

Microwave assisted synthesis of novel 1, ω -bis(quinoxalin-2-yl)phenoxy)alkanes or arenes

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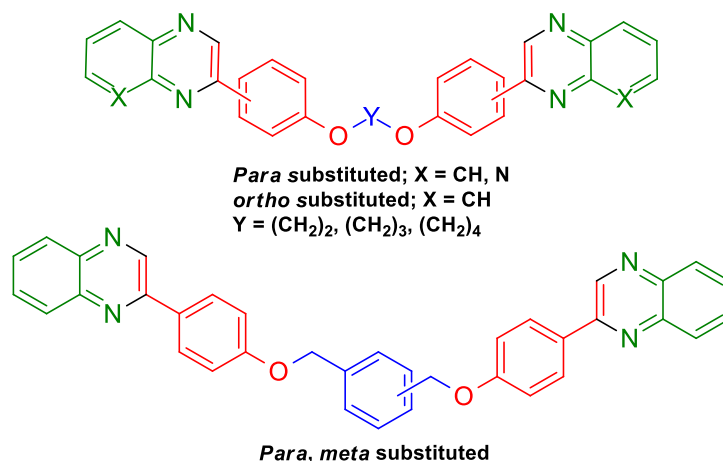
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Abstract

A synthesis of a novel series of bis(quinoxaline) derivatives by the reaction of *o*-phenylenediamine with the appropriate bis(α -bromoketones) was reported. The reactions were performed under thermal as well as under microwave irradiation conditions. The reaction of bis(α -bromoketones) with 2,3-diaminopyridine proceeded to give two regioisomers of the corresponding bis((pyrido[2,3-*b*]pyrazinyl)phenoxy)methanes.



Keywords: Bis(quinoxalines), bis(α -bromoketones), bis((pyrido[2,3-*b*]pyrazinyl)phenoxy)methanes, microwave irradiation

Introduction

Quinoxaline derivatives are an important class of heterocyclic compounds that are found in diverse library of pharmacologically active molecules. Their potentially versatile biological activities, including antiviral, anticancer, antibacterial and antiprotozoal properties are recently reported.^{1–11}

The quinoxaline scaffold is present in several therapeutic and pharmacologically active compounds as well as natural occurring compounds. The usefulness of some quinoxaline derivatives as medicines are well established^{12–14} (Figure 1).

In addition, quinoxaline derivatives were used as building blocks for the synthesis of dyes, electroluminescent material, anion receptors and organic semiconductors.^{15–18}

A number of methods have been developed for the synthesis of quinoxaline derivatives. Among them, condensation of 1,2-diamines with α -diketones¹⁹, 1,4-addition of 1,2-diamines to diazenylbutenes²⁰, cyclization–oxidation of phenacyl bromides²¹ and oxidative coupling of epoxides with ene-1,2-diamines²² are still the most common methods. These reactions were also performed using green methodologies, including recyclable catalysts, microwave-assisted synthesis and reactions in aqueous medium.^{1,23–29}

Novel contributions to develop new, safe and effective methodology for novel quinoxaline scaffolds of pharmacological importance for drug discovery programs are still in demand.

Motivated by these findings and in conjunction with our ongoing research work on bis(heterocycles)^{30–43} we report herein on the synthesis of novel bis(quinoxalines) which are linked *via* aliphatic or aromatic spacers in a cost-effective manner. The synthesis of the target compounds were investigated under microwave irradiation as well as by using traditional heating conditions.

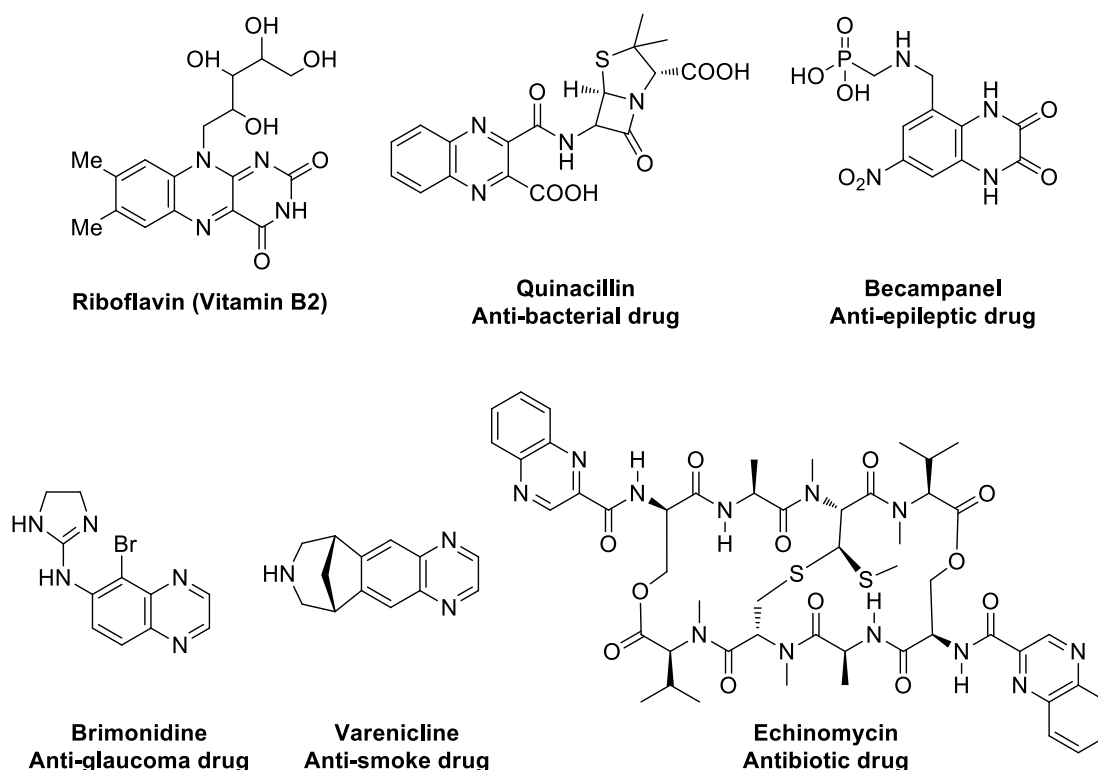
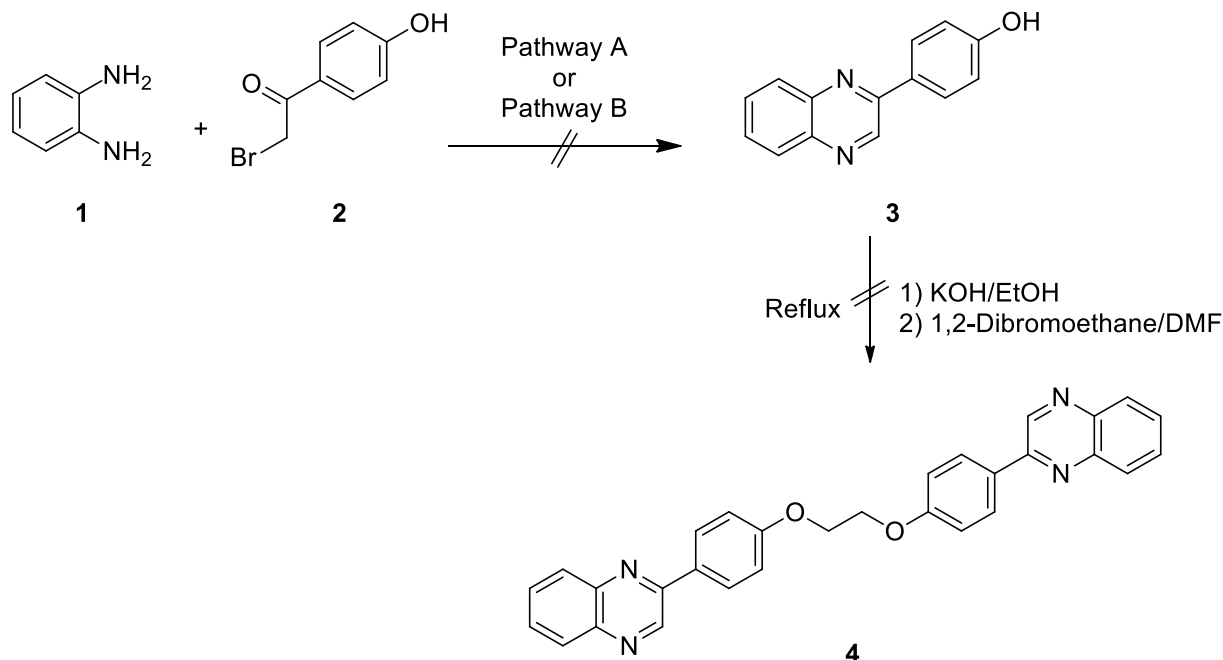


Figure 1. Drugs containing the quinoxaline core.

Results and Discussion

Two strategies were attempted for the synthesis of the novel bis(quinoxaline) **4**. In the first strategy, we studied the synthesis of 4-(quinoxalin-2-yl)phenol (**3**) which should then undergo reaction with 1,2-dibromoethane under basic conditions to give 1,2-bis(4-(quinoxalin-2-yl)phenoxy)ethane (**4**) (Scheme 1).



Scheme 1. Attempts for the synthesis of the novel bis(quinoxalines) **4**.

Unfortunately, repeated attempts to isolate pure sample of **3** were unsuccessful. Reaction of 2-bromo-1-(4-hydroxyphenyl)ethanone (**2**) with one equivalent of *o*-phenylenediamine (**1**) in THF using DABCO as a catalyst, according to the method described by Meshram *et al.*⁴⁴ (Pathway A) did not lead to the formation of **3** and instead the quaternary salt **5** was obtained as a sole product. On the other hand, reaction of **1** with **2** in acetonitrile at reflux in the presence of piperidine as a catalyst (Pathway B) led to the formation of 4-(1,4-dihydroquinoxalin-2-yl)phenol (**6**) in good yield (Figure 2).

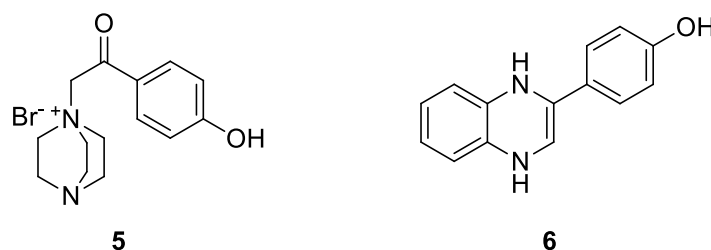
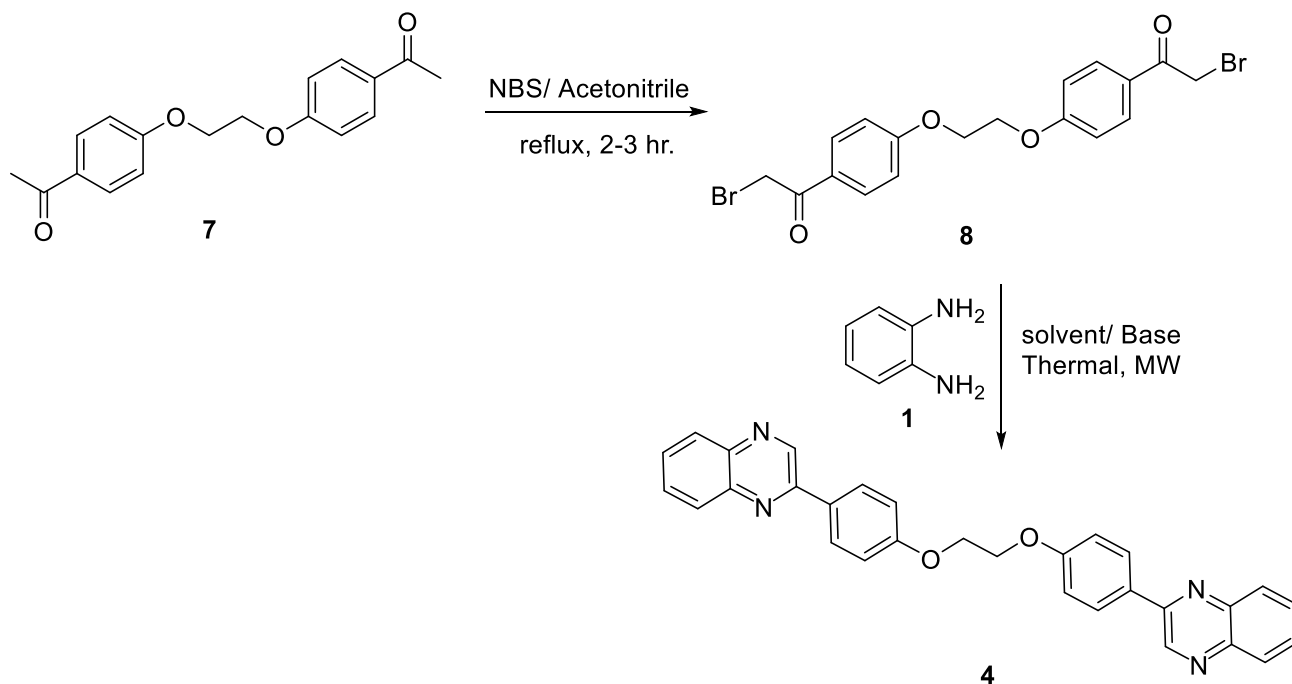


Figure 2. Structures of the quaternary salt **5** and 4-(1,4-dihydroquinoxalin-2-yl)phenol (**6**).

It is worth mentioning that compound **3** has been prepared recently using starting materials and/or reagents that are not readily available in our laboratory.^{45–48} We then turned to the second strategy in which 1,1'-((ethane-1,2-diylbis(oxy))bis(4,1-phenylene))bis(2-bromoethanone) (**8**) was firstly prepared from the

appropriate bis(acetophenone) precursor **7** by the reaction with *N*-Bromosuccinimide in the presence of *p*-toluenesulfonic acid (*p*-TsOH) in acetonitrile.³⁵ Compound **8** was allowed to react with *o*-phenylenediamine (**1**) as a model reaction for the synthesis of **4** (Scheme 2). The reactions were performed under both conventional heating (Method A) as well as MW irradiation (Method B).



Scheme 2. Reaction of **8** with **1** as a model reaction for the synthesis of bis(quinoxaline) **4**.

To find the optimal reaction conditions, the reaction was performed in EtOH using a variety of bases (DABCO, TEA, piperidine, pyridine and KOH) as outlined in Table 1. Compared with other bases, piperidine was found to achieve the best yields and the cleanest products in short reaction time (2 hr.) (entry 3, table 1). It is worthy to mention that prolonged reaction times (up to 7 hours) did not affect the yields of the target products.

Table 1. Effect of base on the synthesis of bis-quinoxalline **4**

Run	Base	Thermal Yield% ^a 4	MW Yield% ^b 4
1	DABCO	64	73
2	TEA	71	79
3	Piperidine	76	87
4	Pyridine	61	67
5	KOH	67	78

^aReaction conditions: **8** (1 mmole), **1** (2 mmole), base (2 mmole), EtOH (25 mL), 2 hr. at reflux temp.

^bReaction conditions: **8** (1 mmole), **1** (2 mmole), base (2 mmole), EtOH (3 mL), microwave irradiation (250 W) at 100 °C, 10 min.

The reaction was also examined in different solvents (ethanol, dioxane, dichloromethane, acetonitrile, water and DMF) as well as under solvent free conditions. The reaction was found to proceed in most solvents but with different degrees of conversion and ethanol was proved to be the best solvent in terms of reaction time and yield as outlined in Table 2. Under solvent free conditions, the reaction also proceeded to give the target molecule **4** but in very low yield (entry 7, table 2). Moreover, attempts to synthesize **4** by direct reaction of **8** with **1** in water without catalyst according to the method described by Kumar et al.⁴⁹ were also unsuccessful (entry 5, table 2).

Table 2. The Solvent effect for synthesis of bis-quinoxalline **4**

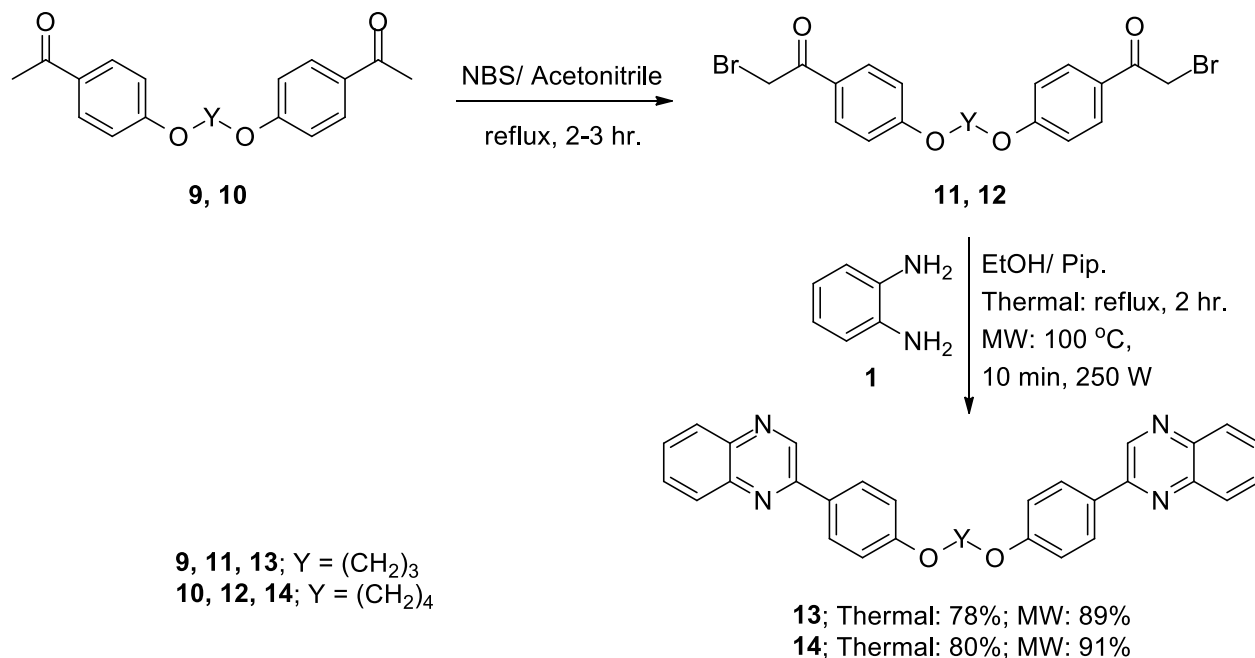
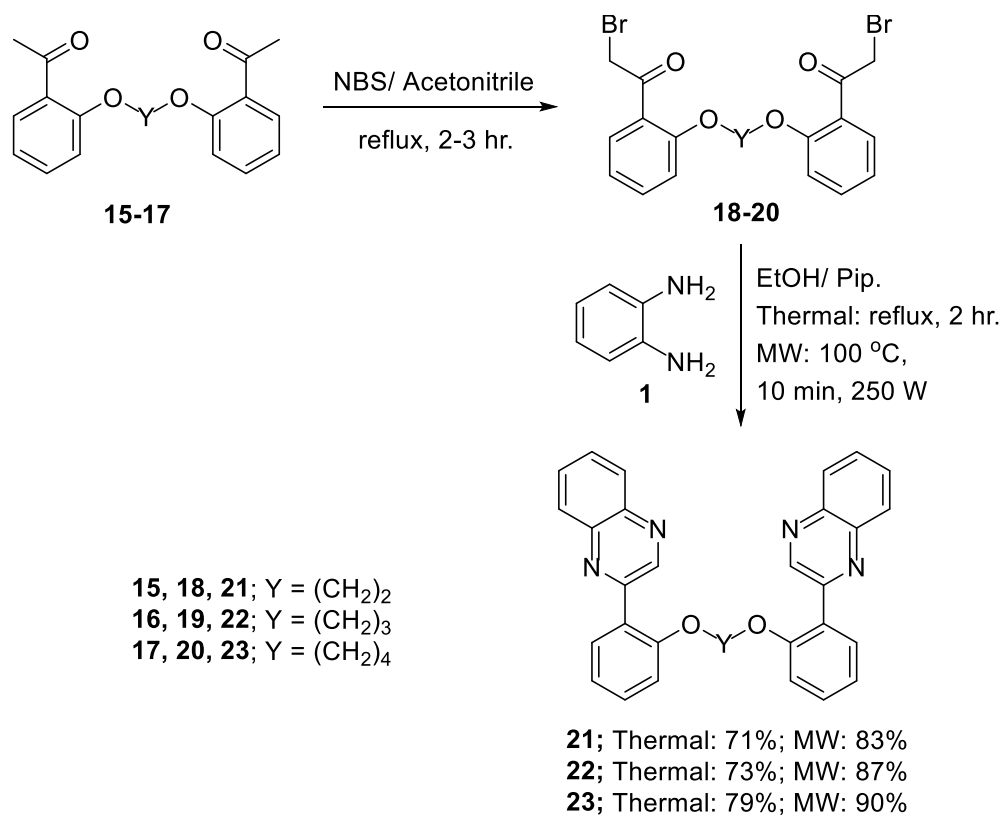
Run	Solvent	Thermal Yield% ^a 4	MW Yield ^b 4
1	Ethanol	76	87
2	Dioxane	70	77
3	Dichloromethane	56	69
4	Acetonitrile	69	78
5	Water	0	0
6	DMF	60	66
7	-	Trace	trace

^aReaction conditions: **8** (1 mmole), **1** (2 mmole), piperidine (2 mmole), solvent (25 mL), 2 hr. at reflux temp.

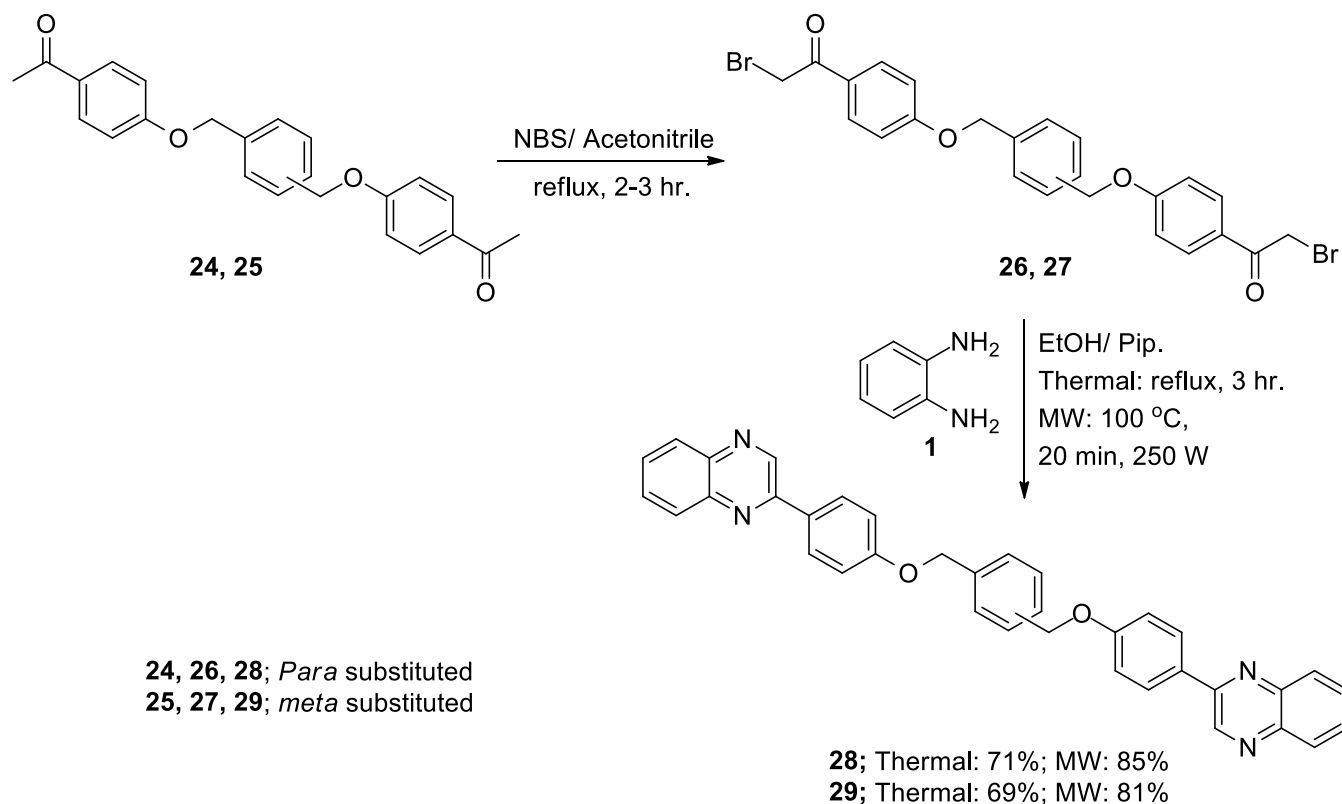
^bReaction conditions: **8** (1 mmole), **1** (2 mmole), piperidine (2 mmole), solvent (3 mL), microwave irradiation (250 W) at 100 °C (EtOH and Acetonitrile), 120 °C (Dioxane and H₂O), 50 °C (Dichloromethane), 160 °C (DMF) and 130 °C (solvent free), 10 min.

To explore the scope of this transformation, *o*-phenylenediamine (**1**) was allowed to react with various bis(α -haloketones) under the optimized reaction conditions. Thus, bis(4,1-phenylene))bis(2-bromoethanones) **11** and **12** were prepared from the appropriate bis(acetophenones) **9** and **10** as previously reported by our group.³⁵ Reaction of compounds **11** and **12** with *o*-phenylenediamine (**1**) afforded bis(quinoxalines) **13** and **14**, respectively (Scheme 3).

Similarly, reaction of bis(2,1-phenylene))bis(2-bromoethanones) **18-20** (obtained from the appropriate bis(acetophenones) **15-17** by bromination with NBS)³⁵ with *o*-phenylenediamine (**1**) afforded the target products **21-23**, respectively, in good yields, (Scheme 4).

Scheme 3. Synthesis of bis(quinoxalines) **13** and **14**.Scheme 4. Synthesis of bis(quinoxalines) **21-23**.

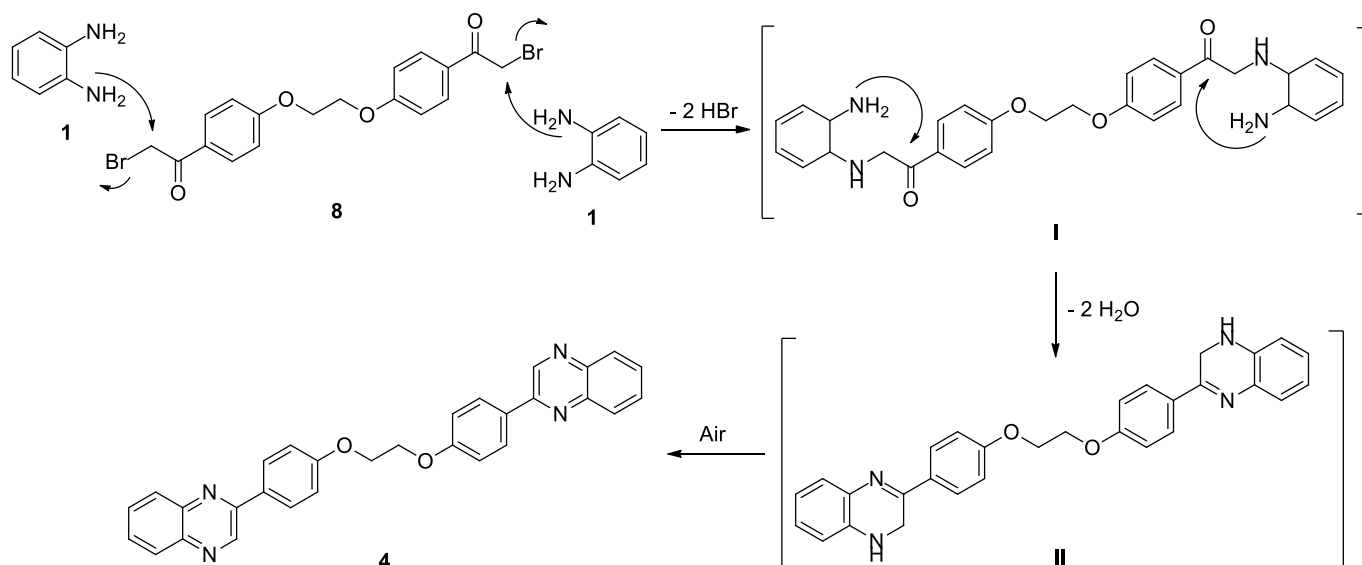
Using a similar approach, reaction of bis(bromoacetyl) arenes **26** and **27** with *o*-phenylenediamine (**1**) in the presence of piperidine in ethanol at reflux as well as under microwave reaction conditions afforded the corresponding bis(quinoxalines) **28** and **29**, respectively. Compounds **26** and **27** were obtained from the corresponding bis(acetophenones) **24** and **25**, respectively, upon treatment with *N*-bromosuccinimide (NBS) in the presence of *p*-toluenesulfonic acid in acetonitrile⁵⁰ (Scheme 5).



Scheme 5. Synthesis of bis(quinoxalines) **28** and **29**.

The structure of the novel bis(quinoxalines) were confirmed by spectral tools as well as elemental analyses. Thus, compound **4** as a representative example showed the correct molecular ion peak at m/z 470 in its mass spectrum. The disappearance of peaks characteristic for CO and NH groups in the IR spectrum confirms the cyclization as well as the aromatization reactions. Furthermore, the IR of compound **4** revealed a peak at 1602 cm^{-1} characteristic for C=N stretching. Moreover, the ^1H NMR of compound **4** featured the methylene ether linkage OCH_2 as a singlet signal at δ 4.50 ppm. The characteristic signal at δ 9.55 ppm is referring to quinoxaline-H3. All other protons were seen at the expected chemical shifts and integral values (See Experimental section and Supporting Information).

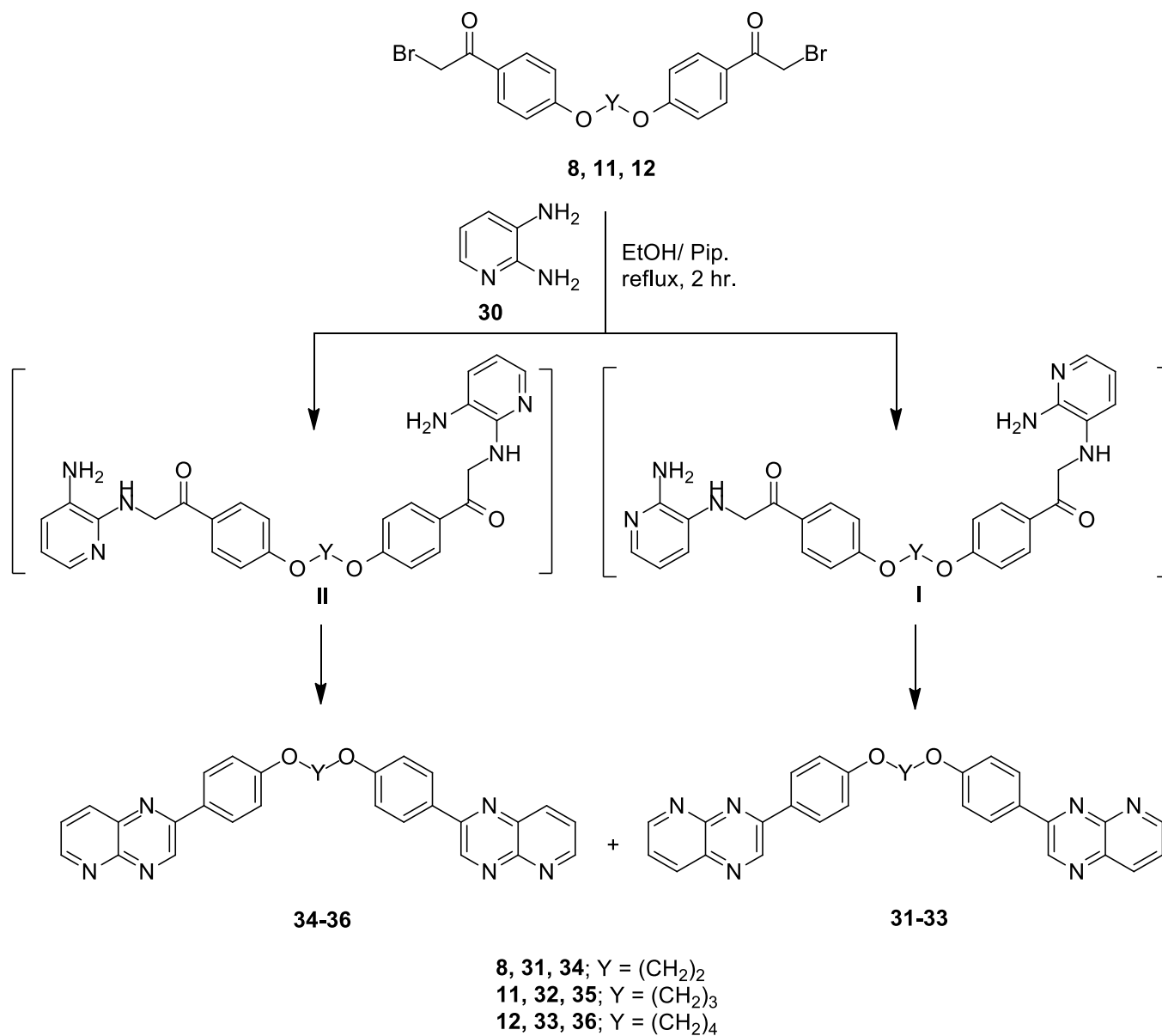
A plausible reaction mechanism for the formation of quinoxaline derivative **4** from *o*-phenylenediamine (**1**) and bis(bromoacetyl) **8** is illustrated in Scheme 6. Initially a nucleophilic substitution occurs on the phenacyl bromide to afford the intermediate **I**. Intermediate **I** was then cyclized to give 3-phenyl-1,2-dihydroquinoxaline **II**. The latter compound underwent air oxidation to afford the aromatized bis(quinoxaline) **4** as the final product (Scheme 6).



Scheme 6. A plausible mechanism for the formation of quinoxaline derivative **4**.

It was noted that when symmetric diamine was used, the reaction proceeded smoothly in all the cases and resulted in the formation of the corresponding bis(quinoxalines) as sole products in good yields. On the other hand, when the reaction was further examined by employing the reaction of 2,3-diaminopyridine (**30**) as an unsymmetrical diamine with bis(4,1-phenylene)bis(2-bromoethanones) **8**, **11** and **12**, an inseparable mixture of two regioisomers were obtained with considerable difference in the isomer ratios (determined by ¹H NMR) depending on the structure of bis(2-bromoethanones). Thus, when **8** was used the two regioisomeric products **31** and **34** were obtained in a ratio of 4:1. On the other hand, the regioisomeric products **32** / **35** and **33** / **36** were obtained in ratios of 3:1 and 1:1, respectively, when **11** and **12** were used (Scheme 7).

The formation of the two regioisomers may be explained as a result of the difference in the reactivities of the two amino groups of compound **30**. The pyridine nitrogen may deactivate the amino group at position 2 and thus, the other amino group participates firstly in the reaction and leads to intermediate **I** which then cyclized and oxidized affording the corresponding products **31-33**. The reaction may also proceed through intermediate **II** that affords the regioisomers **34-36** upon cyclization and oxidation (Scheme 7). Carrying out these reactions under microwave irradiation did not provide a significant advantage in increasing the reaction yield or in changing the regioselective ratio of the products. It is noteworthy to mention that we examined the reaction by employing different substituted *o*-phenylene diamine but unfortunately, the reactions afforded in all cases inseparable mixture of regioisomeric products.



Scheme 7. Regioorientation in the addition reaction of 2,3-diaminopyridine to bis(α -bromoketones).

Conclusions

In conclusion, we synthesized a new series of bis(quinoxaline) derivatives by the reaction of *o*-phenylenediamine or 2,3-diaminopyridine with the appropriate bis(α -bromoketones) under thermal heating as well as under microwave irradiation conditions. The reaction proceeded *via* initially substitution reaction followed by cyclization and subsequent aromatization in a one-pot process under basic conditions.

Experimental Section

General. Melting points were determined in open glass capillaries with a Gallenkamp apparatus. The infrared spectra were recorded in potassium bromide disks on a Pye Unicam SP 3-300 and Shimaduz FTIR 8101 PC

infrared spectrophotometer. NMR spectra were recorded using a Varian Mercury VXR-300 NMR spectrometer or Bruker Ultrashield 400 MHz or Ascend 400 MHz (^1H : 300 or 400 MHz, ^{13}C : 75 or 100.6 MHz) instruments using $\text{DMSO-}d_6$ as solvent. Capillary GC analyses were performed with a Shimadzu GC-14A or GC-14B, a Shimadzu C-R6A Integrator, and a HP 5 column (25 m length, 0.25 mm i.d., 0.25 μm film) or recorded with an Agilent GC 6890N. Mass spectra (EI) were obtained at 70 eV using a type Shimadzu GCMQP 1000 EX Spectrometer. Microwave experiments were carried out using a CEM Discover LabmateTM microwave apparatus (300 W with ChemDriverTM Software). Elemental analyses were performed on a Perkin-Elmer 240 microanalyser at the Micro analytical Center of Cairo University. Compounds **8**, **11**, **12** and **18-20** were prepared according to literature.³⁵ Compounds **26** and **27** were prepared according to literature.⁵⁰

Attempts for synthesis of 4-(quinoxalin-2-yl)phenol (**3**)

Pathway A. A mixture of *o*-phenylenediamine (**1**) (1 mmol), 2-bromo-1-(4-hydroxyphenyl)ethanone (**2**) (1 mmol) and DABCO (20% mol) in THF (20 ml) was stirred at room temperature for 1 hr.⁴⁴ The solid residue was collected and proved to be the quaternary salt **5**.

2-(4-Bromo-1 λ^4 ,4 λ^4 -diazabicyclo[2.2.2]octan-1-yl)-1-(4-hydroxyphenyl)ethan-1-one quaternary salt (5**)** Colorless powder (83%); mp > 300 °C; IR (KBr) ν 3417, 2987, 1681, 1597, 1458 cm^{-1} ; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 3.12 (t, 6H, CH_2N , $J = 6.9$ Hz), 3.60 (t, 6H, CH_2N , $J = 7.2$ Hz), 5.14 (s, 2H, COCH_2N), 7.12 (d, 2H, ArH, $J = 8.7$ Hz), 7.87 (d, 2H, ArH, $J = 6.6$ Hz), 10.81 (s, 1H, OH); MS m/z (%) 326 (M^+). Anal. Calcd for $\text{C}_{14}\text{H}_{19}\text{BrN}_2\text{O}_2$: C, 51.39; H, 5.85; Br, 24.42; N, 8.56. Found: C, 51.48; H, 5.71; Br, 24.35; N, 8.44%

Pathway B. A mixture of *o*-phenylenediamine (**1**) (1 mmol) and 2-bromo-1-(4-hydroxyphenyl)ethanone (**2**) (1 mmol) in acetonitrile (25 mL) in the presence of piperidine (0.1 ml, 1 mmol) was heated at reflux for 5 hr. The solvent was then evaporated in *vacuo* and the solid residue was collected and recrystallized from acetonitrile to give 4-(1,4-dihydroquinoxalin-2-yl)phenol (**6**) in good yield.

4-(1,4-Dihydroquinoxalin-2-yl)phenol (6**)** Creamy powder (71%); mp 262 °C; IR (KBr) ν 3425, 3218, 3024, 1597, 1404 cm^{-1} ; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 6.46 (s, 2H, NH), 7.19-9.01 (m, 9H, ArH & dihydro quinoxaline-3-H), 11.58 (s, 1H, OH); MS m/z (%) 224 (M^+). Anal. Calcd for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.85; H, 5.26; N, 12.57%

Synthesis of bis(2 and 4-(quinoxalin-2-yl)phenoxy)alkane **4**, **13**, **14** and **21-23**.

Method A. To a solution of *o*-phenylenediamine (**1**) (2 mmol) and bis(2-bromoethanone) derivatives **8**, **11**, **12** or **18-20** (1 mmol) in ethanol (25 mL), piperidine (0.19 mL, 2 mmol) was added. The reaction mixture was heated at reflux for 2 hr. The solvent was evaporated in *vacuo*, and the solid residue was collected by filtration and recrystallized from ethanol/DMF to give the corresponding products **4**, **13**, **14** and **21-23**.

Method B. A mixture of *o*-phenylenediamine (**1**) (2 mmol), bis(2-bromoethanone) derivatives **8**, **11**, **12** or **18-20** (1 mmol) and piperidine (0.19 mL, 2 mmol) in ethanol (3 mL) was placed in a closed vessel and irradiated in a focused microwave reactor for 10 min. at 100 °C (250 W). The crude solid was isolated and recrystallized from EtOH/DMF to give corresponding products **4**, **13**, **14** and **21-23**.

1,2-Bis(4-(quinoxalin-2-yl)phenoxy)ethane (4**)**. Colorless powder (A, 76%; B, 87%); mp 247-250 °C; IR (KBr) ν 3053, 1602, 1542, 1431, 1236 cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 4.50 (s, 4H, O- CH_2), 7.10-8.35 (m, 16H, ArH), 9.55 (s, 2H, quinoxaline-3-H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 67.0, 114.8, 115.6, 129.3, 129.4, 129.5, 130.6, 131.0, 141.2, 141.9, 143.9, 151.1, 160.7; MS m/z (%) 470 (M^+). Anal. Calcd for $\text{C}_{30}\text{H}_{22}\text{N}_4\text{O}_2$: C, 76.58; H, 4.71; N, 11.91. Found: C, 76.46; H, 4.55; N, 11.71%.

1,3-Bis(4-(quinoxalin-2-yl)phenoxy)propane (13**)**. Colorless powder (A, 78%; B, 89%); mp 196-200 °C; IR (KBr) ν 3052, 1604, 1538, 1428, 1244 cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 2.26-2.30 (m, 2H, CH_2), 4.29 (t, 4H, OCH_2 ,

$J = 5.7$ Hz), 7.17-8.33 (m, 16H, ArH), 9.53 (s, 2H, quinoxaline-3-H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 64.9, 115.6, 128.9, 129.3, 129.4, 129.5, 129.8, 130.9, 141.1, 141.9, 143.9, 151.1, 160.9; MS m/z (%) 484 (M^+). Anal. Calcd for $\text{C}_{31}\text{H}_{24}\text{N}_4\text{O}_2$: C, 76.84; H, 4.99; N, 11.56. Found: C, 76.75; H, 4.89; N, 11.41%.

1,4-Bis(4-(quinoxalin-2-yl)phenoxy)butane (14). Pale yellow powder (A, 80%; B, 91%); mp 188-192 °C; IR (KBr) ν 3052, 1602, 1509, 1393, 1245 cm^{-1} ; ^1H NMR (400 MHz, DMSO- d_6) δ 1.96 (br. s, 4H, CH_2), 4.18 (br. s, 4H, OCH_2), 7.14-8.32 (m, 16H, ArH), 9.53 (s, 2H, quinoxaline-3-H); MS m/z (%) 498 (M^+). Anal. Calcd for $\text{C}_{32}\text{H}_{26}\text{N}_4\text{O}_2$: C, 77.09; H, 5.26; N, 11.24. Found: C, 76.98; H, 5.08; N, 11.05%.

1,2-Bis(2-(quinoxalin-2-yl)phenoxy)ethane (21). Pale yellow crystals (A, 71%; B, 83%); mp 178-180 °C; IR (KBr) ν 3047, 1595, 1547, 1498, 1234 cm^{-1} ; ^1H NMR (400 MHz, DMSO- d_6) δ 4.54 (s, 4H, O-CH_2), 7.14-8.05 (m, 16H, ArH), 9.25 (s, 2H, quinoxaline-3-H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 67.4, 114.9, 117.7, 129.0, 129.5, 130.0, 130.4, 131.9, 132.1, 135.4, 140.8, 142.3, 147.0, 151.7, 156.6; MS m/z (%) 470 (M^+). Anal. Calcd for $\text{C}_{30}\text{H}_{22}\text{N}_4\text{O}_2$: C, 76.58; H, 4.71; N, 11.91. Found: C, 76.40; H, 4.59; N, 11.77%.

1,3-Bis(2-(quinoxalin-2-yl)phenoxy)propane (22). Colorless powder (A, 73%; B, 87%); mp 128-132 °C; IR (KBr) ν 3045, 1596, 1546, 1450, 1258 cm^{-1} ; ^1H NMR (400 MHz, DMSO- d_6) δ 2.19-2.21 (m, 2H, CH_2), 4.23 (t, 4H, OCH_2 , $J = 6.3$ Hz), 7.13-8.09 (m, 16H, ArH), 9.29 (s, 2H, quinoxaline-3-H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 28.8, 65.6, 113.3, 121.7, 126.4, 129.2, 129.5, 130.2, 130.6, 131.7, 132.0, 140.8, 142.3, 147.3, 152.2, 156.7; MS m/z (%) 484 (M^+). Anal. Calcd for $\text{C}_{31}\text{H}_{24}\text{N}_4\text{O}_2$: C, 76.84; H, 4.99; N, 11.56. Found: C, 76.69; H, 4.88; N, 11.43%.

1,4-Bis(2-(quinoxalin-2-yl)phenoxy)butane (23). Yellow powder (A, 79%; B, 90%); mp 97-100 °C; IR (KBr) ν 3048, 1597, 1548, 1452, 1240 cm^{-1} ; ^1H NMR (400 MHz, DMSO- d_6) δ 1.87 (br. s, 4H, CH_2), 4.13 (br. s, 4H, OCH_2), 7.10-8.08 (m, 16H, ArH), 9.31 (s, 2H, quinoxaline-3-H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 25.9, 68.3, 113.2, 121.5, 126.1, 129.2, 129.5, 130.2, 130.6, 131.7, 132.0, 142.4, 147.3, 152.2, 156.8; MS m/z (%) 498 (M^+). Anal. Calcd for $\text{C}_{32}\text{H}_{26}\text{N}_4\text{O}_2$: C, 77.09; H, 5.26; N, 11.24. Found: C, 77.22; H, 5.35; N, 11.08%.

Synthesis of 1,3 and 1,4-bis((4-(quinoxalin-2-yl)phenoxy)methyl)benzene 28, 29

Method A. To a solution of *o*-phenylenediamine (**1**) (2 mmol) and bis(bromoacetyl) arenes derivatives **26** or **27** (1 mmol) in ethanol (25 mL), piperidine (0.19 mL, 2 mmol) was added. The reaction mixture was heated at reflux for 3 hr. The solvent was evaporated in *vacuo*, and the solid residue was collected by filtration and recrystallized from EtOH/DMF to give compounds **28** and **29**.

Method B. A mixture of *o*-phenylenediamine (**1**) (2 mmol), bis(bromoacetyl) arenes derivatives **26** or **27** (1 mmol) and piperidine (0.19 mL, 2 mmol) in ethanol (3 mL) was placed in a closed vessel and irradiated in a focused microwave reactor for 20 min. at 100 °C (250 W). The crude solid was isolated and recrystallized from ethanol/DMF to give corresponding products **28** and **29**.

1,4-Bis((4-(quinoxalin-2-yl)phenoxy)methyl)benzene (28). Brown powder (A, 71%; B, 85%); mp 208-210 °C; IR (KBr) ν 3039, 1597, 1504, 1427, 1242 cm^{-1} ; ^1H NMR (400 MHz, DMSO- d_6) δ 5.26 (s, 4H, OCH_2), 7.22-8.34 (m, 20H, ArH), 9.56 (s, 2H, quinoxaline-3-H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 69.5, 115.6, 115.9, 128.4, 129.1, 129.2, 129.4, 129.5, 131.0, 131.1, 141.1, 141.9, 143.9, 151.1, 161.1; MS m/z (%) 546 (M^+). Anal. Calcd for $\text{C}_{36}\text{H}_{26}\text{N}_4\text{O}_2$: C, 79.10; H, 4.79; N, 10.25. Found: C, 78.98; H, 4.67; N, 10.08%.

1,3-Bis((4-(quinoxalin-2-yl)phenoxy)methyl)benzene (29). Brown powder (A, 69%; B, 81%); mp 170-174 °C; IR (KBr) ν 3055, 1604, 1543, 1465, 1242 cm^{-1} ; ^1H NMR (400 MHz, DMSO- d_6) δ 5.28 (s, 4H, OCH_2), 7.23-8.33 (m, 20H, ArH), 9.54 (s, 2H, quinoxaline-3-H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 69.7, 115.9, 127.4, 127.8, 129.1, 129.2, 129.3, 129.4, 129.8, 130.9, 137.5, 141.1, 141.8, 143.9, 151.0, 160.7; MS m/z (%) 546 (M^+). Anal. Calcd for $\text{C}_{36}\text{H}_{26}\text{N}_4\text{O}_2$: C, 79.10; H, 4.79; N, 10.25. Found: C, 78.85; H, 4.57; N, 10.07%.

Synthesis of bis(4-(pyrido[2,3-*b*]pyrazinyl)phenoxy)alkane 31-36. To a solution of 2,3-diaminopyridine (**30**) (2 mmol) and bis(2-bromoethanone) derivatives **8**, **11** or **12** (1 mmol) in ethanol (25 mL), piperidine (0.19 mL, 2 mmol) was added. The reaction mixture was heated at reflux for 2 hr. The solvent was evaporated in *vacuo*, and the solid residue was collected by filtration and recrystallized from EtOH/DMF to give compounds **31-36**.

1,2-Bis(4-(pyrido[2,3-*b*]pyrazin-3-yl)phenoxy)ethane (31) and **1,2-bis(4-(pyrido[2,3-*b*]pyrazin-2-yl)phenoxy)ethane (34)**. Colorless powder (63%); mp 266-270 °C; IR (KBr) ν 3055, 1604, 1566, 1404, 1242 cm^{-1} ; ^1H NMR (300 MHz, DMSO-*d*₆) δ 4.52 (s, 4H, OCH₂), 7.10-9.15 (m, 14H, ArH & pyridine-H), 9.68, 9.74 (two s, 2H, pyrazine-2-H, pyrazine-3-H isomeric ratio 4:1); MS *m/z* (%) 472 (M⁺). Anal. Calcd for C₂₈H₂₀N₆O₂: C, 71.17; H, 4.27; N, 17.79. Found: C, 71.43; H, 4.59; N, 17.99%.

1,3-Bis(4-(pyrido[2,3-*b*]pyrazin-3-yl)phenoxy)propane (32) and **1,3-bis(4-(pyrido[2,3-*b*]pyrazin-2-yl)phenoxy)propane (35)**. Brown powder (69%); mp 216-221 °C; IR (KBr) ν 3055, 1604, 1465, 1404, 1242 cm^{-1} ; ^1H NMR (300 MHz, DMSO-*d*₆) δ 2.28-2.29 (m, 2H, CH₂), 4.31 (t, 4H, OCH₂, *J* = 6.0 Hz), 7.18-9.13 (m, 14H, ArH & pyridine-H), 9.66, 9.71 (two s, 2H, pyrazine-2-H, pyrazine-3-H isomeric ratio 3:1); MS *m/z* (%) 486 (M⁺). Anal. Calcd for C₂₉H₂₂N₆O₂: C, 71.59; H, 4.56; N, 17.27. Found: C, 71.77; H, 4.68; N, 17.50%.

1,4-Bis(4-(pyrido[2,3-*b*]pyrazin-3-yl)phenoxy)butane (33) and **1,4-bis(4-(pyrido[2,3-*b*]pyrazin-2-yl)phenoxy)butane (36)**. Brown powder (72%); mp 210-214 °C; IR (KBr) ν 3032, 1604, 1566, 1473, 1249 cm^{-1} ; ^1H NMR (300 MHz, DMSO-*d*₆) δ 1.97 (br. s, 4H, CH₂), 4.20 (br. s, 4H, OCH₂), 7.16-8.53 (m, 14H, ArH & pyridine-H), 9.66, 9.72 (two s, 2H, pyrazine-2-H, pyrazine-3-H isomeric ratio 1:1); ^{13}C NMR (DMSO-*d*₆) δ 25.8, 67.9, 115.6, 115.7, 125.3, 126.5, 128.1, 128.3, 129.7, 130.0, 136.3, 137.2, 138.3, 138.5, 145.0, 146.7, 150.1, 152.0, 153.8, 161.4, 161.6; MS *m/z* (%) 500 (M⁺). Anal. Calcd for C₃₀H₂₄N₆O₂: C, 71.98; H, 4.83; N, 16.79. Found: C, 72.16; H, 5.03; N, 16.91%.

Supplementary Material

Supplementary material related to this article, including Nuclear Magnetic Resonance (^1H and ^{13}C NMR) figures for compounds **4**; **6**; **13**; **14**; **21**; **22**; **23**; **28**; **29**; **31** and **33** are available in the online version of the text.

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