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Synthesis and biological evaluation of functionalized quinoxaline derivatives

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ABSTRACT

*Divergent quinaoxaline analogues were synthesized in good yields from the W (3-fluoro-4-nitrophenoxy) phenyl quinoxaline (**6**) as the key intermediate using triethylamine as base in dimethylsulfoxide.*

Keywords: (3-fluoro-4-nitrophenoxy)-phenyl quinoxaline, Trirthylamine, Anti-cancer activity.

INTRODUCTION

Quinazolinone pharmacophore is a building block for approximately 150 naturally occurring alkaloids isolated to date from a number of families of the plant kingdom, animals and microorganisms. The first quinazolinone was synthesized [1] in the late 1860s from anthranilic acid and cyanogens to give 2-cyanoquinazolinone. Interest in the medicinal chemistry of quinazolinone derivatives was stimulated in the early 1950's with the elucidation of a quinazolinone alkaloid, 3-[β-keto-g-(3-hydroxy-2-piperidyl)- propyl]-4-quinazolone febrifugine [2] , from an Asian plant Dichroa febrifuga, which is an ingredient of a traditional Chinese herbal remedy, effective against maleria.

In a quest to find additional potential quinazolinone-based drugs, various substituted quinazolinones have been synthesized, which led to the synthesis of the derivative, 2-methyl-3-*O*-tolyl-4-(3*H*)-quinazolinone methaqualone. Methaqualone was synthesized [3] for the first time in 1951 and it is the most well-known synthetic quinazolinone drug, famous for its sedative-hypnotic effects [4]. The introduction of methaqualone and its discovery as a hypnotic triggered the research activities toward the isolation, synthesis, and studies on the pharmacological properties of the quinazolinones and related compounds. Quinazolinones and their derivatives are now known to have a wide range of useful biological properties, such as hypnotic, sedative, analgesic, anti-convulsant, anti-tussive, anti-bacterial, anti-diabetic, anti-inflammatory, anti-tumor, and several others such as anti-microbial, anticonvulsant, sedative, hypertensive, anti-depressant, antimflammatory, and anti-allergy properties. [5-7]. Some of these compounds also have interesting biological properties such as anti-malarial activity, biofungicide, and diuretic properties [8-10]. In continuation of our efforts on the sysnthesis of biologically relevant heterocycles, herein, we report the synthesis and application of divergent quinaoxaline analogues [12].

MATERIALS AND METHODS

General Conditions: All the reactants, reagents and solvents were obtained from commercial sources and were of analytical grade. Melting points were determined by open capillary method. ^{1}H NMR ($CDCl_3$ 300 MHz) and ^{13}C NMR ($CDCl_3$, 75 MHz) were recorded on spectrometer TMS as internal standard (chemical shifts and ppm). Mass spectra were recorded on a VG micromass70-70H instrument. The purity of the compounds was checked by TLC on silica gel plates using a mixture of n-hexane and ethyl acetate.

I. General procedure for the synthesis of 2-(4-(3-Fluoro-4-nitrophenoxy) phenyl) quinoxaline(6)
Equimolar mixture of hydroxy ketone (**4**, 291mg, 1 mmol) and *o*-phenylenediamines (**5**, 108 mg, 1 mmol) were heated with IBX (420 mg, 1.5 mmol) in THF: DMSO (9:1) at 80° C for 50 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with EtOAc (20 mL) and brine (2x10 mL), dried over anhydrous Na_2SO_4, removed solvent *in vacua*, and the crude residue was purified by column chromatography on silica gel (5% EtOAc in Hexane) the desired product **6** (342 mg, 95% yield) as brown colour solid, mp 92-94 °C; ^{1}H NMR (300 MHz, $CDC1_3$) δ 6-65- 6.79 (m, 3H, Ar-H), 7.08-7.20 (m, 2H, Ar-H), 7.65-7.80, (m, 2H, Ar-H), 8.05-a (m, 2H, Ar-H), 8.16- 8.25 (m, 2H, Ar-H), 9.27 (s, 1H, Ar-H); ^{13}C NMR (300 MHz, $CDC1_3$) δ 96.1, 107.7, 108.0, 110.5, 110.8, 119.6, 120.9, 127.9, 128.0, 128.2, 129.2, 129.5, 129.6, 129.7, 130.1, 130.2, 142.5, 156.7, 166.8; MS (ESI): *m/z* 362 $(M+H)^+$.

II.General procedure for the synthesis of title compounds quinoxalines (7a-i)
4-(2-Nitro-5-(4-(quinoxalin-2-yl) phenoxy) phenyl) morpholine (7a)
Triethylamine was slowly added to a mixture of 2-(4-(3-fluoro-4-nitrophenoxy) phenyl) quinoxaline (361mg, 1 mmol) and morpholine (95mg, 1.1 mmol) in 5mL of DMSO. The mixture was stirred at 90° C for 10 h. After completion of the reaction (monitored by TLC), reaction mixture was poured in ice water followed by extracted with ethyl acetate (2x40mL). The combined organic phase was washed with brine (lx20mL), dried over anhydrous Na_2SO_4. Concentrated *in vacuo*, and the resulting residue was purified by column chromatography on silica gel (30% EtOAc in hexane) to obtain **7a** (350mg, yield 82%) as yellow colour powder. Decomposition at 175° C; ^{1}H NMR (400 MHz, $CDC1_3$) δ 3.27 (t, 4H), 3.79 (bs, 4H), 6.45 (d, 1H), 6.65 (dd, 1H), 7.14 (d, 2H, *J*=8.58 Hz), 7.67-7.82 (m, 2H), 8.09 (d, 3H, *J*=9.36 Hz), 8.22 (d, 2H, *J*=8.56 Hz), 9.29 (s, 1H); ^{13}C NMR (75MHz, $CDC1_3$): δ 51.8, 66.6, 109.1, 110.4, 116.3, 120.5, 129.1, 129.2, 129.6, 129.8, 130.2, 130.6, 130.8, 133.4, 137.4, 141.5, 143.0, 148.7, 150.8, 157.0, 161.7; MS (ESI) *m/z* 451 $(M+Na)^+$;

All compounds were synthesized by using same experimental procedure described above and obtained in good yield. Therefore, all the following experiments were conducted in same conditions

2-(4-(4-Nitro-3-(piperazin-l-yl)phenoxy)phenyl)quinoxaline(7b)
Orange colour powder; decomposition at173 °C; ^{1}H NMR (300MHz, $CDC1_3$) δ 3.27 (t, 4H), 3.79 (bs, 4H), 6.45 (d, 1H), 6.65 (m, 1H), 7.14 (d, 2H, *J*=8.58), 7.67- 7.82 (m, 2H), 8.09 (d, 3H, *J*=9.36), 8.22 (d, 2H, *J*=8.56), 9.29 (s, 1H); MS (ESI) *m/z* 428 $(M+H)^+$;

1,4-Bis(2-nitro-5~(4-(quinoxaIin-2-yl)phenoxy)phenyl)piperazine (7c)
yellow colour solid; mp 136-138°C; ^{1}H NMR (300 MHz, $CDC1_3$) δ 3.18-3.28 (bs, 4H), 3.54-3.66 (bs, 4H), 6.56-7.01 (m, 5H), 7.05-7.33 (m, 5H), 7.70-7.86 (m, 3H), 7.87-8.14 (m, 6H), 8.25-8.45 (m, 3H), 9.43 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 57.3, 59.7, 113.0, 114.8, 115.0, 115.2, 125.5, 125.6, 127.8, 127.9, 128.0, 128.1, 129.5, 135.0, 135.7, 138.3, 139.7, 144.4, 156.2; MS (ESI) *m/z* 768 (M^+), 769 $(M+H)^+$, 770 $(M+2H)^+$.

5-(2-Nitro-5-(4-(quinoxalin-2-yl) phenoxy) phenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (7d)
Mp 162-165° C; ^{1}H NMR (300MHz, $CDC1_3$) δ 3.03(bs, 2H), 3.48(t, 2H), 4.20 (s, 2H), 6.53 (dd, lH, $J_{(1,2)}$=2.34, $J_{(1,3)}$- 9.36), 6.71-6.80 (m, 2H), 7.08 (d, 1H, .*J*=4.68), 7.20-7.29 (m, 2H), 7.70-7.82(m, 2H), 7.90 (d, 1H, .*J*=9.36), 8.07-8.1 6(m, 2H), 8.27(d, 2H, .7=8.58), 9.3 l(s, 1H); ^{13}C NMR (75 MHz, $CDC1_3$) δ 29.6, 50.4, 50.5, 108.3, 109.1, 120.4, 123.2, 124.7, 129.1, 129.3, 129.4, 129.6, 130.4, 130.7, 132.1, 133.6, 135.9, 141.4, 143.0, 148.0, 157.0, 161.4; MS (ESI) *m/z* 503 $(M+Na)^+$;

2-(4-(3-(4-MethyIpiperazin-l-yl)-4-nitrophenoxy) phenyl) quinoxaline (7e)
Mp 120-123 °C; ^{1}H NMR (300, $CDC1_3$) δ 2.40 (s, 3H), 2.64 (t, 4H, *J*= 5.2), 3.12 ;(t, 4H, *J*=4.5), 6.46- 6.79 (m, 2H) 7.07-7.34 (m, 3H), 7.73- 8.06 (m, 3H), 8.1- 8.33 (m, 3H), 9.35(s, 1H); ^{13}C NMR ($CDC1_3$, 75 MHz) δ 29.7, 65.7,

71.0, 109.4, 118.4, 127.5, 127.6, 128.2, 129.5, 129.7, 129.8, 132.8, 133.3, 135.5/135.8, 166.1; MS (ESI) *m/z* 441$(M)^+$, 442 $(M+H)^+$;

Diethyl 2-methyl-2-(2-nitro-5-(4-(quinoxalin-2-yl) phenoxy) phenyl)malonate (7f)
Brown colour liquid; ^{1}H NMR (300, $CDC1_3$) δ 1.24 (t, 6H, *J*= 7.17 Hz), 1.81 (s, 3H), 4.20 (q, 4H, *J*=7.17Hz), 7.05-7.32 (m, 4H), 7.66-7.81 (m, 2H), 7.93-8.33 (m, 5H), 9.29 (s, 1H); ^{13}C NMR (75 MHz, $CDC1_3$) δ 13.9, 22.0, 58.6, 62.3, 117.8, 118.6, 121.9, 123.5, 125.6, 129.1, 129.3, 129.4, 129.5, 129.6, 130.4, 132.6, 141.4, 142.9, 143.0 145.4, 148.9, 158.0, 170.0; MS (ESI) *m/z* 516 $(M+H)^+$, 517 $(M+2H)^+$, 538 $(M+Na)^+$;

2-(4-(3-(4-((4-Chlorophenyl)(phenyl)methyl)piperazin-l-yl)-4-nitrophenoxy)phenyl) quinoxaline (7g)
Yellow colour solid; mp 145-147 °C; ^{1}H NMR (300, $CDC1_3$) δ 2.54(bs, 4H), ,.05 (bs, 4H), 4.24 (s, 1H), 6.53-6.68 (m, 2H), 7.09-7.41(m, 11H), 7.68- 7.90 (m, 3H), 1.11 (d, 2H, *J*=7.93), 8.27(d, 2H, *J*=8.68), 9.31(s, lH); ^{13}C NMR (75 MHz, $CDC1_3$) δ 16.1, 50.7, 73.5, 106.5, 109.5, 116.7, 127.1, 127.5, 128.5, 128.6, 128.7, 129.0, 129.3, 29.5, 130.0, 130.5, 130.6, 131.4, 140.8, 141.3, 141.4, 141.8, 143.4, 150.2, 150.9, 155.2, 59.0; MS (ESI) *m/z* 628 $(M+H)^+$.

l-Cyclopropyl-6-fluoro-7-(4-(2-nitro-5-(4-(quinoxalin-2-yl) phenoxy) phenyl) piperazin-l-yl)-4-oxo-l,4-dihydroquinoline-3-carboxylic acid (7h)
Decomposes at 152 °C; ^{1}H NMR (500 MHz, $CDC1_3$) δ 0.81-0.93 (m, 1H), 1.15-l.21 (bs, 2H), 1.35-1.42 (m, 2H), 3.48-3.56 (m, 4H), 3.62-3.69 (m, 4H), 6.65 (d, 1H, *J*= 2.14), 6.89 (dd, 1H, J_1,=2.14, J_2=7.50), 7.15 (d, 1H, *J*=8.58), 7.49 (d, 1H, *J*=6.43), 7.71-7.81(m, 2H), 7.85-7.96 (m, 2H), 8.03-8.17 (m, 3H), 8.30 (d, 1H, *J*=8.58), 8.67 (s, 1H), 9.39 (s, 1H), 14.88 (bs, 1H); ^{13}C NMR (75 MHz, $CDC1_3$) δ 7.7, 35.6, 48.2, 49.3, 101.0, 102.4, 105.4, 109.3, 112.8, 115.3, 118.6, 124.4, 126.7, 127.5, 128.5,129.1, 134.4, 142.5,143.8,144.7,147A, 152.6, 157.7,164.1, 166.5, 176.4; MS (ESI) *m/z* 673$(M+H)^+$.

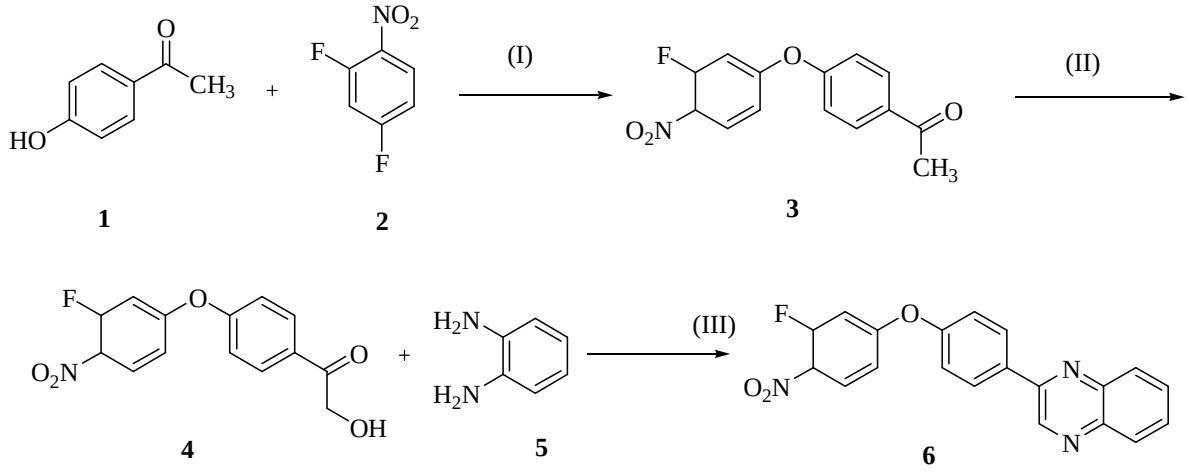
(R)-2-Nitro-N-(l-phenylethyl)-5-(4-(quinoxalin-2-yl) phenoxy) benzenamine (7i)
Mp: 91-93 °C; ^{1}H NMR (300 MHz, $CDC1_3$) δ 1.60 (d, 3H, *J* = 6.80 Hz), 4.34-4.45 (q, 1H, *J*-6.04 Hz), 5.99 (d, 1H, *J* =2.27 Hz), 6.28-6.34 (dd, ,IH), 6.95-7.0 2(m, 2H), 7.08-7.17 (m, 2H), 7.22-7.28 (m, 4H), 7.72-7.84 (m, 2H), 8.10-8.22 (m, 4H), 9.32 (s, 1H); ^{13}C NMR ($CDC1_3$, 75 MHz) δ 20.5, 52.9, 118.0, 118.3, 118.7, 120.8, 120.9, 122.4, 123.9, 125.4, 125.9, 126.1, 128.5, 128.6, 129.1, 129.4, 130.7, 132.1, 135.1, 139.4, 140.9, 152.1, 153.1, 166.2; MS (ESI) *m/z* 463 $(M+H)^+$.

RESULTS AND DISCUSSION

Chemistry
Synthesis of new quinaoxaline analogues was designed based on the possibility of nucleophilic substitution of fluorine atom which is ortho position to electron withdrawing -NO_2 group. Thus the synthetic strategy (**Scheme 1**) depicts the synthetic route for the preparation of compound **6**. Treatment of 4-hydroxy acetophenone **1** with 2,4 difluoro nitrobenzene **2** in presence of base potassium carbonate in acetonitrile under reflux condition afforded l-(4-(3-fluoro-4-nitrophenoxy) phenyl) ethanone **3** in 98% yield. It was characterized by a singlet at δ 2.50 corresponding to -$COCH_3$ and observed with seven protons at aromatic field δ 6.98-8.20. It was further confirmed with appearance of a peak at 276 corresponding $(M+H)^+$ in ESI-MS.

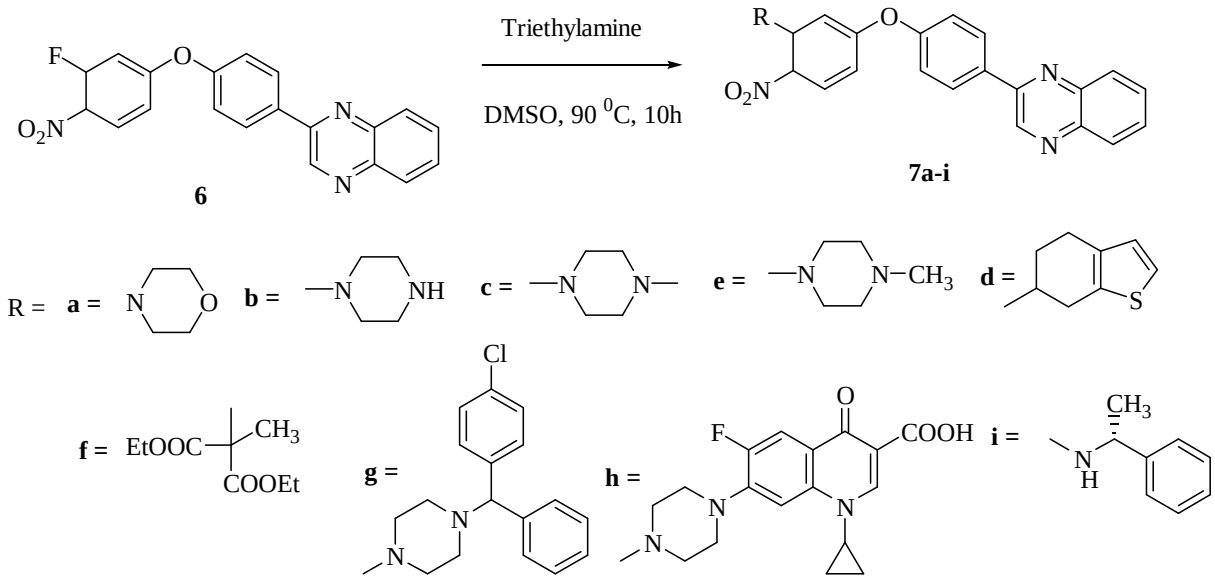
α-Hydroxylation of compound **6** via the α-hydroxy dimethylacetal using Iodosylbenzoic acid in methanol with 83% yield of compound **4**. It showed appearance of singlet peak at δ 4.72 corresponding to -$\underline{CH_2}$-OH and disappearance of δ 2.50 peak relative to -CO$\underline{CH_3}$ in ^{1}H NMR and further confirmed with molecular ion peak 292 $M+H)^+$ in ESI-MS. Then IBX mediated oxidative cyclization of compound **4** with *o*-phenylenediamines **5** in THF+DMSO at 80 °C leads to formation of compound **6**. In the ^{1}H NMR spectrum of compound **6** showed characteristic signal at δ 9.05 and it was further confirmed with ESI-MS showed molecular ion peak at 362 $(M+H)^+$ in ESI-MS.

Compound **6** was the key intermediate for the synthesis of the new quinoxaline analogues, as it was appropriately substituted with various amines using triethylamine as base in dimethyl sulfoxide at 90 °C for 5.5-6 hours afforded a series of novel quinoxaline derivatives. Structures of compounds (**7a-i**) were characterized by ^{1}H NMR, ^{13}C NMR, IR, ESI-MS



Reagent and conditions : **(i)** K_2CO_3 (2.0 equiv), CH_3CN,65°C-75°C, 4h.
(ii) (1) KOH (3.0 equiv.), Iodosyl Benzoic acid, MeOH, 5° C-10° C. (2) 5% H_2SO_4, CH_2Cl_2.
(iii) IBX, THF-Idrop of DMSO, 80° C, 50min.

Scheme 1: synthesis of (3-fluoro-4-nitrophenoxy) phenyl quinoxaline (6)



Scheme 2: Synthesis of title compounds quinoxalines (7a-i)

spectroscopy (**Scheme 2**). For instance compound **7f** was characterized by the appearance of triplet at δ 1.27 (corresponding to –$CH_2\underline{CH_3}$), a singlet at 1.82 (corresponding to –$\underline{CH_3}$), a quartet at δ 4.12-4.29 (corresponding to –$CH_2\underline{CH_3}$), a multiplets at aromatic regions and characteristic singlet at δ 9.30. It was further confirmed by the appearance of peak at 516 $(M+H)^+$.

Anti-Cancer Activity

Cellular viability in the presence of test compounds was determined by MTT- microcultured tetrazolium assay following the reported protocol [11]. All the experiments were carried out in triplicates.

Cytotoxicity assay against three different human cancer cell lines was employed in the current study.

1. A549 (Human lung adeno carcinoma epithelial cell line),

2. SKNSH (Human Neuroblastoma cell line)
3. MDA-MB-231 (Human Breast Adenocarcinoma),

Procedure:
Day one: One full confluent T-25 flask was trypsinized and 5 ml of complete media was added to trypsinized cells and centrifuged in a sterile 15 ml falcon tube at 500 rpm in the swinging bucket rotor (-400 x g) for 5 min. Media was removed and the cells were resuspended to 1.0 ml with complete media and cells were counted. The cells were diluted to 75,000 cells per ml incomplete media. 100 µl of cells (7500 total cells) were added in each well and incubated overnight in a humid incubator with 5% CO_2 at 37 °C so that the cells adhere to the surface. Different concentrations of compounds were prepared by dissolving in DMSO.

Day two: Different concentrations of compounds were added to the adherent cells in triplicates (l µl per each well) and incubated for 48hrs with DMSO alone as control.

Day Four: MTT (3-(4,5-dimethylthiazol-2yl)-2,5diphenyl tetrazolium bromide (sigma catalog no.M2128)was dissolved in PBS at 5 mg/ml and filter sterilized and stored at 4° C.10 µl of MTT solution was added to each well and incubated for 2 hours at 37° C in the incubator. Then the media was aspirated and plates were dried and 100 µl of DMSO (solvent) was added to each well. Plate was covered with tinfoil and agitated on orbital shaker for 15 min. The results were represented as percentage of Cytotoxicity/viability. From the percentage of Cytotoxicity the IC50 values were calculated and presented in the table. Treatment with the compounds reduced the viability of human cancer cell lines in a concentration-dependent manner, with IC_{50} values in the low micromolar range.

In the present study we compared the cytotoxicity of compounds on three cancer cell lines and found that some of the compounds are showing cytotoxicity on cancer cells. IC_{50} values were compared with a standard compound Doxorubicin.

IC_{50} values of different compounds on different cell lines in µM cone.

4 different concentrations of compounds **6** and **7a-i** were tested on three cancer cell lines. IC50 values were given in micromolar concentrations (µM).

Table-1: Anti-cancer activity of title compounds 7a-i

S. No	Compound ID	A549	SKNSH	MDA-MB 231
1	**6**	158.3	>1000	>1000
2	**7a**	84.5	152.4	94.4
3	**7b**	>1000	>1000	>1000
4	**7c**	101.0	14.3	79.1
5	**7d**	>1000	>1000	>1000
6	**7e**	>1000	971.0	147.5
7	**7f**	>1000	113.6	995.8
8	**7g**	73.7	13.2	118.5
9	**7j**	>1000	965.3	13.0
10	**7i**	106.7	96.6	15.5
11	**Doxorubicin**	0.92	8.5	1.1

CONCLUSION

We have successfully synthesized nine novel quinoxalines **(7a-i)** via 2-(4-(3-fluoro-4-nitrophenoxy) phenyl quinoxaline **(6**) in good yields. we have developed by using IBX as an inexpensive, easy to handle, non-corrosive and environmentally benign catalyst for the synthesis of quinoxalines from aromatic *o*-diamines and hydroxy ketone compounds. The structures of all the compounds were confirmed by their spectral data. The advantages of the present procedure are simplicity of operation, very short reaction times compared with other procedures for the preparation of quinoxaline derivatives, and the high yields of products. The functionalized quinoxalines evaluated for its antimicrobial and anti-cancer activity.

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