methoxy substitution (57) and unsubstituted compound (58) (Fig. 20) showed the highest anti-convulsant activity than the potency of phenobarbital sodium [51].

Mohamed Atswah et al. synthesized some novel [1, 2, 4]triazolo[4,3-*a*]quinoxaline derivatives by a condensation reaction. In vivo studies, using Albino mice were done to determine their potency of all the synthesized compounds. Especially male mice with the weight of 20–25 g using PTZ (pentylenetetrazole) seizure animal model. The result obtained was compared with the standard Phenobarbital sodium. The compounds 1-([1, 2, 4]triazolo[4,3-a]quinoxalin-4-ylthio)acetyl-4-cyclohexylsemicarbazide (59), 1-([1, 2, 4]triazolo[4,3-a]quinoxalin-4-yl thio)acetyl-4-phenylthio semicarbazide (60) (Fig. 21) showed highest anti-convulsant activity in the PTZ model [52].

Shivananda Waglt et al. designed and synthesized two new series of quinoxaline derivatives. A series of 27 compounds were synthesized by both the Cyclo-condensation of 2-chloro-3-methyl quinoxaline with azide and reaction of 4-styryl tetrazolo[1,5-a]quinoxaline with aromatic aldehydes. *In vivo* studies using SWISS strain (albino male mice) were performed to test the potency of all the synthesized compounds by the PTZ seizure model. Diazepam was taken as a standard drug (4 mg/kg). The cyclo condensed substitution decreased the anticonvulsant activity. The compounds with fluro, methoxy, trifluoro, and methyl group substitution in 4-styryl-tetrazolo[1,5-*a*]quinoxaline derivatives (61–67) (Fig. 22) showed promising anticonvulsant activity [53].



52: R_1 = H, Ar = 4-OCH_3-Ph

Fig. 18. Chemical structure of quinoxaline-1,4-di-*N*-oxide derivatives.

4. ANTI-TUBERCULOSIS ACTIVITY

Ting wang et al. reported that pyrrolo[1,2-*a*]quinoxaline derivatives as anti-tuberculosis. Docking studies revealed the binding affinity of the designed compounds using the Libdock program with *M. tuberculosis* InhA in complex with NADH (PDB ID: 4DRE). All the compounds were synthesized and evaluated for their activity against the Mtb H_{37}Ra strain. Cytotoxicity was determined by human mammalian cell line LO2 and the cancer cell lines (SKOV3, MDA231) using MTT assay. PAMPA-BBB (Parallel Artificial Membrane Permeation Assay) was carried out to find the permeability. Among the series, the compounds (68, 69, 70) (Fig. 23) having chloro substitution at R_1 position and the phenyl, 4-bromo-phenyl, 3,4-methoxy-phenyl in the R_2 position respectively and only 4-Bromo-phenyl (71) at R_2 position (Fig. 23) which showed lowest MIC value of 5 μg/ml against Mtb H_{37}Ra cell line [54].

A novel series of 6(7)-substituted-quinoxalin-2-carboxylate-1,4-dioxide derivatives was designed and synthesized by Adres Jas et al. In vitro activity of all the synthesized compounds was performed using Mtb H_{37}Rv by MABA assay (Microplate Alamar Blue Assay) with rifampin as the reference drug. Cytotoxicity was measured in VERO cells. Single drug-resistant minimum inhibitory concentration (SDRMIC) was done against seven drug-resistant strains (Ethambutol, Isoniazid, Rifampin, Ethionamide, Thioacetazone, Ciprofloxacin, Kanamycin) of Mtb. Only four compounds ethyl 3-methylquinoxaline-2-carboxylate 1,4-dioxide **(72)**, ethyl 7-chloro-3-methyl quinoxaline-2-carboxylate 1,4-dioxide (73), benzyl 3-methylquinoxaline-2-carboxylate 1,4-dioxide (74), Benzyl 7-chloro-3-methyl quinoxaline-2-carboxylate1,4-dioxide (75) showed good inhibition activity with MIC values of 1.53, 0.20, 0.10, 0.10 μg/mL respectively against the Mtb strains with the comparison of Rifampin. In addition to this, the compounds ethyl 3,6,7-trimethylquinoxaline-2-carboxylate 1,4-dioxide (76), and benzyl 6,7-dichloro-3-methyl quinoxaline-2-car-

boxylate 1,4-dioxide (76) (Fig. 24) showed good responses in SDRMIC [55].

Esters of quinoxaline-1,4-di-*N*-oxide was synthesized by Isidro Palos et al. A stability analysis using UPLC-MS and DNA gyrase inhibitory assay were also carried out for all the compounds. All the compounds were screened against Mtb $H_{37}Rv$ & NRP strains by Modified MABA assay. Rifampicin and Isoniazid employed as reference drug. Eight compounds ethyl 1,4-dihydroxy-3-(napthylcarbonyl)-2-(trifluoromethyl)-quinoxaline-6-carboxylate (78), ethyl 1,4-dihydroxy-3-(thienylcarbonyl)-2-(trifluoromethyl)-quinoxaline-6-carboxylate (79), methyl 1,4-dihydroxy-3-(benzoyl)-2-(trifluoromethyl)-quinoxaline-6-carboxylate (80), propan-2-yl 1,4-dihydroxy-3-(thienylcarbonyl)-2-(trifluoromethyl)-quinoxaline-6-carboxylate (81), propan-2-yl 3-acetyl-1,4-dihydroxy-2-(trifluoromethyl)-quinoxaline-6-carboxylate (82), propan-2-yl 1,4-dihydroxy-3-(napthyl carbonyl)-2-(trifluoromethyl)-quinoxaline-6-carboxylate (83), propan-2-yl 1,4-dihydroxy-3-(2-methy lpropanoyl)-2-(trifluoromethyl)-quinoxaline-6-carboxylate (84) and 2-methyl 7-propyl-1,4-dihydroxy-3-methyl-quinoxaline-6-carboxylate (85) (Fig. 25) showed antituberculosis activity similar to Isoniazid activity with the MIC value of ≤0.15 μg/mL and also showed good responses in Mtb mono-resistant strains and non-replicative Mtb. Structural activity relationship analysis reveals that the compounds with isopropyl, trifluoromethyl, carboxylate substitution showed good responses [56].

Mery Santivanez-Veliz et al. discovered a series of 24 novel quinoxaline derivatives and treated against Mtb $H_{37}Rv$ (ATCC 27294) to observe inhibition by Bac Titer-Glo (BTG) microbial cell viability assay. Ofloxacin, Isoniazid and Rifampin were used as reference drugs. Among the series, only five compounds (2*E*)-1-(7-chloro-1,4-dihydroxy-3-methyl-quinoxalin-2y-l)-3-phenylprop-2-en-1-one (86), 6-chloro-2-(furan-2-carbonyl)-7-(morpholin-4-yl)-3-(trifluoromethyl)-quinoxaline-1,4-diol (87), 1-[6-fluoro-1,4-dihydroxy-7-(piperidin-1-yl)-3-(trifluoromethyl)-quinoxaline-1,4-diol (88), methyl 7-[4-(4-fluorophenyl)piperazin-1-yl]-1,4-dihydroxy-3-(trifluoromethyl)-quinoxaline-2-carboxylate (89), and 2,2,2-trifluoro-1-[6-fluoro-1,4-dihydroxy-3-methyl-7-(thiomorpholin-4-yl)-quinoxalin-2-yl]ethan-1-one (90) (Fig. 26) showed highest inhibitory activity against Mtb $H_{37}Rv$ while the compounds furan (87) and methoxy (89) showed potent action against non-replicative Mtb [57].

A novel 2,3-bifunctionalized quinoxaline derivatives were designed and synthesized by M.J. Waring et al. The synthesis was done by condensation reactions of *o*-phenylenediamine with diketone or diethyl oxalate yield the relevant derivatives of quinoxaline.

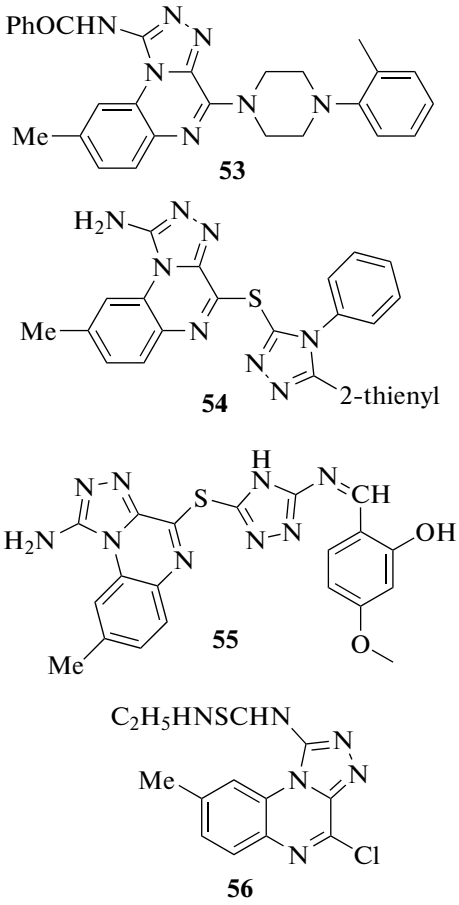
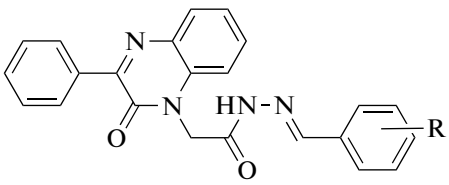
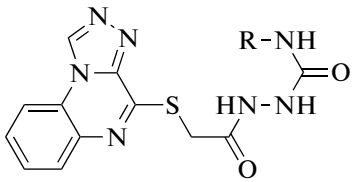


Fig. 19. Chemical structure of [1, 2, 4] triazolo(4,3-*a*)quinoxaline derivatives.



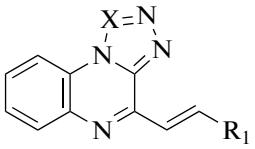
57: R = H
57: R = 4-OCH_3

Fig. 20. Chemical structure of arylidene-quinoxaline derivatives.



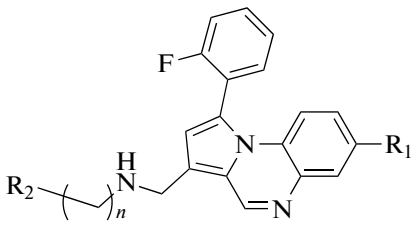
59: R = cyclohexyl
60: R = phenyl

Fig. 21. Chemical structure of [1, 2, 4]triazolo[4,3-*a*]quinoxaline derivatives.



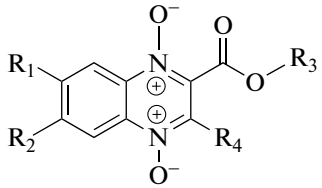
61: R_1 = 4-(F)C_6H_4, X = N
62: R_1 = C_6H_5, X = N
63: R_1 = 4-(OCH_3)–C_6H_4, X = C–CF_3
64: R_1 = 4-(F)–C_6H_4, X = C-CF_3
65: R_1 = 4-(F)–C_6H_4, X = C-CF_3
66: R_1 = 4-(F)–C_6H_4, X = CH
67: R_1 = 4-(OCH_3)C_6H_4, X = 4-(F)–C_6H_4

Fig. 22. Chemical structure of in 4-styryl-tetrazolo[1,5-*a*]quinoxaline derivatives.



68: R_1 = Cl, *n* = 1, R_2 = phenyl
69: R_1 = Cl, *n* = 2, R_2 = 4-Br-phenyl
70: R_1 = Cl, *n* = 2, R_2 = 3,4-OCH_3-phenyl
71: R_1 = H, *n* = 2, R_2 = 4-Br-phenyl

Fig. 23. Chemical structure of pyrrolo[1,2-*a*]quinoxaline derivatives as anti-TB.



72: R_1, R_2 = H, R_3 = CH_3, R_4 = C_2H_5
73: R_1 = Cl, R_2 = H, R_3 = CH_3, R_4 =C_2H_5
74: R_1, R_2 = H, R_3 = CH_3, R_4 = $CH_2C_6H_5$
75: R_1 = Cl, R_2 = H, R_3 = CH_3, R_4 = $CH_2C_6H_5$
76: R_1 = CH_3, R_2 = CH_3, R_3 = CH_3, R_4 = CH_2CH_3
77: R_1 = Cl, R_2 = Cl, R_3 = CH_3, R_4 = $CH_2C_5H_5$

Fig. 24. Chemical structure of 6(7)-substituted-quinoxalin-2-carboxylate-1,4-dioxide derivatives.

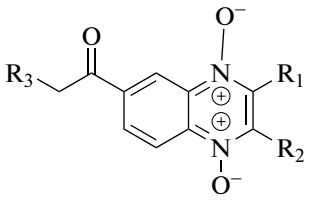
An in vitro Alamar assay against Mtb H_{37}Rv strain was determined for all the compounds. The compounds 2,3-Bis-[(2-hydroxy-2-neopentyl)ethenyl]quinoxaline (91), 2,3-bis-[2-hydroxy-2-(4-chlorophenyl)ethenyl]quinoxaline (92), 2,3-bis-[(2-hydroxy-2-phenyl)ethenyl]-6-nitro-quinoxaline (93) (Fig. 27) were reported with the MIC value of less than 6.25 μg/mL which was considered as the modest activity against the Mtb strain [58].

5. ANTI-MALARIAL ACTIVITY

Leonardo Bonilla-Ramifrez et al. developed two new hybrid series of compounds consisting of primaquine and chloroquine connected to a quinoxaline 1,4-dioxide. Structural modification of the compounds was covalently linked to each other. In silico studies were done for all the designed compounds. Synthesized compounds were evaluated for their multi-drug resistant *Plasmodium falciparum* (FCR-3, 3D7 chloroquine sensitive strains). Chloroquine and primaquine were used as reference drugs. In chloroquine – quinoxaline 1,4-dioxide hybrids, the compounds *N*-[2-(7-chloroquinolin-4-yl amino)ethyl]-7-chloro-3-methyl quinoxaline-2-carboxamide-1,4-di-*N*-oxide (94), *N*-[2-(7-chloroquinolin-4-ylamino)ethyl]-3,6,7-trimethylquinoxaline-2-carboxamide-1,4-di-*N*-oxide (95) (Fig. 28) showed moderate activity against the malarial parasites with the IC_{50} value ranging from 0.40 to 0.90μM but not higher than the reference drug chloroquine. In primaquine – quinoxaline 1,4-dioxide hybrids, the compounds *N*-[4-(6-methoxyquinolin-7-ylamino)-4-pentyl]-3-methylquinoxaline-2-carboxamide-1,4-di-N-oxide (96), *N*-[4-(6-methoxyquinolin-7-ylamino)-4-pentyl]-7-chloro-3-methylquinoxaline-2-carboxamide-1,4-di-*N*-oxide (***97***) (Fig. 29) showed the most activity. Compounds showed inhibition against the exo-erythrocytic forms (EEFs) and also inhibited the liver stage of species *P. yoelii* and *P. bergheri* with the IC_{50} value of 1.39 and 1.14 μM respectively. Further, the compound 6a primaquine hybrid showed no genotoxicity [59].

Another novel series of quinoxaline 1,4-di-*N*-oxide derivatives was designed, synthesized, and evaluated by Ana Gil et al. Synthesis of quinoxaline moiety was done by classic Beirut reaction followed the reduction of *N*-oxide groups for their analogs. All the compounds were evaluated against the FCR-3 strain of *P. falciparum* using chloroquine as a standard drug. All the compounds possessed some inhibition activity against the strain of parasite but none of the compounds showed good activity than the standard drug. The compounds 3,4,5-trimethoxyphenyl (98) and naphthyl (99) (Fig. 30) showed the highest antimalarial activity against the FCR-3 with the IC_{50} values of 6.2 and 5.8 μM respectively [60].

Carlos Barea et al. synthesized novel amide derivatives of quinoxaline 1,4-di-N-oxide. The malononitrile reacts with the quinoxaline (obtained from Beirut reaction), using triethylamine as catalyst & DMF as



78: R_1 = CO–napthyl, R_2 = CF_3, R_3 = C_2H_5
79: R_1 = CO–thienyl, R_2 = CF_3, R_3 = C_2H_5
80: R_1 = CO–phenyl, R_2 = CF_3, R_3 = CH_3
81: R_1 = CO–thienyl, R_2 = CF_3, R_3 = $(CH_3)_2CH$
82: R_1 = $COCH_3$, R_2 = CF_3, R_3 = $(CH_3)_2CH$
83: R_1 = CO–naphthyl, R_2 = CF_3, R_3 = $(CH_3)_2CH$
84: R_1 = $COCH(CH_3)_2$, R_2 = CF_3, R_3 = $(CH_3)_2CH$
85: R_1 = $COOCH_3$, R_2 = CH_3, R_3 = $CH_3CH_2CH_2$

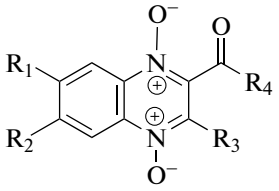
Fig. 25. Chemical structure of esters based quinoxaline-1,4-di-*N*-oxide derivatives.

solvent (*N*,*N*-dimethylformamide). Chloroquine-resistant strains (FCR-3) of *Plasmodium falciparum* were used to evaluate its anti-malarial activity for all the synthesized compounds. A standard agent as chloroquine was used. The compounds cyclopentyl (100), cyclohexyl (101), 3-chloropropyl (102) (Fig. 31) showed the highest activity against the strain with the IC_{50} value of 2.9, 7.5, and 5.7 μM respectively [61].

Esther Vicente et al. reported a series of 3-furyl and 3-thienyl quinoxaline-2-carbonitrile-1,4-di-*N*-oxide derivatives were synthesized and evaluated against 3D7 sensitive strain and K1 strains of *P. falciparum*. Chloroquine was used as a standard agent. Mammalian KB cells were used to measure its cytotoxicity. The compound 7-methoxy-3-(2'-furyl) quinoxaline-2-carbonitrile 1,4-di-*N*-oxide (103) (Fig. 32) showed the highest activity with 0.63 μM as the IC_{50} value having no cytotoxicity [62].

Miguel Quiliano et al. also reported a new series of hydrazine and hydrazide derivatives of quinoxaline 1,4-di-*N*-oxide against anti-malarial. The compounds were designed, synthesized, and performed spectral analysis. All the synthesized compounds were evaluated using the FCR-3 multi-drug resistant strain of *P. falciparum*, 3D7 chloroquine sensitive strain. Chloroquine was used as a standard drug. Cytotoxicity was done against anti-malarial activity using HepG-2 cells. Compounds 104 and 105 with 7-chloro-4-hydrazinoquinoline (Fig. 33) showed the highest activity with an IC_{50} value of 1.40, 0.24 μM in 3D7 strain, and 2.56, 2.8 μM in FCR-3 strain respectively [63].

Nicolus Primas et al. discovered a new series of 4-trichloromethyl pyrrolo[1,2-*a*]quinoxaline. An *in vitro* assay was done on the compounds against K1 multi-drug resistant strain and cytotoxicity determination using HepG2 human cell line. Chloroquine, doxorubicin, and doxycycline were used as reference agents. The compounds 4-(trichloromethyl) pyrrolo [1,2-*a*] quinoxaline (106), 7-methyl -4-(trichloromethyl)pyrrolo[1,2-a]quinoxaline (107), 4-(trichloromethyl)pyrrolo[1,2-a]quinoxaline-7-carbonitrile (108) (Fig. 34) showed the highest activity with IC_{50} value of 1.5, 2.4, and 1.5 μM against the *P. falciparum* strain. The cytotoxicity of the compounds ranges from 17 to 53 μM. The structural activity relationship studies reveal that the presence of the trichloromethyl group provides a promising antimalarial activity [64].



86: R_1 = Cl, R_2 = H, R_3 = CH_3, R_4 =

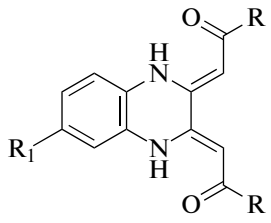
87: R_1 = , R_2 = Cl, R_3 = CF_3, R_4 =

88: R_1 = , R_2 = F, R_3 = CF_3, R_4 = CH_3

89: R_1 = , R_2 = H, R_3 = CF_3, R_4 = –O–CH

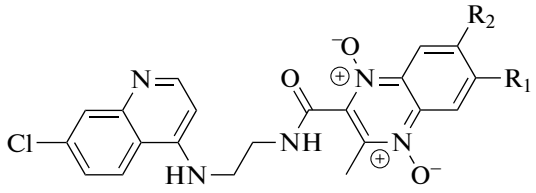
90: R_1 = , R_2 = F, R_3 = CF_3, R_4 = –O–CH_3

Fig. 26. Chemical structure of quinoxaline-2-carboxylate 1,4-dioxide derivatives.



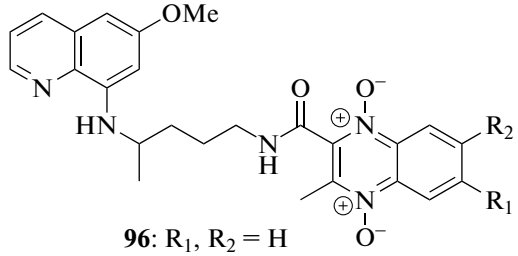
91: R_1 = H, R = neopentyl
92: R_1 = H, R = *p*-Cl-pheny
93: R_1 =NO_2, R = phenyl

Fig. 27. Chemical structure of 2,3-bifunctionalized quinoxaline derivatives.



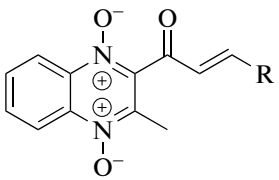
94: R_1 = H, R_2 = Cl
95: R_1 = CH_3, R_2 = CH_3

Fig. 28. Chemical structure of chloroquine–quinoxaline 1,4-dioxide hybrids.



96: R_1, R_2 = H
97: R_1 = H, R_2 = Cl

Fig. 29. Chemical structure of primaquine–quinoxaline 1,4-dioxide hybrids.



98: R = 3,4,5-trimethoxyphenyl
99: R = napthyl

Fig. 30. Chemical structure of quinoxaline 1,4-di-*N*-oxide compounds.

6. ANTI-LEISHMANIAL ACTIVITY

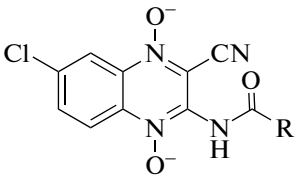
Carlos Barea et al. synthesized novel derivatives of 2-cyano-3-(4-phenylpiperazine-1-carboxamido)quinoxaline 1,4-dioxide. An MTT assay was done to evaluate its potency against *L. infantum amastigotes* strain. The standard drug was doxorubicin. Only two compounds 7-chloro-2-cyano-3-(4-(4-(trifluoromethyl) phenyl) piperazine-1-carboxamido) quinoxaline 1,4-dioxide (109) and 6,7-dichloro-2-cyano-3-(4-(4-(trifluoromethyl) phenyl) piperazine-1-carboxamido) quinoxaline 1,4-dioxide (110) (Fig. 35) showed good activity against the strain and also proved that it has four times lesser cytotoxicity than the standard drug [65].

A novel series of 4-alkapolyenylpyrrolo[1,2-*a*]quinoxaline was designed, synthesized, and evaluated its activity as anti-Leishmanial by Luisa Ronga et al. In *vitro* testing of the compounds against *L. major* (MHOM/IL/81/BNI), *L. mexicana* (MHOM/MX/95/NAN1) and *L. donovani* (MHOM/IN/00/DEVI) strains were evaluated. Pentamidine as a reference agent. Cytotoxicity was determined using Murine J774A.1 macrophage and human hepatocyte HepG2 cell lines. The compounds 4-[(1*E*,3*E*,5*E*)-hepta-1,3,5-trienyl]pyrrolo[1,2-*a*]quinoxaline (111) and 3-ethoxy-4-[(1*E*,3*E*)-penta-1,3-dienyl] pyrrolo [1,2-*a*]quinoxaline (112) (Fig. 36) with IC_{50} value of 1.2 and 1.5 μM, respectively, showed the highest activity against the *L. major*. Compound (112) with an IC_{50} value of 4.5 μM against *L. denovani* showed significant activity [66].

Juliano Cogo et al. reported a new series of novel 2,3-disubstituted quinoxaline derivatives and evaluated them for their biological activity against *Leishmania* species (*L. amazonesis*). Standard drug amphotericin was used. All the compounds were synthesized and characterized. Only four compounds 2-chloro-6-methoxy-3-(methyl sulfinyl) quinoxaline (113), 2,7-dichloro-3-(methyl sulfinyl)quinoxaline (114), 6-bromo-3-chloro-2-(methylsulfonyl)quinoxaline (115), and 3,6-dichloro-2-(methylsulfonyl)quinoxaline (116) (Fig. 37) showed potent against the strain of leishmanial species. The structural relationship analysis revealed that sulfinyl and sulfonyl groups highly influenced the activity [67].

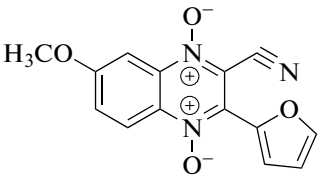
7. ANTI-HIV ACTIVITY

A novel series of 6-chloro-7-fluroquinoxaline derivatives were designed and synthesized by Saloni-B Patel et al. using a Ligand-based drug design. In silico and 3D-QSAR studies were reported. An in-vitro evaluation was performed based on HIV-induced cytopathogenic effect (CPE) using the strain IIIB in HTLV-1 transformed T4 cells (MT-4). Reference agents such as nevirapine, zidovudine, lamivudine,



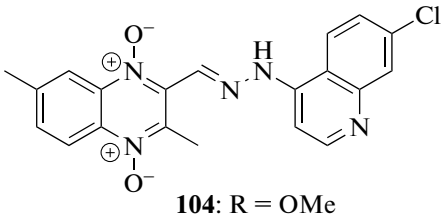
100: R = cyclopentyl
101: R = cyclohexyl
102: R = 3-chloropropyl

Fig. 31. Chemical structure of amide derivatives of quinoxaline 1,4-di-*N*-oxide.



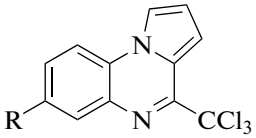
103

Fig. 32. Chemical structure of 3-furyl quinoxaline-2-carbonitrile-1,4-di-*N*-oxide derivatives.



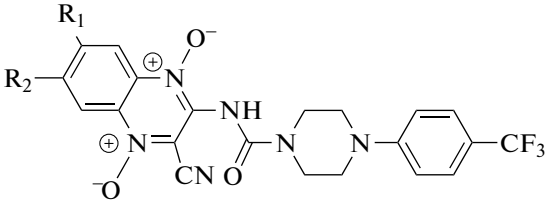
104: R = OMe
105: R = Cl

Fig. 33. Chemical structure of hydrazine derivatives of quinoxaline 1,4-di-*N*-oxide.



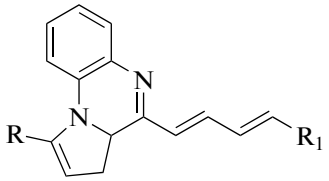
106: R = H
107: R = Me
108: R = CN

Fig. 34. Chemical structure of 4-trichloromethyl pyrrolo[1,2-*a*]quinoxaline.



109: R_1 = Cl, R_2 = H
110: R_1 = Cl, R_2 = Cl

Fig. 35. Chemical structure of 2-cyano-3-(4-phenylpiperazine-1-carboxamido)quinoxaline-1,4-dioxide derivative.



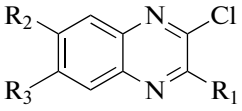
111: R = H, R_1 = CH–CH–CH_3
112: R = OC_2H_5, R_1 = CH_3

Fig. 36. Chemical structure of 4-alkapolyenylpyrrolo[1,2-*a*]quinoxaline derivative.

and didanosine were used. The compounds (117) and (118) substituted with phenyl and *p*-fluoro-phenyl respectively (Fig. 38) showed the best inhibition activity in VERO cells [68].

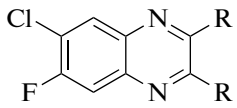
Lucas Fabian et al. reported two new series of quinoxaline as HIV reverse transcriptase inhibitors using in silico studies. Synthesis of tQXN (1,2,3,4-tetraquinoxaline-2-one) and dQXN (1,2-dihydroquinoxalin-2-one derivatives by nucleophilic displacement reaction using the microwave-assisted method was reported. HIV-RT activity was done by measuring dTTP incorporation on a poly (rA)-oligo (dT) template primer duplex using a reverse transcriptase assay kit using nevirapine as a standard. The compound 4-propanoyl-3,4-dihydroquinoxalin-2(1*H*)-one (119) and 2-methyl propyl (2*S*)-2-methyl-3-oxo-3,4-dihydro quinoxaline-1(2*H*)-carboxylate (120) (Fig. 39) showed good inhibition activity against the infected cells. Especially the compound (119) showed the similar activity of nevirapine drug [69].

Ling-Ling Fan et al. designed and synthesized a novel series of 5,6-dihydro-indolo[1,2-*a*]quinoxaline. All the compounds were evaluated against HIV-infected cells C8166 by MTT assay. Zidovudine was used as a standard drug. The 4-methyl on indolyl ring and 4-methoxy phenyl on the 6th position of C-ring gave compound (121) and 6th position of C-ring substituted with furanyl ring gave compound (122) (Fig. 40) possessed the most potent anti-HIV activity with the EC_{50} values of 2.24 and 3.39 μg/mL respectively [70].



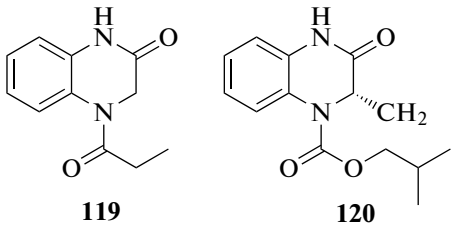
113: R_1 = SOMe, R_2 = H, R_3 = OCH_3
114: R_1 = SOMe, R_2 = Cl, R_3 = H
115: R_1 = SO_2Me, R_2 = Br, R_3 = H
116: R_1 = SO_2Me, R_2 = Cl, R_3 = H

Fig. 37. Chemical structure of 2,3-disubstituted quinoxaline derivative.



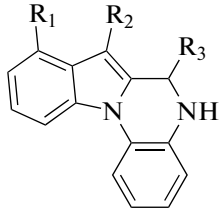
117: R = $-C_6H_5$
118: R = $-p$-F-C_6H_5

Fig. 38. Chemical structure of 6-chloro-7-fluroquinoxaline derivatives.



119 **120**

Fig. 39. Chemical structure of quinoxaline as HIV reverse transcriptase inhibitors.



121: R_1 = Me, R_2 = H, R_3 = 4-Me–C_6H_4
122: R_1 = H, R_2 = Me, R_3 = furan

Fig. 40. Chemical structure of 5,6-dihydro-indolo[1,2-*a*]quinoxaline.

8. ANTI-INFLAMMATORY ACTIVITY

Rahul Gajanan Ingle et al. designed 10 compounds based on 2,3-diphenyl-7-sulfonamide quinoxaline. *N*-substituted sulfonamide quinoxaline derivatives were synthesized by treating 2,3-diphenyl quinoxaline with chlorosulfonic acid. In vivo evaluation using Wistar Albino rats of all the compounds was reported. Diclofenac sodium was used as a standard drug. The compounds 2,3-diphenyl-7-sulfonamidoquinoxaline (123), 2,3-diphenyl-7-(*N*-phenyl)-sulfonamido quinoxaline (124), and 2,3-diphenyl-7-(*N*-acetyl)-sulfonamido quinoxaline (125) (Fig. 41) showed a good response for about 2.25 to 22.95% inhibition when compared to the standard drug [71].

9. ANTI-OXIDANT ACTIVITY

Hossain M.M. et al. proposed a study of novel quinoxaline derivatives as an anti-oxidant property. The synthesis was based on a reduced cyclization reaction to yield indole-quinoxaline derivatives. DPPH assay was carried out using standard ascorbic acid. The compound (126) (Fig. 42) containing 5-methyl on indolyl ring showed the highest antioxidant activity with the IC_{50} value of 500.42 μg/mL [72].

10. ANTI-ALZHEIMER'S ACTIVITY

A multi-target directed ligand as quinoxaline-bisthiazoles were designed, synthesized, and evaluated for anti-Alzheimer's activity and anti-inflammatory by Sneha R. Sagar et al. *In silico* study was performed and the binding affinity was compared with diclofenac, celecoxib for anti-inflammatory activity, and AZD3839 for anti-Alzheimers activity. In vitro studies were done against BACE-1 using FRET-based enzymatic assay for the anti-Alzheimers. AZD 3839 was used as the positive control. Various studies as the Y-maze test conditioned avoidance response test, elevated plus maze test, hematological parameters estimation, serum biochemical parameters, lipid peroxidase assay (anti-oxidant), histopathological studies of rat brain, and gastrointestinal safety was reported. The compound 5,5'-(6,7-dimethyl quinoxaline-2,3-diyl)bis(thiazol-2-amine) (127) (Fig. 43) showed more potency against BACE-1 inhibitor with IC_{50} value of 3 ± 0.07 μM and inhibition against carrageenan and formalin-induced rat paw edema showed 69 ± 0.45% (acute) and 55 ± 0.7% (chronic) respectively. The compound **(127)** also showed inherited gastrointestinal safety [73].

Ashish M. Kanhed et al. reported a novel series of indole quinoxaline series as a multi-targeted ligand. All the synthesized compounds were evaluated by Ellman's assay against Ache from human erythrocytes and Bche from equine serum. Tacrine and Donepezil were used as standard drugs. PAMPA (parallel artificial membrane permeation assay) was carried out for all the compounds to find the blood-brain barrier permeation. DPPH radical scavenging assay for anti-oxidant and $A\beta_1$-42 aggregation inhibition studies were done. Ascorbic acid and curcumin were used as stan-

dard drugs respectively. The compound 6-(6-(piperidin-1-yl)hexyl)-6*H*-indolo[2,3-*b*]quinoxaline (128) (Fig. 44) showed higher anti-BchE inhibition with 0.96μM as an inhibition constant value. And also showed 51.24% inhibition in self-induced $A\beta_1$-42 aggregation activity [74].

A series of styryl quinoxaline-2(1*H*)-ones were synthesized in Malononitrile-activation by Sheena Mahajan et al. All the compounds were evaluated against *Electrophorus electricus* acetylcholinesterase (EeAche) by Ellman's assay. Donepezil was employed as a reference drug. The compound (*E*)-3-(3-bromo-4-fluorostyryl)quinoxalin-2(1*H*)-one (129) (Fig. 45) was potent among all the compounds [75].

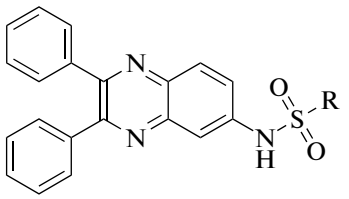
11. ANTI-DIABETIC ACTIVITY

Mohamed K. Ibrahim et al. reported the anti-hyperglycemic activity against Peroxisome proliferator-activated receptor gamma (PPARγ) and sulfonylurea receptor (SURs) agonist. A novel series of quinoxaline with sulfonylurea or sulfonylthiourea were designed and synthesized. In vitro studies on the streptozotocin-induced hyperglycemic rats were done. Fluorescence polarization assay and Sandwich enzyme immunoassay for PPARγ-ligand binding and insulin-secreting activities respectively were carried out. Glimepiride and Rosiglitazone were used as reference drugs. In this series, four compounds cyclohexylcarbamoyl (130), butylcarbamoyl (131), cyclohexylcarbamothioyl (132), and butyl carbamothioyl (133) (Fig. 46) showed the significant activity possessing IC_{50} value in the range of 0.35 to 0.491 μM. The compounds (130**)** and (131) were more potent in insulin-secreting activity with EC_{50} values of 0.92 and 0.98 μM respectively [76].

A novel series of quinoxaline-thiazolidine-amino hybrids against anti-diabetic activity was reported by Suhas A. Shintre et al. All the compounds were evaluated for *in vitro* inhibition against alpha-glucosidase and alpha-amylase enzyme. Acarbose was employed as a reference agent. The compounds 3-isopropyl-7-(2-(4-nitrophenyl)-4-oxothiazolidin-3-yl)quinoxalin-2(1*H*)-one (134) and 3-(4-hydroxybenzyl)-7-(2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)quinoxalin-2(1*H*)-one (135**)** (Fig. 47) showed promising activity against alpha-glucosidase with IC_{50} value of 301.15 and 276.27 μM respectively and against alpha-amylase with IC_{50} value of 356.32 and 301.59 μM, respectively [77].

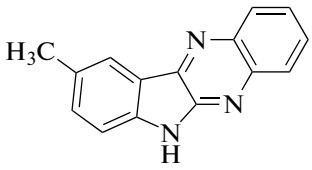
12. ANTI-COVID ACTIVITY

Raviteja Chemboli et al. synthesized novel a novel series of 2-substituted pyrrolo[1,2-*b*]quinoxalines for the inhibition of phosphodiesterase 4B (PDE4B) particularly tumor necrosis factor-alpha (TNF-α) to reduce the cytokine storm in the COVID patients. The synthesis of the compounds was done by copper-catalyst coupling-cyclization between 3-alkynyl-2-chloroquinoxalines with *t*-butyl sulfonamide. Rolipram and



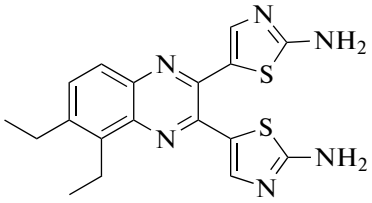
123: R = -NH_2
124: R = -NH–C_6H_5
125: R = -$NHCOCH_3$

Fig. 41. Chemical structure of 2,3-diphenyl-7-sulfonamide quinoxaline.



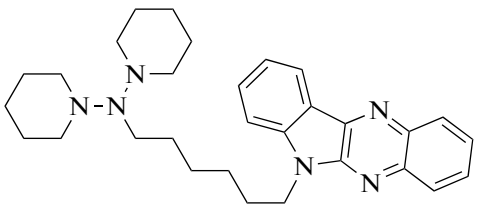
126

Fig. 42. Chemical structure of indole-quinoxaline derivatives.



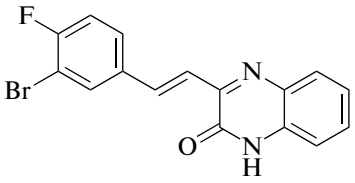
127

Fig. 43. Chemical structure of quinoxaline-bisthiazoles.



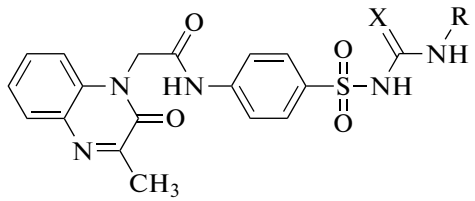
128

Fig. 44. Chemical structure of indole quinoxaline derivatives.



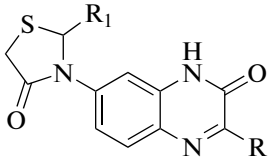
129

Fig. 45. Chemical structure of 3-substituted styryl quinoxalin-2(1*H*)-ones derivative.



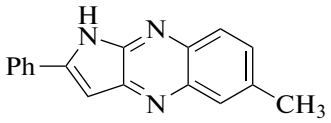
130: R = cyclohexyl, X = O
131: R = butyl, X = O
132: R = cyclohexyl, X = S
133: R = butyl, X = S

Fig. 46. Chemical structure of sulfamoylphenyl quinoxaline derivatives.



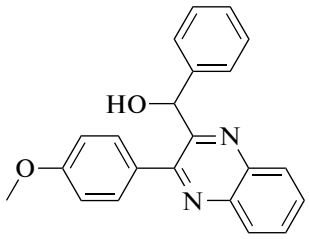
134: R = valine, R_1 = 4-NO_2Ph
135: R = tyrosine, R_1 = 4-OMePh

Fig. 47. Chemical structure of quinoxaline-thiazolidine-amino hybrids.



136

Fig. 48. Chemical structure of 2-substituted pyrrolo[1,2-*b*]quinoxaline derivative.



137

Fig. 49. Chemical structure of 3-arylquinoxaline derivative.

Thalidomide were used as a standard. The compound (136) (Fig. 48) substituted with phenyl ring on the 2nd position inhibited the most with the IC_{50} value of 5.14 μM. Docking with SARS-COV-2 nucleocapsid *N*-terminal RNA binding protein (PDB ID: 6M3M) was reported with a docking score of – 89.37, – 7.94, and – 6.33 kcal/mol in GEMDOCK, DOCKTHOR, and SWISS DOCK respectively. ADME parameter analysis for (136) was found to be high gastrointestinal absorption and acceptable bioavailability with log *P* greater than three that facilitates required permeation at the site of action [78].

13. ANTI-DENGUE ACTIVITY

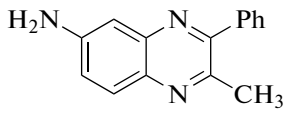
Chih-Hua Tseng et al. discovered a 3-arylquinoxaline derivative as the potent dengue virus (DENV) replication inhibitors. These derivatives were synthesized by the conventional method. The compounds were evaluated for the anti-dengue property by firefly luciferase activity with Ribavirin as a standard drug. The compound (137) (Fig. 49) containing methoxy group (electron-donating group) at R_1 position strongly inhibited the replication. It was also observed to be non-cytotoxic with 85% cell viability using Huh-7-DV-Fluc cells. The compound (137) is 10times more active than the standard drug Ribavirin. Western blotting and RT-qPCR were also performed to witness the reduced DENV protein synthesis and RNA replication. It also suppressed the COX-2 protein that attenuates the DENV replication [79].

14. ANTI-PARKINSONS ACTIVITY

A regio-selectivity method of 2,3-disubstituted-6-amino quinoxaline was designed and synthesized by Gael Le Douaron et al. Passive diffusion studies were done to evaluate the blood-brain barrier permeation. This was further confirmed by HPLC-MS/MS quantification and MALDI-TOF in mice brain homogenate extraction. Mid-brain culture was used to evaluate the neuroprotective activity of the synthesized compounds. The compound 2-methyl 3-phenyl 6-aminoquinoxaline (138) (Fig. 50) has shown the potential promising neuroprotective activity. Moreover, free radical scavenging of the compound was found out by ABTS (2,2'-azino-bis(3-ethyl benzothiazoline-6-sulfonic acid)) competition assay with Trolox as a standard drug [80].

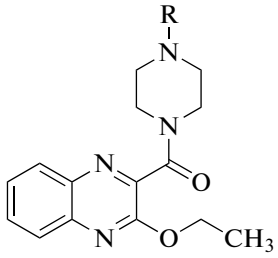
15. $5HT_3$ RECEPTOR ANTAGONIST ACTIVITY

Radha Krishnan Mahesh et al. synthesized a novel series of 3-ethoxyquinoxalin-2-carboxamides and evaluated the potency against $5HT_3$ receptor antagonist. *In vivo* studies were done with Dunkin Hartley



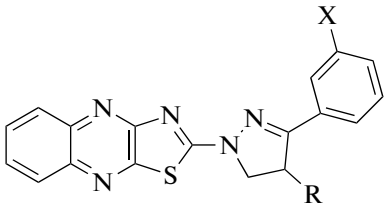
138

Fig. 50. Chemical structure of 2,3-disubstituted-6-amino quinoxaline derivative.



139: R = *o*-MeO-C_6H_4-
140: R = CH_3-
141: R = CH_3-CH_2-
142: R = 2-(indol-3yl)ethyl

Fig. 51. Chemical structure of 3-ethoxyquinoxalin-2-carboxamides derivatives.



143: R = H, X = Cl
144: R = CH_3, X = Br
145: R = CH_3, X = Cl

Fig. 52. Chemical structure of 1-(thiazole [4,5-*b*]quinoxaline-2-yl)-3-phenyl-2-pyrazoline derivative.

male guinea pigs for serotonin antagonist activity and Albino Swiss mice for anti-depression activity. Ondansetron was used as a standard drug. The compounds with *o*-methoxy phenyl (139), methyl (140), ethyl (141), 2(indolo-3-yl)ethyl (142) substituted derivatives (Fig. 51) showed good antagonist activity against $5HT_3$ receptor [81].

16. ANTI-AMOEBIASIS ACTIVITY

Mohammad Abid et al. designed a novel series of 1-(Thiazole[4,5-*b*]quinoxaline-2-yl)-3-phenyl-2-pyrazoline derivatives. The synthesis involved the cyclization of different mannich bases with unsubstituted thiosemicarbazide followed by condensation with 2,3-dichloroquinoxaline to yield the desired derivative. The compounds were screened against the HM1:1MSS strain of *Entamoeba histolytica* by microdilution method. The compounds 3-chloro (143), 3-bromo-4-methyl (144), and 3-chloro-4-methyl (145) (Fig. 52) were found to be more potent with an IC_{50} value of 1.09, 1.45, and 0.72 μM, respectively, and compared with the reference drug metronidazole [82].

DISCUSSION

The overview of the quinoxaline derivatives were simplified (Fig. 53) and tabulated (Table 1) based on their structural activity relationship according to their activities. Quinoxaline dioxides showed improved anti-microbial activity. Substituting at R_2 and R_3 positions cross the blood brain barrier to act against CNS related activities. Cyclisation of quinoxaline to pyrrole or pyrazole gave significant activity. Even the cyclisation of R_2 and R_3 exhibited anti-COVID activity. R_2 and R_3 are the most effective site for substitution in many activities. Thereby this review will help the

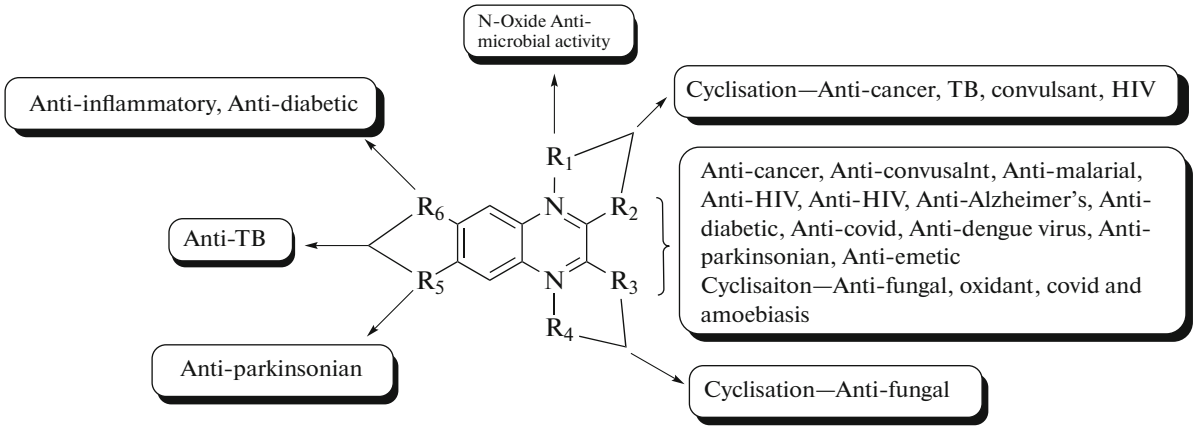


Fig. 53. Structural activity relationship of quinoxaline for different activities in a pictorial format.

Table 1. Structural activity relationship of quinoxaline for different activities.

S. no.	Activity	Structural activity relationship
1	ANTI-CANCER ACTIVITY	R1 and R2 cyclisation to triazole inhibits Bromodomain and Extra Terminal proteins. R2 substituted with SH or NH linked groups inhibits DNA Topoisomerase II activity, and arrest G2/M phase cell cycle. Arrest G0/G1 cell phase by substituting tertiary nitrogen R3 is a ketone or nitrogen linked heterocyclic groups are c-Met kinase inhibitors
2	ANTI-BACTERIAL ACTIVITY	N-Oxide, R2 or R3 substituted with NH, S, CONH, Ar, electron withdrawing groups
3	ANTI-FUNGAL ACTIVITY	N-Oxide, R3 substituted with S or R2 substituted with NH linked heterocyclic groups, cyclisation of R2 and R3 or R3 and R4
4	ANTI-MYCOBACTERIUM ACTIVITY	R1 and R2 cyclization, *N*-oxide gives good inhibition, R3 carboxylated increases activity, R5 with thiomorpholine or R6 with chlorine increases activity
5	ANTI-CONVULSANT ACTIVITY	R2 substituted by phenyl or cyclized to triazole with R1, R2 substituted by ketone or semicarbazide
6	ANTI-MALARIAL ACTIVITY	N-Oxide, R2 substituted by ketone, methyl, NHCOR, Furan, CCl_3 R3 substituted with –CO–R, CN, cyclized with R4
7	ANTI-LEISHMANIAL ACTIVITY	N-Oxide, R2 substituted with NHCOR, CH_2, Cl and R3 substituted with CN, SOMe, SO_2Me or cyclized with R4
8	ANTI-HIV ACTIVITY	R2 and R3 substituted with phenyl groups, or R1 and R2 cyclization or R4 is substituted with CO/COOR
9	ANTI-INFLAMMATORY ACTIVITY	R2 and R3 substituted with phenyl and R5 with sulphonamide groups
10	ANTI-OXIDANT ACTIVITY	R2 and R3 cyclisation
11	ANTI-ALZHEIMER'S ACTIVITY	R2 and R3 with bisthiazole–inhibits BACE, indole quinoxale inhibit beta amyloid, R2 by ketone and R3 by CH=CH–Ph–R inhibits acetylcholinesterase
12	ANTI-DIABETIC ACTIVITY	R2 with ketone, R3 with methyl or amino acids and R5 with thiazole derivative inhibits PPAR-γ, SURs, α-glucosidase and α-amylase receptors
13	ANTI-COVID ACTIVITY	R2 and R3 cyclized to pyrazole derivatives and R5 with methyl
14	ANTI-DENGUE VIRUS ACTIVITY	R2 with secondary alcohol derivative and R3 with phenyl substitutions
15	ANTI-PARKINSONIAN ACTIVITY	R2 with phenyl, R3 with methyl and R6 with amine 5HT3 receptor antagonist R2 with ketone linked piperazine substitutions, R3 with $-OC_2H_5$
16	ANTI-AMOEBIASIS ACTIVITY	R2 and R3 cyclized to thiazole

researchers to design the novel ligands against the specific activity.

CONCLUSIONS

In the present review, quinoxaline derivatives with various pharmacological activities are enumerated based on the substitution pattern around the nucleus. This enables medicinal chemists the development of SAR on quinoxaline for each activity. This comprehensive overview summarizes the chemistry of different quinoxaline derivatives along with their Pharmacological activities like anti-cancer, anti-microbial, anti-convulsant, anti-tuberculosis, anti-malarial, anti-leishmanial, anti-HIV, anti-inflammatory, anti-oxidant, anti-Alzheimer's, anti-diabetic, anti-COVID, anti-dengue, anti-Parkinson, anti-amoebiasis, and $5HT_3$ receptor antagonist. This review would give more ideas to researchers to develop pharmacologically active quinoxaline derivatives.

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HUMAN AND ANIMAL RIGHTS

No animals/humans were used for studies that are base on this research.

AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting the findings of this study are available within the article.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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