Review Article

Pharmacological Profile of Quinoxalinone

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Quinoxalinone and its derivatives are used in organic synthesis for building natural and designed synthetic compounds and they have been frequently utilized as suitable skeletons for the design of biologically active compound. This review covers updated information on the most active quinoxalinone derivatives that have been reported to show considerable pharmacological actions such as antimicrobial, anti-inflammatory, antidiabetic, antiviral, antitumor, and antitubercular activity. It can act as an important tool for chemists to develop newer quinoxalinone derivatives that may prove to be better agents in terms of efficacy and safety.

1. Introduction

The quinoxalinones are a class of heterocyclic compounds with different applications in various fields; these have been studied intensively as important heterocyclic system for the synthesis of biologically active compounds ranging from herbicides and fungicides to therapeutically usable drugs. A literature survey identified several quinoxalinones derivatives in the development phase as potential new drugs. The versatility of the quinoxalinones skeleton, in addition to its relative chemical simplicity and accessibility, makes these chemicals amongst the most promising sources of bioactive compounds. This has led to the discovery of a wide variety of compounds that are of high interest from the point of view of antimicrobial, antifungal, antiviral, anti-inflammatory, and antitumor effects among others.

2. Antimicrobial Activity

Antimicrobial agents are essential for the treatment of a number of diseases of bacterial or fungal origin, and many such agents are used clinically and industrially. Recently, however, bacteria have acquired drug resistance and so the

development of new antimicrobial agents is required [1–3]. A number of compounds based on nitrogen-containing heterocycles show antimicrobial activity and have been developed for clinical use [4]. Among the various classes of heterocyclic units, the quinoxaline ring has frequently been used as a component of various antibiotic molecules, such as hinomycin, levomycin, and actindeutin, which inhibit the growth of Gram-positive bacteria and are active against various transplantable tumors [5–7].

Another notable activity of quinoxalinones is the antimicrobial one. In fact, Kotharkar and Shinde [8] have shown that 9,10-dimethyl-2-methoxy-6-oxo-7,12-dihydro-chromo-[3,4-b]quinoxaline **1** has both antibacterial and antifungal activities. In another study [9], it has been shown that quinoxalinones **2**, **3**, **4**, and **5** (Figure 1) possess the same activities.

In the search for new antimicrobial agents, 2(1H)-quinoxalinones and their hexahydro derivatives were prepared [10]. Thiosemicarbazide **6** (Figure 2) derived from hexahydro-2(1H)-quinoxalinone showed a high in vitro antibacterial activity.

A series of 3-(3-oxo-3,4-dihydroquinoxalin-2-yl) propionic acid derivatives was synthesized and then treated with hydrazine hydrate to yield its hydrazones **7** (Figure 3). This

FIGURE 1: Chemical structures of compounds tested.

FIGURE 2: Chemical structure of compound 6.

was further reacted with substituted aromatic aldehydes to produce final compounds **7a–r** (Table 1). All the synthesized compounds were evaluated for their antimicrobial and anti-inflammatory activity [11].

Ishikawa et al. [12] synthesized some derivatives of 2,3-bis(bromomethyl)quinoxaline with substituents at the 6-and/or 7-positions and evaluated their activities against bacteria and fungi. Of the 12 compounds (Table 2), nine **9a–h**, **9j**, **9k** showed antibacterial activity. The derivative **9g**, which bears a trifluoromethyl group at the 6-position, showed the highest activity against Gram-positive bacteria, while **16c**, which has a fluoro-group at the 6-position, showed the widest antifungal activity spectrum. However, only the derivative with an ethyl ester substitution **9k** showed activity against Gram-negative bacteria (Figure 4 and Table 3).

Seven derivatives of thiadiazolo[20,30:2,3]imidazo[4, 5b] quinoxalines **10a–g** were synthesized [13] for potential antimicrobial agents. The antimicrobial evaluation of the newly synthesized products against a broad spectrum of bacteria was performed using the disc diffusion technique and the agar streak dilution method. It was found that, among the synthesized compounds, only the unsubstituted and electron donating group containing molecules has shown better antimicrobial activity when compared to electron withdrawing compound on the phenyl group. Of all the synthesized

TABLE 1: List of compounds prepared **7a–r**.

Compounds	R	R ₁	Compounds	R	R ₁
7a	H	4-F-C ₆ H ₄	7j	H	4-NO ₂ -C ₆ H ₄
7b	H	2-Cl-C ₆ H ₄	7k	CH ₃	4-F-C ₆ H ₄
7c	H	3-Cl-C ₆ H ₄	7l	CH ₃	2-Cl-C ₆ H ₄
7d	H	4-Cl-C ₆ H ₄	7m	CH ₃	3-Cl-C ₆ H ₄
7e	H	4-OH-C ₆ H ₄	7n	CH ₃	4-Cl-C ₆ H ₄
7f	H	4-OCH ₃ -C ₆ H ₄	7o	CH ₃	4-OH-C ₆ H ₄
7g	H	3,4-OCH ₃ -C ₆ H ₃	7p	CH ₃	4-OCH ₃ -C ₆ H ₄
7h	H	3,4,5-OCH ₃ -C ₆ H ₂	7q	CH ₃	2-NO ₂ -C ₆ H ₄
7i	H	2-NO ₂ -C ₆ H ₄	7r	CH ₃	4-NO ₂ -C ₆ H ₄

TABLE 2: List of compounds tested.

Compounds	R ₁	R ₂	Compounds	R ₁	R ₂
9a	CH ₃	CH ₃	9g	CF ₃	H
9b	CN	H	9h	NO ₂	H
9c	F	H	9i	CO ₂	H
9d	Cl	H	9j	CO ₂ CH ₃	H
9e	Br	H	9k	CO ₂ CH ₂ CH ₃	H
9f	OCH ₃	H	9l	OH	H

compounds **10a**, **10b**, and **10d** had shown good antibacterial and antifungal activity (Scheme 1).

The compound 2,6-dimethyl-3-f-quinoxaline 1,4-dioxide **11f** was found to inhibit 50% of Leishmania growth at 8.9 μ M,

TABLE 3: Antifungal activities of compounds **9a–l**.

	R ₁	R ₂	MIC (μg/mL)							Yeast	
			A. n. ^a	P. c. ^b	C. c. ^c	Mold A. p. ^d	A. s. ^e	M. s. ^f	G. v. ^g	R. r. ^h	S. c. ⁱ
9a	CH ₃	CH ₃	>100	>100	>100	>100	>100	>100	>100	>100	>100
9b	CN	H	50	25	25	50	25	25	>100	100	50
9c	F	H	50	50	50	100	50	25	100	100	50
9d	Cl	H	50	100	25	>100	>100	50	>100	>100	>100
9e	Br	H	100	100	50	>100	>100	50	>100	>100	>100
9f	OCH ₃	H	50	>100	50	100	100	50	>100	>100	100
9g	CF ₃	H	50	50	100	50	100	25	>100	100	50
9h	NO ₂	H	100	100	50	100	25	50	100	>100	50
9i	COOH	H	>100	>100	>100	>100	>100	>100	>100	>100	>100
9j	CO ₂ CH ₃	H	50	100	100	50	100	25	>100	>100	50
9k	CO ₂ CH ₂ CH ₃	H	>100	>100	>100	100	>100	100	>100	100	100
9l	OH	H	>100	>100	>100	>100	>100	>100	>100	>100	>100

^a *Aspergillus niger*, ^b *Penicillium citrinum*, ^c *Cladosporium cladosporioides*, ^d *Aureobasidium pullulans*, ^e *Alternaria* sp., ^f *Mucor spinescens*, ^g *Gliocladium virens*, ^h *Rhodotorula rubra*, ⁱ *Saccharomyces cerevisiae*.

SCHEME 1: Synthesis of compounds **10a–g**.

FIGURE 3: Chemical structures of compounds tested.

TABLE 4: List of compounds prepared.

Compound	R	R ₁
13a		—Cl
13b		—SCH ₂ COOH
13c		—OMe
13d		—SCH ₂ COOH
13e		—Cl
13f		
13g		—N(CH ₃)
13h	—C ₃ H ₇	—N(CH ₃)
13i		—SCH ₂ COOH
13j		

TABLE 5: List of compounds prepared.

	a	b	c	d	e	F	g
R ₁	CH ₃	2-Furyl	CH ₃	2-Furyl	CH ₃	H	CH ₃
R ₂	Ph	2-Furyl	Ph	2-Furyl	Ph	Ph	Ph
R ₃	H	CH ₃	H	PhCO	PhCO	H	MeOPhCO
R ₄	H	CH ₃	Cl	H	H	CH ₃	H
X	N	C	C	C	C	C	C

with no impact against proliferative kidney cells and with low toxicity against THP-1 cells and murine macrophages. The compounds belonging to the propenone quinoxaline series were moderately active against *T. cruzi*. Among these compounds (Figure 5), two were particularly interesting, (2E)-1-(7-fluoro-3-methyl-4 quinoxalin-2-yl)-3-(3,4,5-trimethoxy-phenyl)-propenone and **12b** (2E)-3-(3,4,5-trimethoxy-phenyl)-1-(3,6,7-trimethyl-quinoxalin-2-yl)-propenone **12f**. The former possessed selective activity against proliferative cells (cancer and parasites) and was inactive against murine peritoneal macrophages; the latter was active against Leishmania and inactive against the other tested cells [14].

Novel 8-chloro-1,4-substituted-[1,2,4]triazolo[4,3-a]quinoxaline derivatives **13a–j** have been synthesized by Suresh et al. [15] (Figure 6 and Table 4). All the above compounds were screened for antimicrobial activity and antioxidant activity and their bioassay showed them to possess significant antimicrobial activity and anti-oxidant activity.

TABLE 6: List of compounds tested.

Compound	R
16a	
16b	
16c	
16d	NHNH ₂
16e	
16f	
16g	
16h	
16i	OH

FIGURE 4: Chemical structure of compound **9a–l**.

In an effort to develop potent antimicrobial agents, Ghadage and Shirote [16] have synthesized some substituted quinoxalin-2(1H)-one derivatives. Final derivatives **14a–e** (Figure 7) were screened for their in vitro antibacterial activity against range of Gram positive and Gram-negative; also for their anti-fungal activity against a strain of *Candida albicans* species. It was found that all the selected compounds exhibit wide antimicrobial activity. Amongst these compounds, compound **14b** was highly active against *E. coli*. The compounds **14d** and compound **14c** were highly active against *P. aeruginosa* and *S. aureus*. The compounds **14c** and **14d** were highly active against *C. albicans*.

A series of quinoxalines **15a–g** (Figure 8 and Table 5) screened for antibacterial activity among them compound **15a** was displayed activity against *E. coli*, compounds **15d** and **15f** against *P. mirabilis*, compound **15c** against *B. subtilis*, and compound **15e** against *S. aureus* shows maximum activity at 200 µg/disc [17].

A series of ethyl 2-[(3-methyl-2-oxoquinoxalin-1(2H)-yl)acetyl]-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate derivatives **16a–i** (Figure 9 and Table 6) was prepared and

$R_1/R_2 = \text{H/H (a); H/F (b); H/Cl (c); H/CH}_3 \text{ (d); H/OCH}_3 \text{ (e); CH}_3/\text{CH}_3 \text{ (f)}$

FIGURE 5: Chemical structures of compounds tested.

FIGURE 6: Chemical structures of compounds 13a-j.

FIGURE 8: Chemical structures of compounds 15a-g.

a, Ar = $\text{C}_6\text{H}_4\text{CH}_2\text{CH}=\text{CHCHO}$
b, Ar = $3\text{-Cl-C}_6\text{H}_4\text{CHO}$
c, Ar = $(\text{CH}_3)_2\text{N-C}_6\text{H}_4\text{CHO}$
d, Ar = $3,4\text{-Cl}_2\text{C}_6\text{H}_3\text{CHO}$
e, Ar = $\text{OHC}_{12}\text{H}_8\text{CHO}$

FIGURE 7: Chemical structures of compounds tested.

FIGURE 9: Chemical structures of compounds tested 16a-i.

evaluated for their antitubercular activities [18]. All compounds were screened for in vitro antitubercular activity against *Mycobacterium tuberculosis* H37Rv (MTB). Minimum inhibitory concentrations were determined and interpreted for *Mycobacterium tuberculosis* H37Rv according to the procedure of the approved macrodilution reference method of antimicrobial susceptibility testing. Among all the compounds synthesized **16b**, **16c**, and **16f** were found to be the most active compounds against MTB with MIC (25 $\mu\text{g/mL}$) [18].

A series of 2-quinoxalinone-3-hydrazone derivatives (Figure 10) synthesized was evaluated for their antimicrobial

activities [19]. The results showed that this skeletal framework exhibited marked potency as antimicrobial agents. The most active antibacterial agent was 3-[2-[1-(6-chloro-2-oxo-2H-chromen-3-yl) ethylidene]hydrazinyl]quinoxalin-2(1H)-one **23**, while 3-[2-(propan-2-ylidene)hydrazinyl]quinoxalin-2(1H)-one **18**, appeared to be the most active antifungal agent.

The compound 1-methyl-7-nitro-4-(5-(piperidin-1-yl)pentyl)-3,4-dihydroquinoxalin-2(1H)-one **34** (Figure 11) was evaluated [20] against a blood-induced infection with chloroquine-sensitive *Plasmodium yoelii yoelii* lethal strain in CD1 mice in a 4-day test scheme. The results obtained

FIGURE 10: Chemical structures of compounds 17–33.

FIGURE 11: Chemical structures of compound 34.

in this study showed that the infection outcome of *P. yoelii* *yoelii*-infected mice is affected by compound **34** by slowing down the parasite replication, retarding the patency time, and increasing their survival time. Although compound **34** was active at higher doses than chloroquine, these results leave a door open to the study of its structure in order to improve its antimalarial activity.

Some novel pyrido[2,3-*g*]quinoxalinones **35–46** (Figure 12), variously substituted at the C-3 position, were synthesized [21], structurally determined, and submitted to

a preliminary *in vitro* evaluation for antibacterial, *anti-Candida* activities (1). Results of the antimicrobial screening showed that all compounds, with the exception of **38**, **43**, and **44**, exhibited interesting activity against all strains tested.

3. Anti-Inflammatory Activity

In the search for new anti-inflammatory agents, 2(1H)-quinoxalinones and their hexahydro derivatives were prepared [10]. The 2(1H)-quinoxalinone derivative bearing

FIGURE 12: Chemical structures of compounds tested.

FIGURE 13: Chemical structures of compound 45.

4-chlorophenyl-2,3-dihydrothiazole moiety **45** (Figure 13) exhibited the highest anti-inflammatory activity without causing any ulcer side effects like the selective COX-2 inhibitor celecoxib.

Burguete et al. [22] studied the anti-inflammatory and antioxidant activity of several quinoxalines. Compound **46** (Figure 14) presented the most interesting activity.

Similarly, in the study of the same anti-inflammatory activity, Li et al. [23] have evaluated the activity of the

quinoxaline **47** by varying R and R' substituents. Compounds B1 and B2 (Figures 14 and 15) were found to be nonpeptide antagonists of the interleukin-8 molecule receptor, which is involved in several inflammatory diseases and cancer [23].

4. Antiviral Activity

Since 2005, the World Health Organization (WHO) estimated that worldwide more than 40 million people were

FIGURE 14: Chemical structures of compounds **46** and **47**.

FIGURE 15: Chemical structures of compounds tested.

infected with the human immunodeficiency virus (HIV). In particular, South America is facing a rapidly growing number of HIV infections which require an effective antiviral therapy. Ideally, anti-HIV drugs should be highly selective and have good oral availability and favorable pharmacokinetics. Moreover, large-scale production, at low costs to make them accessible for patients in developing countries, would constitute a crucial advantageous feature. Several derivatives of quinoxaline display interesting activity against HIV as nonnucleosidic inhibitors of the reverse transcriptase (RT) [24, 25]. Some of quinoxalinone derivatives synthesized by Gris et al. [26] exhibited good inhibitor activity against some human tumoral cells and the lymphoma related to HIV-1. The studies against HIV were developed for compound **48e** and the methyl ester of **49c**, and no activity was observed, as compared to efavirenz, though it is worth mentioning that the assayed concentrations up to the order 10^{-6} M were not cytotoxic. On the other hand, potential antitumoral activity of compounds **49a** and **49b** has been investigated in the National Cancer Institute (USA). Compound **49a** displayed in vitro activity against a nonsmall lung cell line (EKVX) and human kidney cells (CL A498), while **49b** displayed in vitro activity against central nervous system (CNS) human cells. However, the cytotoxicity shown in both cases was higher than the minimal required to continue the screening. **4c** was evaluated by the Biological Evaluation committee (BEC). Findings indicated a higher activity against AIDS-related lymphoma than the reference compound employed by

the NCI. Nevertheless, it did not reach the lower toxicity level to perform in vivo studies (Figure 16).

Great efforts have been dedicated to the design of compounds acting as selective inhibitors of the HIV-1, and in this case a series of novel N4-(hetero)arylsulfonylquinoxalinone derivatives **50** (Figure 17) was prepared by Xu et al. in a straight and efficient way [27]. Of all the synthesized compounds, five compounds exhibited potent anti-HIV-1 replication activities with IC_{50} value at the level of 10^{-7} mol/L. Preliminary structure-activity relationships were studied in detail and that will shed light on the discovery of more potent nonnucleoside reverse-transcriptase inhibitors [27] (Table 7).

Similarly, other quinoxalinone derivatives have antiviral properties [28, 29]. Many studies have shown the activity of a few quinoxaline compounds towards the human immunodeficiency virus (HIV-1), including the 6,7-dimethyl-2-(pent-4-enyloxy)quinoxaline **52**, [30] and **53**, which not only inhibited HIV-1 RT, but also prevented its replication at the cellular membrane [31] (Figures 18 and 19, Table 8).

5. Enzyme Inhibitory Activity

We will mention a few patents showing various activities of quinoxalinone, as an inhibitor of the kinase protein [32].

The compound **54** [33] is a new molecular macrocycle derived from the quinoxalin-2-one inhibitor of cyclin-dependent kinases CDK1, 2, 4, and 6, while the compound **55** [34] inhibiting glycogen phosphorylase is the enzyme

TABLE 7: Antiviral activity of compounds **50a–h**.

Compound	R ₃	ArSO ₂	IC ₅₀ (μM)
50a	H	Quinoline-8-sulfonyl	0.98
50b	H	3-Cyanobenzene-1-sulfonyl	>100
50c	H	2-Methyloxycarbonylthiophene-3-sulfonyl	2.02
50d	CH ₃	Quinoline-8-sulfonyl	7.0
50e	CH ₃	4-Nitrobenzene-1-sulfonyl	>100
50f	CH ₃	3-Cyanobenzene-1-sulfonyl	55
50g	CH ₃	2-Methyloxycarbonylthiophene-3-sulfonyl	0.2
50h	CH ₃	2,5-Dichlorothiophene-3-sulfonyl	>100

FIGURE 16: Chemical structures of Compounds tested.

FIGURE 17: Chemical structure of compound **50a–h**. FIGURE 18: Chemical structures of compounds **51a–h**.

responsible for the metabolism of glycogen to glucose since glucose is overproduced in patients suffering from diabetes (Figure 20).

Imidazo[1,5-a]quinoxalines were synthesized that function as irreversible Bruton's tyrosine kinase (BTK) inhibitors. The syntheses and SAR of this series of compounds are presented as well as the X-ray crystal structure of the lead compound **56** in complex with a gate-keeper variant of ITK enzyme (Figures 21 and 22). The lead compound showed good in vivo efficacy in preclinical RA models [35].

6. Antitumor Activity

Multidrug resistance (MDR) is a critical issue in cancer chemotherapy. Overexpression of P-gp is the most frequent cause of MDR. P-gp, a transmembrane glycoprotein, functions as an ATP-dependent drug transporter which

FIGURE 19: Chemical structures of compounds prepared.

FIGURE 20: Chemical structures of compounds 54 and 55.

TABLE 8: List of compounds tested.

Compound	R ₃	IC ₅₀ (μM)
51a	H	2.02
51b	CH ₃	0.2
51c	C ₂ H ₅	5.0
51d	CH ₂ CH ₂ SCH ₃	>100
51e	CH ₂ COOCH ₃	>100

unilaterally transports intracellular drugs out of cells to acquire drug resistance. A range of agents that can reverse the MDR phenotype and restore drug sensitivity to cancer cells have been developed [36, 37]. However, most of these agents have proven to be intrinsic toxic and having undesired effects on the pharmacokinetics of accompanying anticancer drugs. For instance, initial attempts to develop MDR modulators focused on verapamil and cyclosporin A [38–40]; these compounds demonstrated excellent *in vitro* reversal of MDR but failed to achieve clinical success due to

their toxicity and/or their alteration of the pharmacokinetics of the coadministered anticancer drugs [40, 41]. Screening 11,000 compounds from commercially available libraries, Lawrence et al. [42] identified several structural platforms with good potential as MDR antagonists. Among these, the 2-oxoquinoxaline or quinoxalinone scaffold showed promise as a versatile scaffold to study P-gp antagonist [42]. Sun et al. [43] have designed and synthesized a series of substituted 1,3-dimethyl-1H-quinoxalin-2-ones. They found that some of the compounds displayed potential inhibition effect on MDR of cancer.

The compounds 57 and 58 (Figure 23) are the novel substituted 1,3-dimethyl-1H-quinoxalin-2-ones with high reversal folds on multidrug resistance in K562/A02 cells. These compounds might be the candidate agents for reversing MDR of cancer.

Quinoxalinone derivatives continue to be a standing interest of lot of research groups. So far, a great deal of data concerning the anticancer activity of more than 300 compounds constitute a library for the antifolc analogs [44–57]. During their investigation, Piras et al. [58] have taken into

FIGURE 21: Chemical structure of compound **56**. FIGURE 22: X-ray structure of **56** in complex with a gate-keeper variant of ITK enzyme in the ATP binding site.

account as antifolate models either the classical methotrexate or the nonclassical trimetrexate as well as the corresponding dideazafolic derivatives. In this context they have proved that bioisosteric replacement of pteridine ring with Trifluoro-6-methylquinoxaline and trifluoro-7-quinoxaline affords a good substrate for the biological activity in the series of the classical antifolate analogs, whereas this was so in a few cases of the series of nonclassical ones. Another aspect being considered was also the bioisosteric replacement of 2-NH group with an oxygen that in some cases was of relevance in the anticancer activity. However, for development of the knowledge about the pharmacophoric pattern, the authors [58] thought to replace the 2-NH bridge in the above-cited series with oxygen on the ground that very recently American authors have found that quinoxalines bearing a 2-(4-substituted phenoxy) substituent were endowed with potent antitumor activity [59]. Thus, the list of compounds **59a–v** (Figure 24 and Table 9) was prepared and the results of their activity presented in Table 10.

There are many quinoxaline derivatives which showed antitumor activity; Corona et al. [60] showed that 5,7-diamino-3-phenyl-2-[(3,5-dimethoxy)phenoxy]quinoxaline

TABLE 9: List of compounds prepared.

Compound	R	R ₁	R ₂
59a	H	6,7-F	OMe
59b	Ph	H	OMe
59c	2-Th	H	OMe
59d	COOEt	H	OMe
59e	COOEt	7-CF ₃	OMe
59f	COOEt	6,7-F	OMe
59g	Ph	H	OH
59h	2-Th	H	OH
59i	COOH	H	OH
59j	COOH	7-CF ₃	OH
59k	COOH	6,7-F	OH
59l	Ph	H	NHgluH
59m	2-Th	H	NHgluH
59n	CONHgluEt	H	NHgluH
59o	COOH	7-CF ₃	NHgluH
59p	CONHgluEt	7-CF ₃	NHgluH
59q	Ph	H	NHgluH
59r	2-Th	H	NHgluH
59s	CONHgluH	H	NHgluH
59t	COOH	7-CF ₃	NHgluH
59v	CONHgluH	7-CF ₃	NHgluH

TABLE 10: $-\log \text{GI}_{50}$, $-\log \text{TGI}$, and $-\log \text{LC}_{50}$ mean graph mid-points (MG-MID)^a of in vitro inhibitory activity against human tumor cell lines^b.

Compounds	$-\log \text{GI}_{50} = \mu\text{M}$	$-\log \text{TGI} = \mu\text{M}$	$-\log \text{LC}_{50} = \mu\text{M}$
59c	4.14 = 72.44	4.02 = 95.49	4.00 = 100
59f	4.10 = 79.43	4.01 = 97.72	4.00 = 100
59g	4.22 = 60.25	4.01 = 97.72	4.00 = 100
59h	4.26 = 54.95	4.01 = 97.72	4.00 = 100
59i	4.20 = 63.09	4.00 = 100	4.00 = 100
59m	4.13 = 74.13	4.00 = 100	4.00 = 100
59n	4.63 = 23.44	4.15 = 70.79	4.02 = 95.49

60 has an antitumor activity in vitro, towards several types of tumors. Also the 3-(4-bromophenyl)-2-(ethylsulfonyl)-6-methylquinoxaline-1,4-dioxide **61** (Figure 25), has an activity against the tumor in the hypoxia stage, which is a phase

FIGURE 23: Chemical structures of compounds **57** and **58**. FIGURE 24: Chemical structure of compound **59a-v**. FIGURE 25: Chemical structures of compounds **60** and **61**. FIGURE 26: Chemical structure of compound **62**.

where the tumor shows a resistance during chemotherapy and radiotherapy [61].

Other compounds, derivatives of quinoxalinone, were submitted to a primary screening for anticancer activity following the known in vitro disease-oriented antitumor screening program, against a panel of about 60 human tumor cell lines [21]. The activity of each compound tested was deduced

from a dose-response curve according to the data provided by NCI while compound **62** (Figure 26) was found to have encouraging in vitro anticancer activity at a concentration of 10^{-4} M.

Fourteen out of 21 quinoxaline derivatives described by Piras et al.'s [62] present paper were selected at NCI for evaluation of their in vitro anticancer activity. Preliminary

FIGURE 27: Chemical structures of compounds tested.

FIGURE 28: Chemical structures of compounds 65–71.

screening showed that some derivatives exhibited a moderate to strong growth inhibition activity on various tumor panel cell lines between 10^{-5} and 10^4 M concentrations. Interesting selectivities were also recorded between 10^{-8} and 10^{-6} M for the compounds **63** and **64** (Figure 27).

Based on screening hit 1, a series of tricyclic quinoxalinones **65–71** (Figure 28) has been designed and evaluated for inhibition of PARP-1 [63]. Substitutions at the 7- and 8-positions of the quinoxalinone ring led to a number of compounds with good enzymatic and cellular potency. The tricyclic quinoxalinone class is sensitive to modifications of both the amine substituent and the tricyclic core.

The antitumor activity of synthesized quinoxalines **72–77** (Figure 29) has been evaluated by studying their possible inhibitory effects on Epstein-Barr virus early antigen (EBV-EA) activation induced by 12-O-tetradecanoylphorbol-13-acetate (TPA). Said compounds demonstrated strong inhibitory effects on the EBV-EA activation without showing any cytotoxicity and their effects being stronger than that of a representative control, oleanolic acid. Furthermore, compound **72** exhibited a remarkable inhibitory effect on skin tumor promotion in an in vivo two-stage mouse skin carcinogenesis test using 7,12-dimethylbenz[a]anthracene (DMBA) as an initiator and TPA as a promoter [64].

FIGURE 29: Chemical structure of compound 72–77.

FIGURE 30: Chemical structure of compound 78.

A series of ruthenium(II) arene complexes with 3-(1H-benzimidazol-2-yl)-1H-quinoxalin-2-one **78** (Figure 30), bearing pharmacophoric groups of known protein kinase inhibitors, related benzoxazole and benzothiazole derivatives have been synthesised, therefore antiproliferative activity in three human cancer cell lines (A549, CH1, and SW480) was determined by MTT assays, yielding IC_{50} values of 6–60 μM for three unsubstituted metal-free ligands, whereas values for the metal complexes vary in a broad range from 0.3 to 140 μM . Complexation with osmium of quinoxalinone derivatives results in a more consistent increase in cytotoxicity than complexation with ruthenium [65].

FIGURE 31: Chemical structure of compound 79.

Deregulation of cellcycle control is a hallmark of cancer. Thus, cyclin-dependent kinases (Cdks) are an attractive target for the development of anticancer drugs. Rübsamen-Waigmann et al. [28] report the biological characterization of a highly potent pan-Cdk inhibitor with a macrocycle-quinoxalinone structure. Compound **79** (Figure 31) inhibited Cdk1, 2, 4, 5, 6, and 9 with equal potency in the nM range and was selective against kinases other than Cdks. This compound

TABLE 11: Enzyme inhibition activity of compound **79** against the Cdk family and other kinases.

Kinases	IC ₅₀ (nM)	Selectivity (fold)
Cdk4	4.1	1.0
Cdk6	12	
Cdk2	3.4	
Cdk1	1.0	
Cdk5	4.5	
Cdk7	660	
PKA		>730
PKC		230
ERK1		>730
ERK2		>730
P38 α		>2400
KDR		250
Flt-1		330
Flt-4		71
FGFR1		2000
FGFR2		610
Src		260
Tle-2		>4900
PDGF β		480
EGFR		>2400

inhibited multiple events in the cell cycle in vitro, including retinoblastoma protein (pRb) phosphorylation, E2F-dependent transcription, DNA replication (determined by bromodeoxyuridine incorporation), and mitosis completion (assayed by flow cytometry) in the 10 nM range (Table 11).

Moreover, this compound induced cell death, as determined by induction of the subG1 fraction, activated caspase-3, and an exin V. In vivo, compound **79** showed antitumor efficacy at a tolerated dose. In a nude rat xenograft tumor model, an 8 h constant infusion of compound **79** inhibited pRb phosphorylation and induced apoptosis in tumor cells at 30 nM, which led to the inhibition of tumor growth. Immunosuppression was the only liability observed at this dose, but immune function returned to normal after 10 days. Suppression of pRb phosphorylation in tumor cells was clearly correlated with tumor cell growth inhibition and cell death in vitro and in vivo. In vivo, compound **79** inhibited pRb phosphorylation in both tumor and gut crypt cells. Rb phosphorylation may be a suitable pharmacodynamic biomarker in both tumors and normal tissues for monitoring target engagement and predicting the efficacy of compound **79** [66].

The KRAS oncogene is found in up to 30% of all human tumors. In 2009, RNAi experiments revealed that lowering mRNA levels of a transcript encoding the serine/threonine kinase STK33 was selectively toxic to KRAS-dependent cancer cell lines, suggesting that small-molecule inhibitors of STK33 might selectively target KRAS-dependent cancers. To test this hypothesis [67], we initiated a high-throughput screen using compounds in the Molecular Libraries Small Molecule Repository (MLSMR). Several hits were identified,

FIGURE 32: Chemical structure of compound **80**. FIGURE 33: Chemical structure of compounds **81a-t**.

and one of these, a quinoxalinone derivative, was optimized. Extensive SAR studies were performed and led to the chemical probe **53** that showed low nanomolar inhibition of purified recombinant STK33 and a distinct selectivity profile as compared to other STK33 inhibitors that were reported in the course of these studies. Even at the highest concentration tested (10 μ M), **80** (Figure 32) had no effect on the viability of KRAS-dependent cancer cells. These results are consistent with other recent reports using small-molecule STK33 inhibitors. Small molecules having different chemical structures and kinase-selectivity profiles are needed to fully understand the role of STK33 in KRAS-dependent cancers. In this regard, **80** is a valuable addition to small-molecule probes of STK33.

P-glycoprotein-mediated drug efflux from cells is believed to be an important mechanism in multidrug resistance (MDR) in cancer chemotherapy. The identification and development of P-glycoprotein inhibitors with high potency and low cytotoxicity hold great promise for overcoming MDR. A series of quinoxalinone derivatives was synthesized and evaluated primarily for their antiproliferative effect and MDR reversal activity in in vitro assay systems [56]. Biological assays demonstrated that the compounds **81a-t** (Figure 33 and Table 12) were, in general, endowed with good activity as P-glycoprotein inhibitors. Among them, compounds which showed the highest MDR reversal activity without significant cytotoxicity displayed potent P-glycoprotein inhibition activities and may be worthy of further research as potential adjunctive agents for tumor chemotherapy [68].

TABLE 12: List of compounds tested.

Compound	R ₁	R ₂	Compound	R ₁	R ₂
81a	H		81l	H
81b	H		81m	H
81c	H		81n	H
81d	H		81o	H
81e	H		81p	F
81f	H		81q	OCH ₃
81j	F		81r	H
81k	OCH ₃		81s	H
			81t	H

7. Receptor Antagonist Activity

A series of quinoxalinones was synthesized as antagonists of bradykinin, which is a peptide responsible for the dilatation of blood vessels, thus leading to the lowering of blood pressure [69].

Bayoumi et al. [70] showed that 1,2,4-triazolo(4,3-a)quinoxalin-4-5H-one derivatives **82** and **83** (Figure 34) act as AMPA receptor antagonists.

8. Antithrombotic Activity

Excessive uncontrolled activation of the hemostatic system results in thromboembolic diseases, a major cause of morbidity and mortality in our society. The central role of the

serine proteases factor Xa and thrombin in hemostasis make them attractive targets for antithrombotic therapy. Factor Xa, factor Va, calciums and phospholipids form the prothrombinase complex, which converts prothrombin into thrombin. Thrombin very efficiently initiates fibrin formation, platelet aggregation, and activation of factors V and VIII. Selective inhibitors of thrombin and factor Xa are expected to be therapeutically useful in the treatment or prophylaxis of thromboembolic diseases [71–73].

In order to design and develop orally active coagulation inhibitors containing heterocyclic core structures, Ries et al. [74] identified some compounds as potent thrombin inhibitors 2 in vitro.

Based on this lead structure novel coagulation inhibitors having quinoxalinone **84** (Figure 35) as the central template

FIGURE 34: Chemical structures of compounds tested.

FIGURE 35: Chemical structure of compound 84.

have been designed. These compounds inhibited thrombin and factor Xa in the nanomolar range.

9. Antidiabetic Activity

Diabetes is a serious metabolic disorder with micro- and macrovascular complications which causes significant morbidity and mortality. In the developing world, the diabetes epidemic is accelerating with an increased proportion of affected people in the younger population.

Recently, some reports described that type 2 diabetes was being diagnosed even in children and adolescents [75]. The latest WHO Global Burden of Disease estimate the worldwide burden of diabetes in adults to be around 173 million in the year 2002 [76] and around two-thirds of these live in developing countries. So, nowadays, it has become a growing public health concern worldwide causing severe and costly complications including blindness cardiac and kidney diseases [77]. Current therapies do little in preventing complications although they provide good glycemic control.

Besides this, these drugs are also associated with side effects. Thus, it is necessary to continue research for new and, if possible, more efficacious drugs, particularly bioactive quinoxalinone-based compounds, which are effective in the treatment of diabetes and its complications. Through this procedure, a new class of quinoxalinone-based aldose reductase inhibitors were synthesized successfully **85**. Most of the inhibitors, with an N1-acetic acid head group and a substituted C3-phenoxy side chain, proved to be potent

and selective. Their IC_{50} values ranged from 11.4 to 74.8 nM. Among them, 2-(3-(4-bromophenoxy)-7-fluoro-2-oxoquinoxalin-1(2H)-yl)acetic acid **57** and 2-(6-bromo-3-(4-bromophenoxy)-2-oxoquinoxalin-1(2H)-yl)acetic acid were the most active **86** [78] (Figure 36).

To conclude this review of biological activity of the quinoxalinone derivatives, we will mention that the compounds **87–89** (Figure 37) are considered as a novel potential therapeutic avenue for autism [79]; it is pharmacophore models are a promising milestone to a class of SSRIs with dual action.

Finally, a series of new quinoxaline derivatives **90** (Figure 38), which could act as modulators of the AMPA receptor mediators of synaptic responses, has been synthesized [80].

The circle containing nitrogen designates a heterocycle of 5 to 8 rings, and the group R' may be a group 2- or 3-alkyl, cycloalkyl, hydroxy, alkoxy, alkoxy-alkyl, hydroxy-alkyl, or carbamoyl.

10. Conclusion

In recent years, the quinoxalinone made a tremendous achievement in the biological and pharmacological fields. Also, the modifications in the basic structure of the quinoxalin-2-one have enabled the emergence of new derivatives with a wide spectrum of biological activities.

In conclusion a wide variety of biological activities of quinoxalinone have been described. Quinoxaline moiety containing 1,4-di-N oxide shows broad spectrum of activity

FIGURE 36: Chemical structure of compounds tested.

FIGURE 37: Chemical structures of compounds 87–89.

FIGURE 38: Chemical structure of compound 90.

against wide number of bacterial species and also exhibited cytotoxic activity. Those drugs containing quinoxaline moiety are Carbadox and Brimonidine. Carbadox, a well-known synthetic antibacterial agent used for treatment of various bacterial diseases, and Brimonidines showed the importance of quinoxalines as a pharmaceutical agent as it palliates the symptoms of glaucoma through reducing intraocular pressure.

Studies of these derivatives have shown that structural modification can improve its pharmacological profile conferring antibacterial, anticancer, anti-HIV, antidiabetic, and anti-inflammatory properties.

Conflict of Interests

The authors certify that there is no actual or potential conflict of interests in relation to their paper titled “Pharmacological Profile of Quinoxalinone.” This manuscript updated information on the most active quinoxalinone derivatives that have been reported to show considerable pharmacological actions.

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