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Synthesis of novel hybrid heterocycles tethered 2,3-diphenoxyquinoxaline moiety *via* Michael addition reaction

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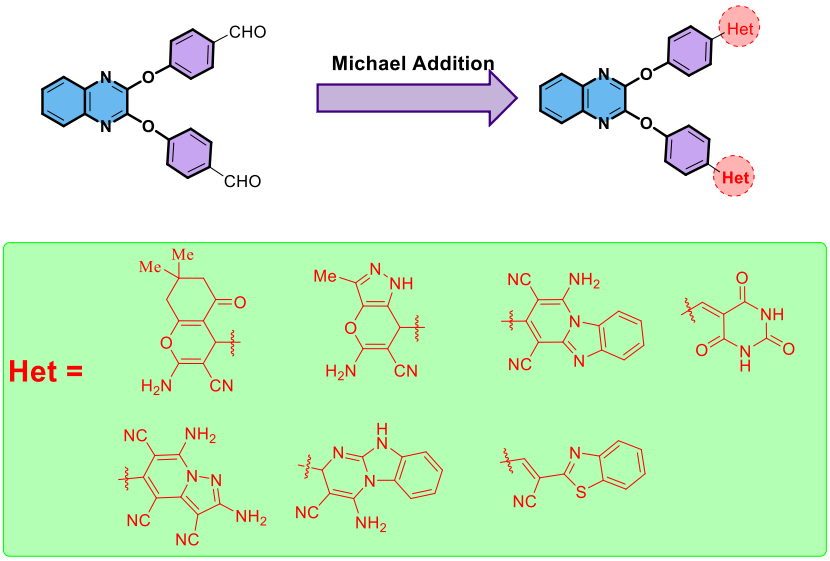
Abstract

This article demonstrates the development of novel hybrid molecules by linking bis-heterocycles to a 2,3-diphenoxyquinoxaline core. This is accomplished by using Michael addition reactions to combine 4,4'-(quinoxaline-2,3-diylbis(oxy))dibenzaldehyde with the required precursors. The structures of the newly synthesized compounds are elucidated using elemental analysis, ^{1}H NMR, ^{13}C NMR, IR, and MS spectra.



Keywords: 4,4'-(Quinoxaline-2,3-diylbis(oxy)dibenzaldehyde; malononitrile; active methylene reagent; Michael addition reaction; bis-heterocycles

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Introduction

Multicomponent reactions (MCRs) are a fast and efficient way to synthesize complex molecules. By lowering reaction steps and byproducts, atom- and step-economy are accomplished[1–5].

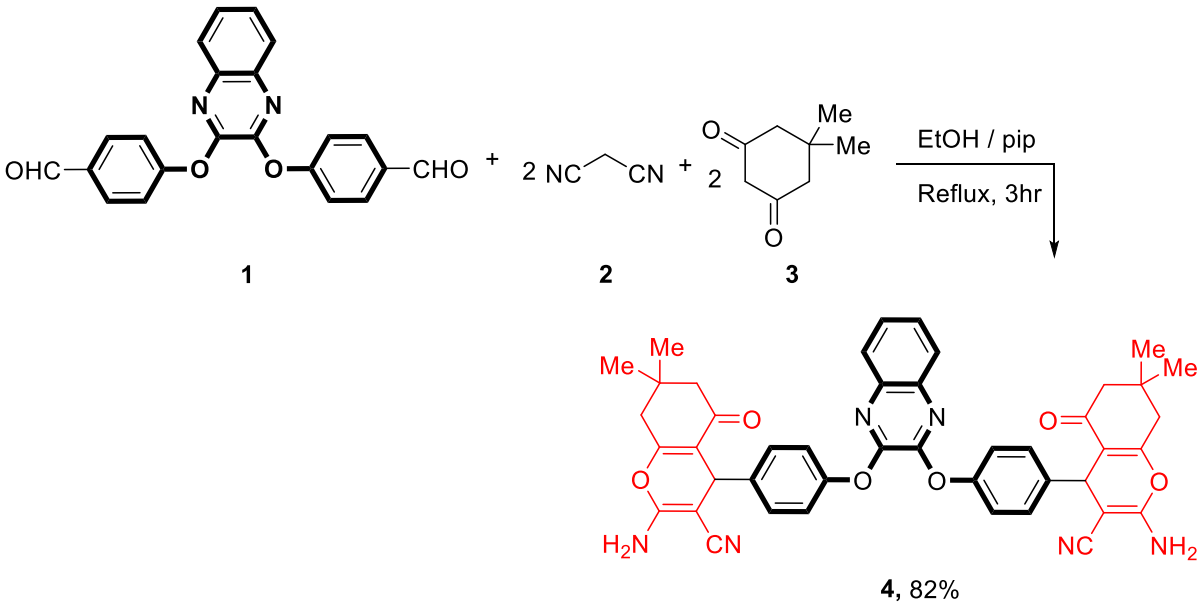
The Michael addition reaction[6,7] is a popular multicomponent technique for generating heterocycles by forming carbon-carbon bonds. Numerous reports of reactions employing the Michael reaction for synthesizing bioactive heterocycles.[8–11] Heterocyclic compounds are essential in medicinal chemistry, and numerous existing medications feature heterocyclic rings. Among various heterocycles, quinoxaline holds a significant position in the development and manufacturing of drugs. Quinoxaline is a considerable framework that contributes to the synthesis of compounds exhibiting various biological activities[12–15]. It has been reported that molecules containing a quinoxaline moiety exhibit several bioactivities, including antifungal[16–18] and anticancer[19–21] properties.

Fused pyran derivatives demonstrate various biological activities owing to their distinctive structural architecture, which improves their interaction with biological targets. Several important biological functions linked to fused pyran compounds are reported[22,23] . Different fused pyridine derivatives also exhibit various biological activities, including antimicrobial, antiviral, antioxidant, anti-diabetic, anticancer, anti-malarial, analgesic, and anti-inflammatory properties. Their distinct heterocyclic configuration boosts bioavailability, stability, and receptor interactions, rendering them significant in drug development[24–27]. Moreover, fused pyrimidine has attracted considerable research attention due to its various biological effects and possible pharmaceutical uses[28–30].

Moreover, molecular hybridization has drawn significant interest in medication development throughout the past few decades. The hybrid idea is an innovative and efficient synthetic approach for incorporating two or more distinct entities into a singular integrated unit with unique biological attributes. The resulting scaffolds can improve activity and binding affinity and overcome drug resistance[31–34]. A hybrid molecule with two interconnected heterocyclic skeletons is called a bis-heterocycle. Scientific organizations have recently begun to consider these compounds due to their more extensive range of applications compared to individual molecules[35–37]. This study broadens our current focus on creating hybrid heterocycles incorporating 2,3-diphenoxyquinoxaline moieties through carbon-carbon bond formation processes[38–49].

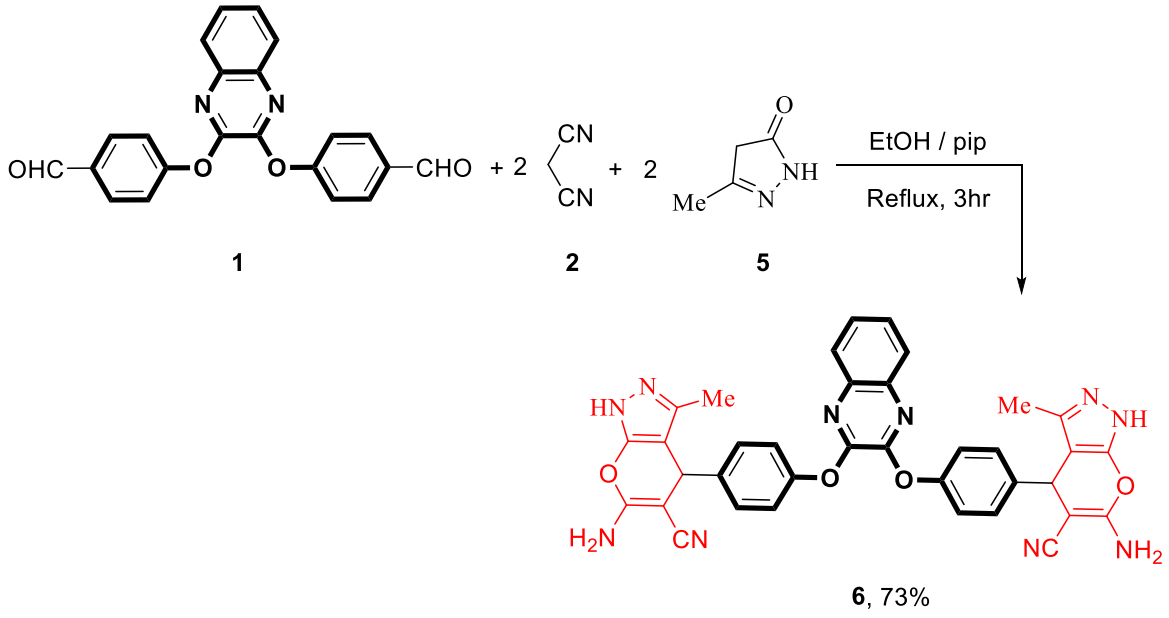
Results and Discussion

Inspired by the results mentioned above, we have investigated the Michael addition reaction of 4,4'-[quinoxaline-2,3-diylbis(oxy)]dibenzaldehyde **1** with active methylene-containing reagents. Therefore, the 4,4'-[(quinoxaline-2,3-diylbis(oxy)]bis(4,1-phenylene))bis(2-amino-tetrahydro-4*H*-chromene-3-carbonitrile) **4** was produced by the interaction of **1** with two mole equivalents of malononitrile **3** and dimedone **2** in EtOH when piperidine is present as a basic catalyst (Scheme 1). The structure of the formed product was confirmed based on ^{1}H-NMR which indicated the presence of chromene-H4 at 4.28 ppm in addition to the amino group at 7.04 ppm. Besides, it featured methyl, CH_2, and aromatic hydrogens at expected positions.



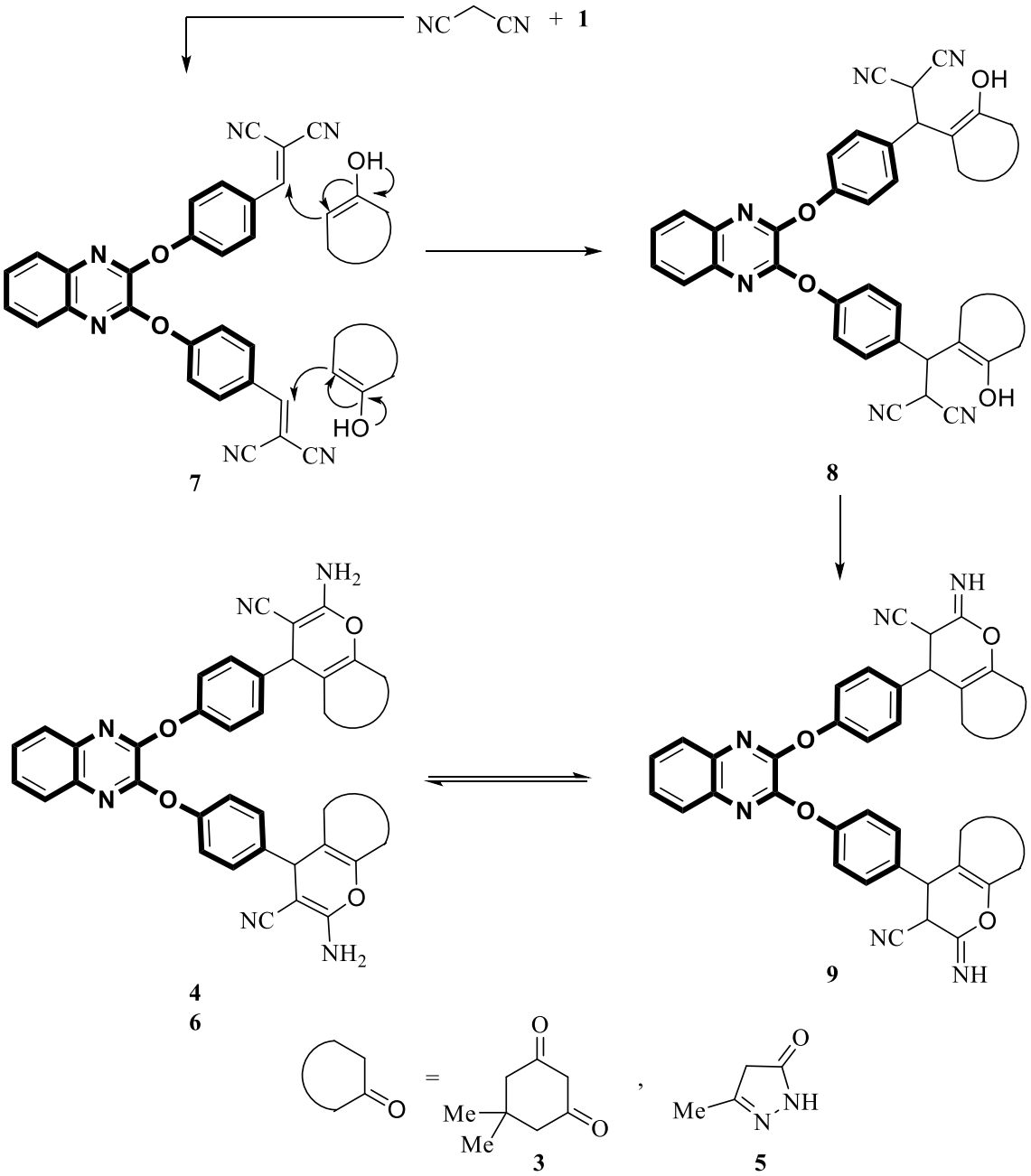
Scheme 1. Synthesis of 4,4'-[(quinoxaline-2,3-diylbis(oxy)]bis(4,1-phenylene)bis(2-amino-tetrahydro-4*H*-chromene-3-carbonitrile) **4.**

Encouraged by the above result, our study was extended by the replacement of dimedone with pyrazolone to include the synthesis of 4,4'-[(quinoxaline-2,3-diylbis(oxy)]bis(4,1-phenylene)bis(1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile) derivative. Thus, the cyclocondensation of bis(aldehyde) **1** with both, malononitrile **2** and 5-methyl-2,4-dihydro-3*H*-pyrazol-3-one **5** afforded bis(6-amino-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile) **6** in good yield (Scheme 2).



Scheme 2. Synthesis of 4,4'-[(quinoxaline-2,3-diylbis(oxy)]bis(4,1-phenylene)bis(6-amino-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile) **6.**

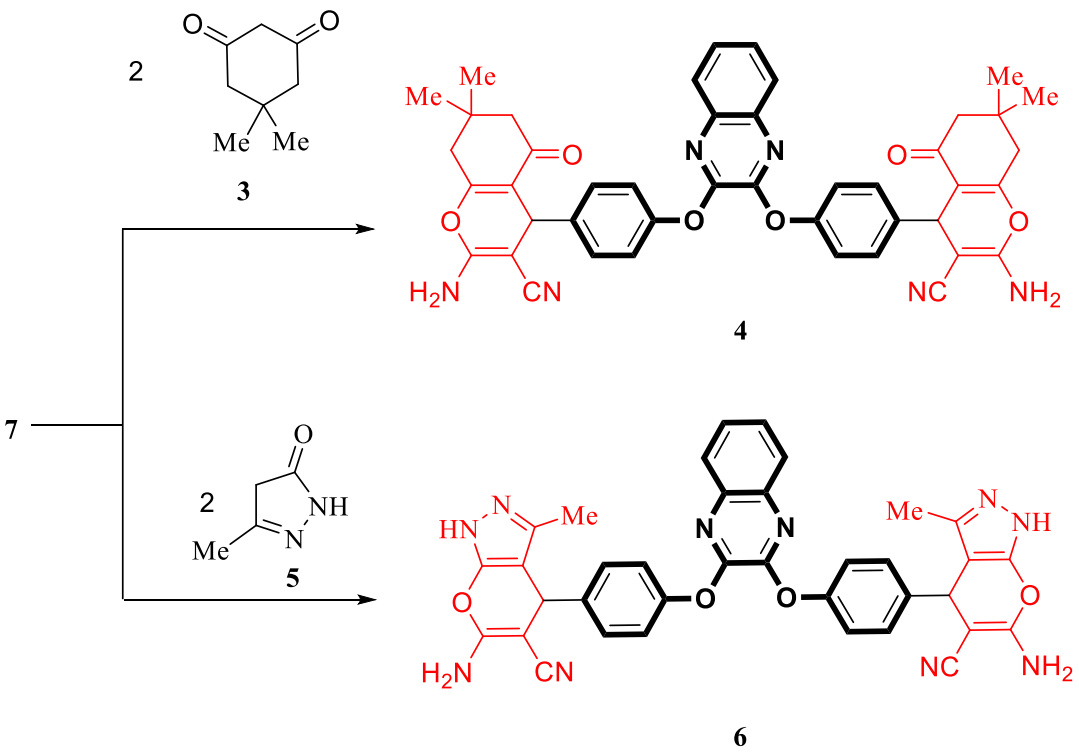
As shown in Scheme 3, we provide an acceptable route for this reaction based on the classical Michael reaction. Generally, the reaction pathway comprises the Knoevenagel condensation of bis(aldehyde) **1** to malononitrile **2** to yield 2,2'-{[(quinoxaline-2,3-diylbis(oxy)]bis(4,1-phenylene)}bis(methaneylylidene)dimalononitrile **7**. The bis(arylidene) then interacts with two-mole equivalents of active methylene compounds (dimedone **3** or pyrazolone **5**) to generate the intermediate adduct **8**. Cyclization of **8** afforded intermediates **9** that tautomerize to the final isolable products **4** and **6**, correspondingly (Scheme 3).



Scheme 3. A plausible mechanism for the formation of compounds **4** and **6.**

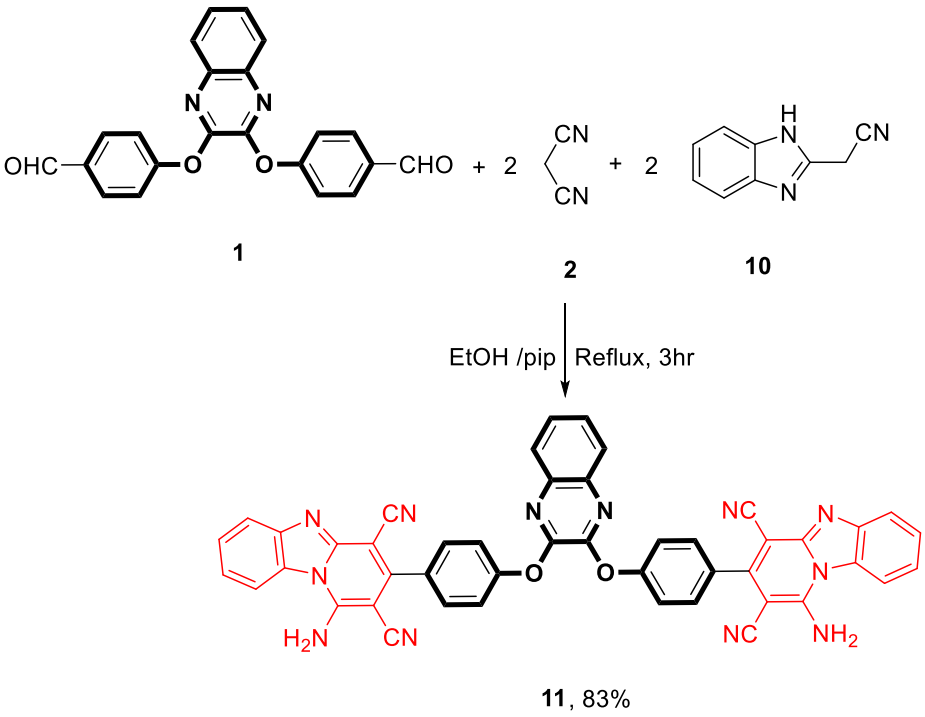
The evidence for this reaction pathway comes from our ability to separate the Knoevenagel condensation product. Consequently, the 2,2'-{[(quinoxaline-2,3-diylbis(oxy)]bis(4,1-

phenylene)}bis(methaneylylidene)dimalononitrile **7** was generated by the combination of one mole of 4,4'-[quinoxaline-2,3-diylbis(oxy)]dibenzaldehyde **1** with two moles of malononitrile **2** in EtOH /piperidine as a basic catalyst. Subsequently, the reaction of **7** with two moles of either dimedone **3** or pyrazolone **5** in EtOH and piperidine yielded the respective **4** and **6** in good yields (Scheme 4).



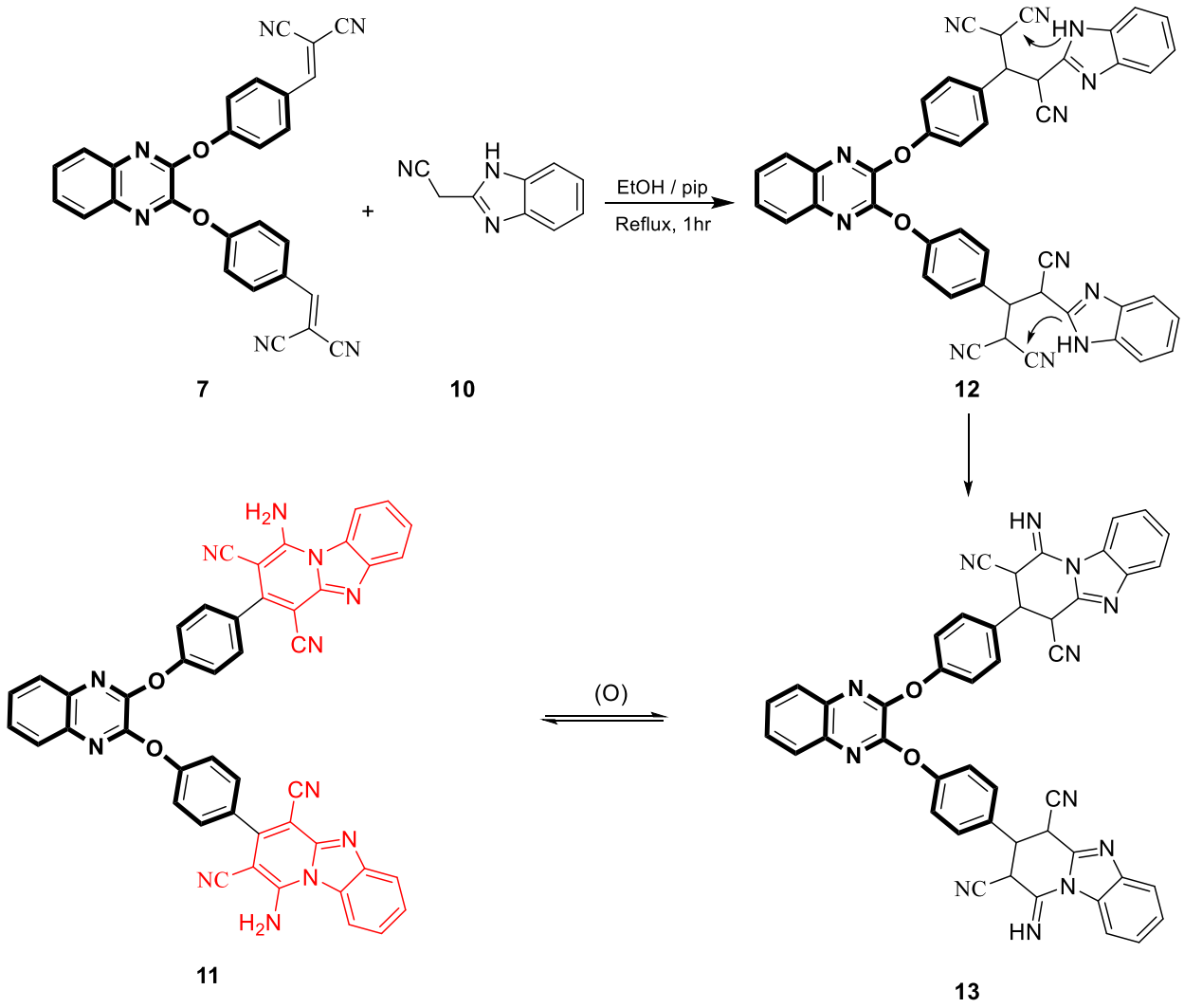
Scheme 4. Synthesis of **4** and **6** using bis(methaneylylidene)dimalononitrile **7.**

The three component reaction of bis(aldehyde) **1** with malononitrile **2** and 2-(1*H*-benzo[*d*] imidazol-2-yl)acetonitrile **10** leads to the formation of bis(1-aminobenzo[4,5]imidazo[1,2-*a*] pyridine-2,4-dicarbonitrile) **11** linked to 2,3-diphenoxyquinoxaline moiety (Scheme 5).



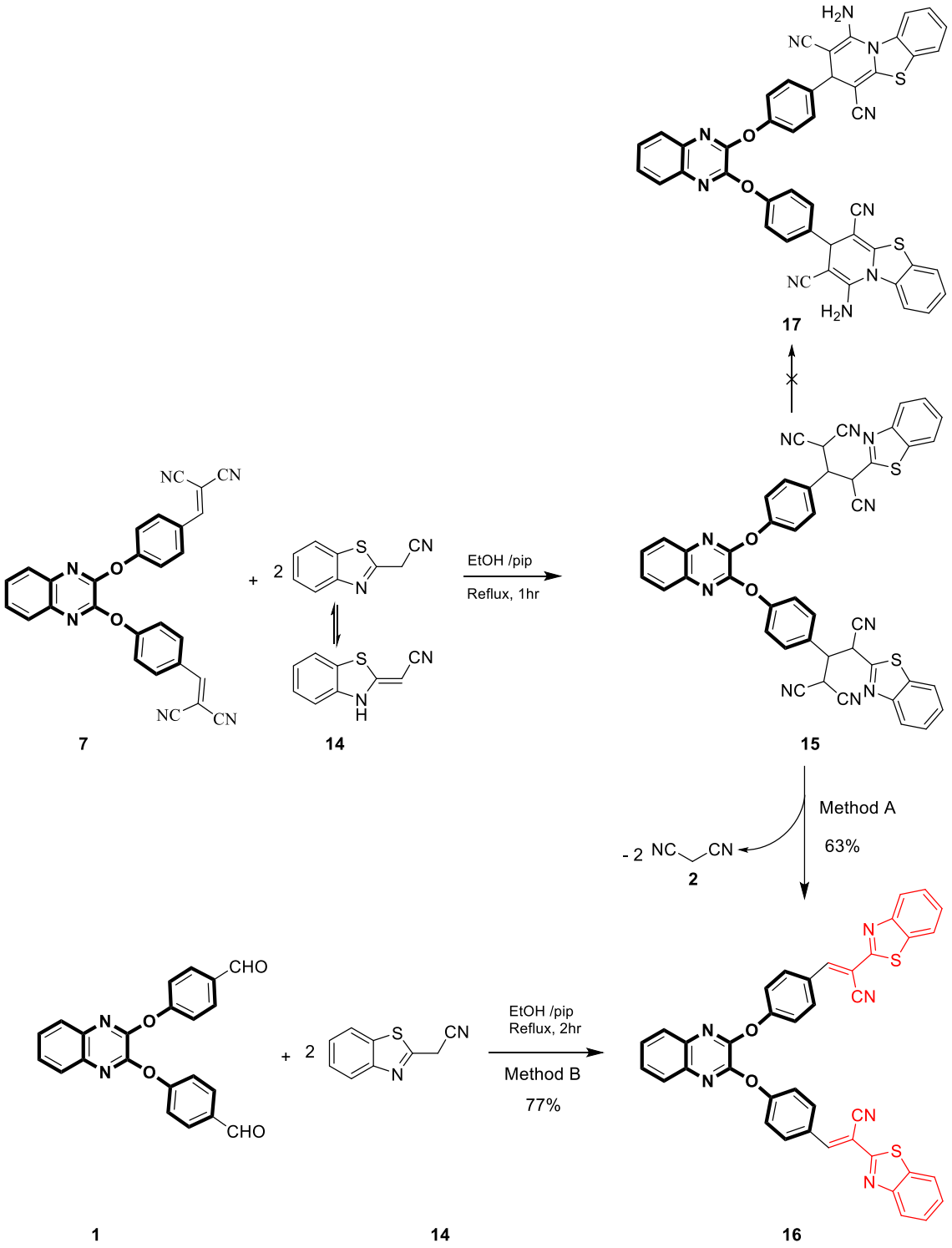
Scheme 5. Synthesis of 3,3'-[(quinoxaline-2,3-diylbis(oxy)]bis(4,1-phenylene)bis(1-aminobenzo[4,5]imidazo[1,2-a]pyridine-2,4-dicarbonitrile) **11.**

The reaction pathway involves the Michael addition reaction of the initially formed bis(arylidene) **7** with the activated methylene NC-CH_2- group, affording the Michael adduct **12** that cyclized readily into **13**. Tautomerism and oxidation of **13** resulted in the formation of **11** (Scheme 6).



Scheme 6. A plausible mechanism for the formation of compounds **11.**

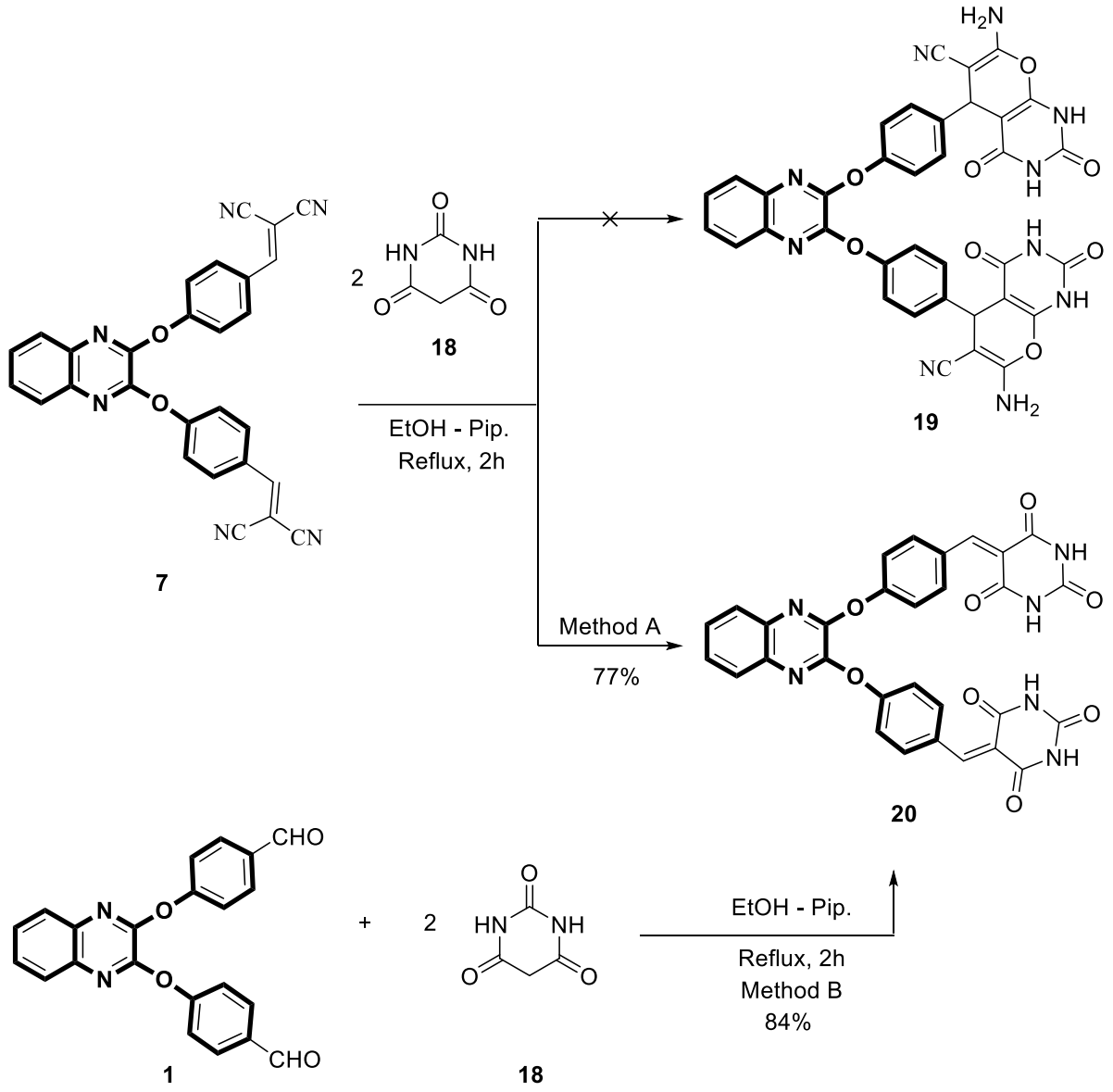
On the other hand, repeated attempts to produce 3,3'-[(quinoxaline-2,3-diylbis(oxy)]bis(4,1-phenylene)bis(1-amino-3*H*-benzo[4,5]thiazolo[3,2-*a*]pyridine-2,4-dicarbonitrile) **17** by heating one mole of bis-aldehyde **1** with two moles of malononitrile **2** and 2-(benzo[*d*]thiazol-2-yl)acetonitrile **14** under the same reaction conditions were unsuccessful. Instead, the procedure yielded bis[2-(benzo[*d*]thiazol-2-yl)acrylonitrile] **16** as a single product in excellent yield. The structure of compound **16** was validated through the comparison of their physical data to authentic samples generated from condensing one mole of bis(aldehyde) **1** with two moles of 2-(benzo[*d*]thiazol-2-yl)acetonitrile **14** in EtOH with piperidine as a basic catalyst. The production of **16** is considered to begin with the formation of the adduct **15,** which subsequently decomposes to yield **16** by the removal of malononitrile (Scheme 7). A similar sequence has been described.[50,51]



Scheme 7. Synthesis of bis(methaneylylidene)bis(1*H*-indene-1,3-dione) **16.**

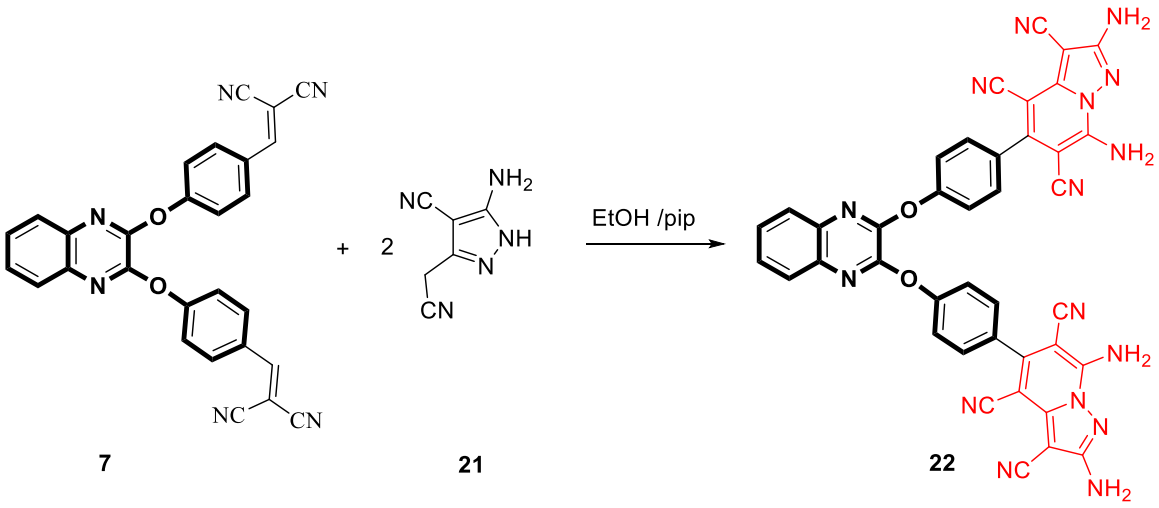
Under identical, similar conditions and following a similar reaction pathway, the reaction of bis(arylidene) **7** with two-mole equivalents of pyrimidine-2,4,6-triones **18** produces bis(methaneylylidene)bis(pyrimidine-2,4,6-triones) **20** instead of bis(tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile) **19**. Compound **20** was also synthesized via the reaction of bis(aldehyde) **1** with two mole equivalents of pyrimidine-2,4,6-triones **18** (Scheme 8). The composition of compound **20** was confirmed based

on spectral data. ^{1}H NMR spectrum of compound **20** showed the ylidene-H as a singlet signal at 8.25 ppm. In addition, the aromatic protons appeared as multiplets at their expected positions.



Scheme 8. Synthesis of bis(methaneylylidene))bis(pyrimidine-2,4,6-trione) **8.**

Moreover, the interaction of bis(aldehyde) **1** with malononitrile **2** and 5-amino-3-(cyanomethyl)-1*H*-pyrazole-4-carbonitrile **21** in refluxing ethanol containing few drops of piperidine yielded bis(2,7-diaminopyrazolo[1,5-*a*]pyridine-3,4,6-tricarbonitrile) **22** tethered 2,3-diphenoxyquinoxaline moiety (Scheme 9). The constitution of structure **22** was elucidated based on spectral data. The ^{1}H NMR spectrum of **22** indicated the four NH_2 groups as two broad signals at 6.69 and 8.58 ppm. It also indicated the aromatic protons as multiplets around 7.18 - 7.51 ppm. Based on which tautomeric form of aminopyrazole combines with the bis(arylidenemalononitrile), the reaction may also produce another two potential products: bis(pyrazolopyrimidine) **23** and bis(benzopyrazole) **24** (Figure 1). The 1H NMR spectra, which indicated the -CH_2CN group vanishing at 3-5 ppm, resulted in the exclusion of compound **23.** Furthermore, compound **24** was ignored since the mass spectrum lacked evidence that HCN had been removed.



Scheme 9. Synthesis of bis(2,7-diaminopyrazolo[1,5-a]pyridine-3,4,6-tricarbonitrile) **22.**

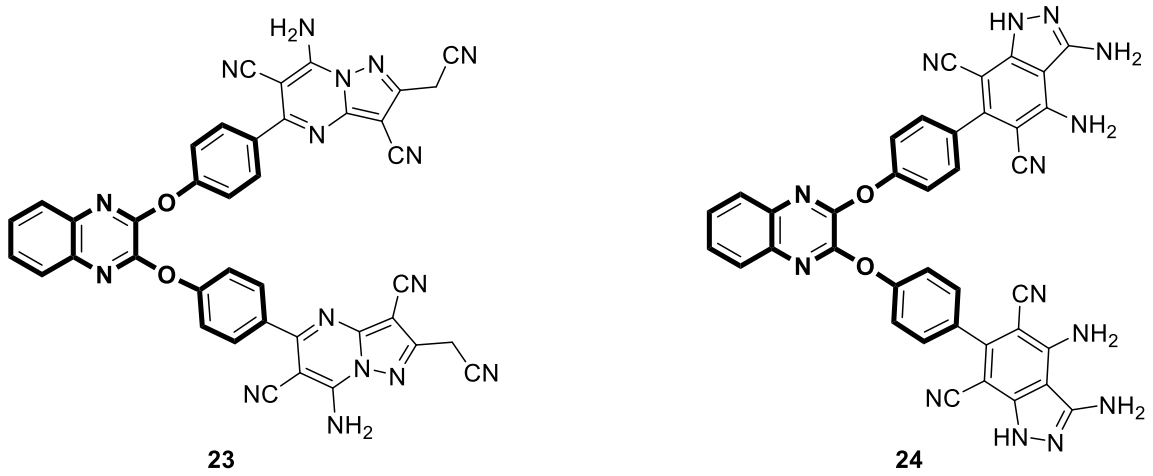
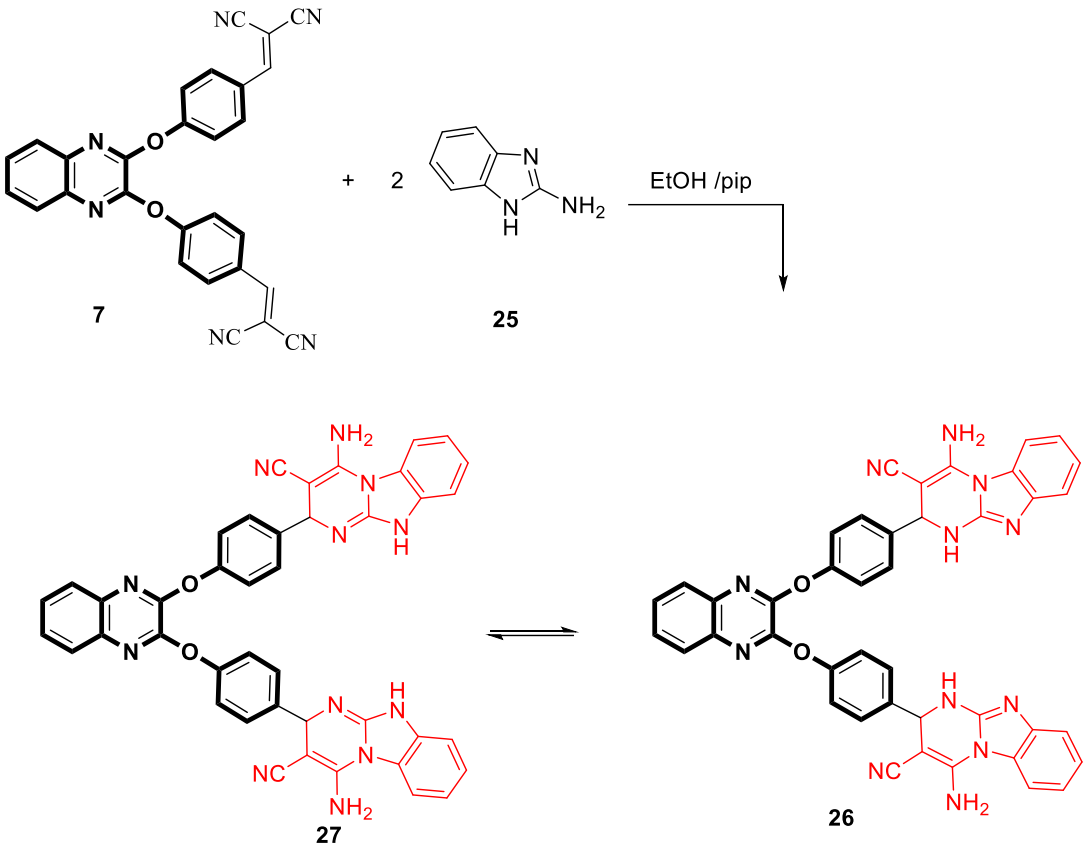


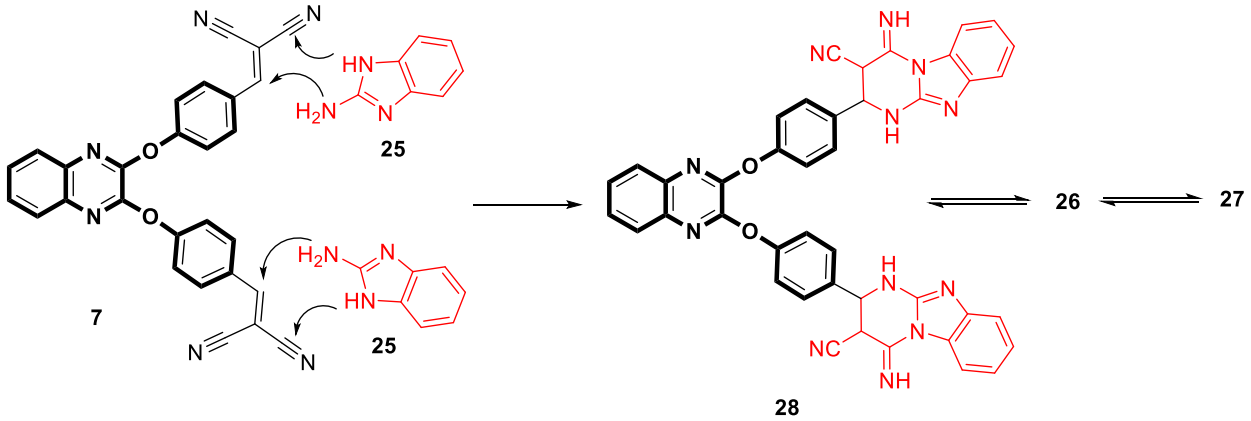
Figure 1. Structures of bis(pyrazolopyrimidine) **23** and bis(benzopyrazole) **24**.

In continuation of our investigation, and using similar reaction conditions, the direct reaction of bis(arylidene) **7** with two-mole equivalents of benzo[*d*]imidazol-2-amine **25** afforded the non-oxidized 2,2'-((quinoxaline-2,3-diylbis(oxy))bis(4,1-phenylene))bis(4-amino-1,2-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile) **27** in a good yield (Scheme 10).



Scheme 10. Synthesis of 2,2'-((quinoxaline-2,3-diylbis(oxy))bis(4,1-phenylene))bis(4-amino-1,2-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carbonitrile) **26.**

The reaction starts by combining the exo-NH_2 group of the 1*H*-benzo[*d*]imidazol-2-amine **25** with the *β*-C of the arylidene of **7,** followed by the interaction of the ring-NH group with the cyano group to create intermediate **28**. The formed intermediate tautomerizes into **27** *via* intermediacy of **26** (Scheme 11). Similar behavior has been reported[46,52,53]. The constitution of the formed product was confirmed based on the ^{1}H NMR spectrum, which showed the presence of a singlet signal for the SP^3 C2-*H* at 5.30 ppm. Besides, it indicated the two amino groups and the NH group as two broad singlets at 6.90 and 8.70 ppm, respectively. The aromatic and amino signals appeared at their expected positions at 7.0-7.69 ppm.



Scheme 11. Possible route for the synthesis of compound **27.**

Conclusions

We have established a rapid and efficient technique for synthesizing diverse bis(heterocycles) by a three-component Michael addition cyclocondensation process. The precursor 4,4'-(quinoxaline-2,3-diylbis(oxy)dibenzaldehyde was utilized for the synthesis of the target compounds

Experimental Section

General. Melting points were determined in open glass capillaries with a Gallenkamp apparatus. Infrared spectra were recorded in potassium bromide disks on a PyeUnicam SP3-300 and Shimadzu FTIR 8101 PC infrared spectrophotometer. ^{1}H and ^{13}C NMR spectra were determined on a Varian Mercury VX 300NMR spectrometer using TMS as an internal standard and DMSO-d_6 as a solvent. Mass spectra were measured on a GC MS-QP1000 EX spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt.

General procedure for the synthesis of compounds 4 and 6. A mixture of bis(aldehyde) **1** (1 mmol) and malononitrile **2** (2 mmol) in ethanol (10 mL) containing two drops of piperidine was heated at reflux for 30 min. Dimedone **3** (2 mmol), or 3*H*-pyrazol-3-one **6** (2 mmol) was then added. The mixture was heated further for 3 h. The formed precipitate was filtered, dried, and recrystallized from DMF / EtOH to give **4** or **6**, respectively.

4,4'-{[Quinoxaline-2,3-diylbis(oxy)]bis(4,1-phenylene)}bis(2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile) (4). Pale Yellow Solid (DMF/EtOH), (82%), mp: 210–212 °C; IR (KBr, υ cm^{-1}): 3445, 3350 (NH_2), 2190 (CN). ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.99 (s, 6H, -CH_3) δ 1.06 (s, 6H, -CH_3), 2.17-2.54 (m, 8H, -CH_2), 4.28 (s, 2H, CH), 7.04 (s, 4H, -NH_2), 7.23 –7.77 (m, 12H, Ar-H). MS (EI, 70 eV): *m/z* (%) 746 [M$^+$] . Anal. For $C_{44}H_{38}N_6O_6$ Calcd: C, 70.76; H, 5.13; N, 11.25 Found: C, 70.56; H, 5.03; N, 11.07%.

4,4'-{[Quinoxaline-2,3-diylbis(oxy)]bis(4,1-phenylene)}bis(6-amino-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile) (6). Brown Solid (DMF/EtOH), (73%), mp: > 300 °C; IR (KBr, υ cm^{-1}): 3395, 3203 (NH, NH_2), 2201 (CN). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.88 (s, 6H, -CH_3), 4.70 (s, 2H, CH), 6.91 (s, 4H, -NH_2), 7.29-7.74 (m, 12H, Ar-H), 12.14 (s, 2H, -NH). ^{13}C NMR (75 MHz, DMSO) δ 9.9, 35.8, 57.2, 97.8, 121.1, 121.6, 126.6, 127.9, 128.9, 135.9, 137.0, 138.7, 141.7, 149.2, 151.3, 154.9, 161.2. MS (EI, 70 eV): *m/z* (%) 662 [M$^+$] . Anal. For $C_{38}H_{26}N_{10}O_4$ Calcd: C, 65.25; H, 3.95; N, 21.14. Found: C, 65.13; H, 3.78; N, 21.03%.

Synthesis of 2,2'-{[(quinoxaline-2,3-diylbis(oxy))bis(4,1-phenylene)]bis(methaneylylidene)}dimalononitrile (7). A mixture of bis(aldehyde) **1** (1 mmol), malononitrile **2** (2 mmol), and two drops of piperidine in ethanol (10 mL) was refluxed for 1 hour. The formed precipitate was filtered and recrystallized from DMF/EtOH to give **7** as a pale yellow solid (DMF/EtOH), (88%), mp: 248-250 °C; IR (KBr, υ cm^{-1}): 2205 (CN). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.61 – 7.75 (m, 8H, Ar-H), 8.12 (d, *J* = 8.7 Hz, 4H, Ar-H), 8.58 (s, 2H, CH). ^{13}C NMR (75 MHz, DMSO) δ 81.0, 113.4, 114.4, 122.6, 126.7, 128.6, 132.7, 137.1, 148.4, 157.0, 160.4. MS (EI, 70 eV): *m/z* (%) = 466 [M$^+$], Anal. For $C_{28}H_{14}N_6O_2$ Calcd: C, 72.10; H, 3.03; N, 18.02. Found: C, 72.23; H, 3.22; N, 18.24%.

General procedure for the synthesis of compounds 11 and 16. A mixture of bis(aldehyde) **1** (1 mmol), and malononitrile **2** (2 mmol) in ethanol (10 mL) containing two drops of piperidine was heated at reflux for 30 min. 2-(1*H*-benzo[*d*]imidazol-2-yl)acetonitrile **10** (2 mmol), or 2-(benzo[*d*]thiazol-2-yl)acetonitrile **14** (2 mmol), was then added. The mixture was heated further for 3 h. The formed precipitate was filtered, dried, and recrystallized from DMF / EtOH to give **11** or **16**, respectively.

Synthesis of 3,3'-{[quinoxaline-2,3-diylbis(oxy)]bis(4,1-phenylene)}bis(1-aminobenzo[4,5]imidazo[1,2-a]pyridine-2,4-dicarbonitrile) (11). Yellow Solid (DMF/EtOH), (83%), mp: > 300 °C; IR (KBr, υ cm^{-1}): (NH_2), 2205 (CN). ^{1}H NMR (501 MHz, DMSO-d_6) δ 7.44- 7.71 (m, 20H, Ar-H), 7.87 (br.s, 4H, -NH_2). MS (EI, 70 eV): *m/z* (%) = 776 [M^+], Anal. For $C_{46}H_{24}N_{12}O_2$ Calcd: C, 71.13; H, 3.11; N, 21.64. Found: C, 71.02; H, 3.23; N, 21.55%.

Synthesis of 3,3'-{[quinoxaline-2,3-diylbis(oxy)]bis(4,1-phenylene)}bis(2-(benzo[d]thiazol-2-yl)acrylonitrile) (1). Yellow solid (DMF/EtOH), (method A: 63%, method B: 77%), mp: 272-274 °C; IR (KBr, υ cm^{-1}): 2205 (CN). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.53-7.70 (m, 12H, Ar-H), 8.09-8.27 (m, 8H, Ar-H), 8.47 (s, 2H, CH).MS (EI, 70 eV): *m/z* (%) = 682 [M^+], Anal. For $C_{40}H_{22}N_6O_2S_2$ Calcd: C, 70.37; H, 3.25; N, 12.31. Found: C, 70.24; H, 3.13; N, 12.22%.

General procedure for the synthesis of compounds (20)

Method A. A mixture of bis(arylidene-malononitrile) **7** (1 mmol) and barbituric acid **18** (2 mmol), and two drops of piperidine in ethanol (10 mL) was refluxed for 2 hours. The formed precipitate was filtered and recrystallized from DMF/EtOH.

Method B. A mixture of bis(aldehyde) **1** (1 mmol), barbituric acid **18** (2 mmol), and two drops of piperidine in ethanol (10 mL) was heated at reflux for 2 hours. The formed precipitate was filtered and recrystallized from DMF/EtOH.

5,5'-{[(Quinoxaline-2,3-diylbis(oxy))bis(4,1-phenylene)]bis(methaneylylidene)}bis(pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione) (20). Yellow solid (DMF/EtOH), mp > 300 °C. Yield (method A; 77%, method B; 84%); IR (KBr, υ cm^{-1}): 1695, 1680 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.17 (s, 2H, CH), 7.53 – 7.75 (m, 10H, Ar-H), 8.34 (m, 2H, Ar-H), 10.14 (s, 2H, -NH), 11.40 (s, 2H, -NH). MS (EI, 70 eV): *m/z* (%) = 590 [M^+], Anal. Calcd. for $C_{30}H_{18}N_6O_8$: Calcd: C, 61.02; H, 3.07; N, 14.23. Found: C, 60.89; H, 3.22; N, 14.08%.

Synthesis of 5,5'-{[Quinoxaline-2,3-diylbis(oxy)]bis(4,1-phenylene)}bis(2,7-diamino pyrazolo[1,5-*a*]pyridine-3,4,6-tricarbonitrile) (22). A mixture of bis(aldehyde) **1** with malononitrile **2** and 5-amino-3-(cyanomethyl)-1*H*-pyrazole-4-carbonitrile **21** was heated in refluxing ethanol containing a few drops of piperidine. The crude product was collected and recrystallized from DMF/EtOH. Dark Brown solid (DMF/EtOH) (88%), mp > 300 °C., IR (KBr, υ cm^{-1}): 1695, 1680 (CO). ^{1}H NMR (501 MHz, DMSO-d_6) δ 6.74 (br.s, 4H, -NH_2), 7,47-7,77 (m, 12H, Ar-H and -NH_2), 8.70 (br, 4H, Ar-H). ^{13}C NMR (126 MHz, DMSO) δ 71.7, 79.3, 84.3, 113.1, 114.7, 115.6, 122.0, , 122.9, 127.1, 128.7, 131.2, 137.6, 142.6, 148.0, 149.2, 151.2, 154.6, 161.2. MS (EI, 70 eV): *m/z* (%) = 756 [M^+], Anal. Calcd. for $C_{40}H_{20}N_{16}O_2$: Calcd: C, 63.49; H, 2.66; N, 29.62. Found: C, 63.31; H, 2.78; N, 29.49%.

2,2'-{[Quinoxaline-2,3-diylbis(oxy)]bis(4,1-phenylene)}bis(4-amino-2,10-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile) (27). A mixture of bis(arylidene-malononitrile) **7** (1 mmol) and 1*H*-benzo[*d*]imidazol-2-amine **25** (2 mmol), and two drops of piperidine in ethanol (10 mL) was heated at reflux for 2 hours. The formed precipitate was filtered and recrystallized from DMF/EtOH. Pale Brown solid, (DMF/EtOH) (76%), mp > 300 °C; IR (KBr, υ cm^{-1}): 1695, 1680 (CO). ^{1}H NMR (501 MHz, DMSO-d_6) δ 5.30 (s, 2H, CH), 6.90 (s, 4H, -NH_2), 7.00-7.03 (m, 2H, Ar-H), 7.09 – 7.18 (m, 2H, Ar-H), 7.26 (s, 2H, Ar-H), 7.37 – 7.46 (m, 8H, Ar-H), 7.55 – 7.58 (m, 2H, Ar-H), 7.65 – 7.69 (m, 4H, Ar-H), 8.70 (s, 2H, -NH). ^{13}C NMR (126 MHz, DMSO-H_6) δ 53.3, 62.2, 113.0, 116.6, 119.7, 120.4, 122.4, 122.8, 123.9, 127.0, 127.9, 129.8, 137.3, 140.8, 144.1, 149.5, 149.7, 152.1, 152.6. MS (EI, 70 eV): *m/z* (%) = 732 [M^+], Anal. Calcd. for $C_{42}H_{28}N_{12}O_2$: Calcd: C, 68.84; H, 3.85; N, 22.94. Found: C, 68.67; H, 3.74; N, 22.83%.

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Supplementary Material

Spectral data including copies of ^{1}H and ^{13}C NMR spectra of new compounds are given in the supplementary material associated with this manuscript.

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