Dihydro-3*H*-chromeno[3,4-*b*][4,7]phenanthrolin-3-one and Chromeno-[4,3-*b*]pyrano[3,2-*f*]quinolin-3(13*H*)-one Derivatives by Aza-Diels–Alder Reaction

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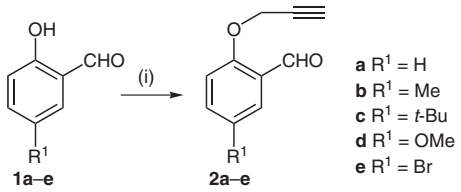
Abstract: Dihydro-3*H*-chromeno[3,4-*b*][4,7]phenanthrolin-3-one and chromeno[4,3-*b*]pyrano[3,2-*f*]quinolin-3(13*H*)-one derivatives have been synthesized by aza-Diels–Alder reaction of O-propargylated salicylaldehyde with 6-aminoquinolone and 6-aminocoumarin respectively. The reaction occurs in a single-step operation and provides potentially bioactive polycyclic heterocycles in high yields.

Key words: aza-Diels–Alder reaction, dihydro-3*H*-chromeno[3,4-*b*][4,7]phenanthrolin-3-one, chromeno[4,3-*b*]pyrano[3,2-*f*]quinolin-3(13*H*)-one, Lewis acid catalysis, annulated quinoline

Quinoline and its annulated-derivatives are important due to their interesting diverse applications.[1] Compounds containing quinoline moiety have wide application in medicinal chemistry.[2] They possess a broad spectrum of biological activities like antimalarial, anti-inflammatory, antiasthmatic, antihypertensive, antibacterial, anticancer, and tyrosine kinase inhibiting agents.[3] On the other hand, 2*H*-chromene nucleus is found in many naturally occurring biologically active compounds. They have been shown to possess antihypertensive and anti-ischemic activities and exhibit anti-HIV activity.[4] Chromenoquinoline derivatives have been used as drugs that modulate the transcriptional activity of human progesterone receptor, which play an important role in medicine, and have been used therapeutically.[5] Some chromenoquinolines have shown antagonists activity and androgen receptor antagonist activity.[6] Alkaloids containing the pyranoquinoline core constitute a significant group of the quinoline alkaloids and these compounds have been shown to exhibit a range of biological activities.[7] Some examples of natural products containing the pyranoquinoline core structure include helietidine, dutadrupine, and geibalansine.[8] Therefore, chromene-annulated pyranoquinoline and 4-alkyl-4,7-phenanthrolin-3(4*H*)-one derivatives are expected to possess bioactivity. With this end in view we became interested to synthesize chromene-annulated pyranoquinoline and phenanthrolinone derivatives.

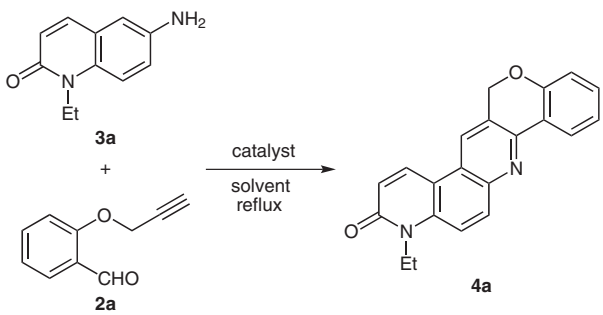
There are reports on the synthesis of chromenoquinolines[9] and pyranoquinolines.[10] However, most of them are of limited synthetic scope due to low yields, long reaction time, multiple steps, and harsh reaction conditions. Furthermore, there is no report on the synthesis of chromene-annulated pyranoquinoline and 4-alkyl-4,7-phenanthrolin-3(4*H*)-one derivatives. In continuation of our work on the synthesis of quinoline-annulated heterocyclic compounds,[10,11] we became interested to undertake a study on the synthesis of chromene-annulated pyranoquinoline and 4-alkyl-4,7-phenanthrolin-3(4*H*)-one derivatives. Herein, we report our results.

The required precursors **2a**–**e** were prepared in high yields by the reaction of various substituted salicylaldehydes **1a**–**e** with propargyl bromide in the presence of anhydrous potassium carbonate in anhydrous DMF at room temperature[12] (Scheme 1).



Scheme 1 *Reagents and conditions*: (i) propargyl bromide, anhyd K_2CO_3, anhyd DMF, r.t.

To examine the aza-Diels–Alder reaction of 6-aminoquinolones **3a**,**b** and 6-aminocoumarin (**3c**) with various *O*-propargylsalicylaldehydes **2**, the parent *O*-propargylsalicylaldehyde (**2a**) was first used as a precursor of the heterodiene. We chose 6-amino-1-ethylquinolin-2(1*H*)-one (**3a**) and *O*-propargylsalicylaldehyde (**2a**) as model substrates to optimize the reaction conditions (Scheme 2). The results are summarized in Table 1.



Scheme 2 Aza-Diels–Alder reaction

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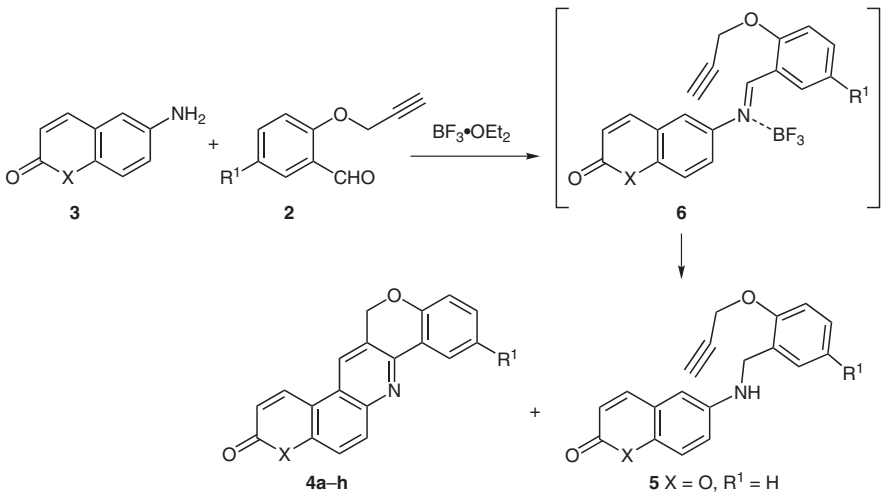
Table 1 Effect of Catalyst and Solvent on the Aza-Diels–Alder Reaction of **3a** with **2a**

Entry	Catalyst (mol%)	Solvent	Time (h)	Yield (%)
1	$BF_3{\cdot}OEt_2$ (10)	toluene	4	78
2	$Yb(OTf)_3$ (10)	toluene	4	73
3	CuBr (10)	toluene	8	53
4	CuI (10)	toluene	6	60
5	CF_3CO_2H	toluene	5	50
6	$BF_3{\cdot}OEt_2$ (10)	MeCN	4	60
7	$BF_3{\cdot}OEt_2$ (10)	THF	4	62
8	$BF_3{\cdot}OEt_2$ (10)	DMF	4	65
9	$BF_3{\cdot}OEt_2$ (10)	DMSO	4	57
10	$BF_3{\cdot}OEt_2$ (10)	EtOH	4	48
11	$BF_3{\cdot}OEt_2$ (5)	toluene	4	69
12	$BF_3{\cdot}OEt_2$ (15)	toluene	4	77

We have examined the influence of catalysts and solvents in the reaction. When the reaction of **3a** and **2a** was carried out in toluene at reflux for four hours in the presence of $BF_3{\cdot}OEt_2$ (10 mol%) the product **4a** was obtained in 78% yield (Table 1, entry 1). However, when $Yb(OTf)_3$ (10 mol%) was employed as a catalyst, the desired product **4a** was obtained in 73% yield after refluxing for four hours in toluene (entry 2). When the same reaction was carried out in the presence of copper(I) bromide (10 mol%) for eight hours, 53% yield of the product was obtained (entry 3). The yield of the product was slightly increased when the reaction was carried out in the presence of copper(I) chloride (10 mol%) for six hours in refluxing toluene, but did not exceed than that of $BF_3{\cdot}OEt_2$ (10 mol%) (entry 4). When the same reaction was carried out in the presence of CF_3CO_2H for five hours a 50% yield of the product was obtained (entry 5). Among the various solvents (toluene, MeCN, THF, DMF, DMSO, EtOH) used, toluene was found to be superior to others when $BF_3{\cdot}OEt_2$ (10 mol%) was used as the catalyst (entries 1, 6–10). We then varied the amount of catalyst loading. A yield of 69% of the product was obtained when the reaction was carried out with 5 mol% $BF_3{\cdot}OEt_2$ for four hours in refluxing toluene (entry 11). Increasing the amount of catalyst loading (15 mol%) did not improve the yield of the product (entry 12). The reaction failed in the absence of $BF_3{\cdot}OEt_2$ catalyst, perhaps imine formation is inhibited in the absence of the catalyst. Among the various conditions employed, the reaction in refluxing toluene in the presence of 10 mol% $BF_3{\cdot}OEt_2$ catalyst was found to give the best results (Table 1).

To extend the utility of this methodology, the aza-Diels–Alder reaction of other O-propargylated salicylaldehydes **2b–e** with 6-aminoquinolones **3a**,**b** and 6-aminocoumarin (**3c**) was then carried out using the optimized conditions. The results are listed in Table 2. The reaction of **3a** with one equivalent of **2b** in refluxing toluene and in the presence of $BF_3{\cdot}OEt_2$ (10 mol%) gave the product **4b** in 72% yield (Table 2, entry 2). When the same reaction was carried out with **2c** the desired products **4c** was obtained in 75% yield (entry 3). The aza-Diels–Alder reaction of 6-amino-1-methylquinolin-2(1*H*)-one (**3b**) with *O*-propargylsalicylaldehyde (**2a**) in refluxing toluene in the presence of $BF_3{\cdot}OEt_2$ (10 mol%) gave 77% yield of the product **4d** (entry 4). When the same reaction was carried out with **2d** and **2e**, 74 and 70% yield of the products **4e** and **4f** were obtained, respectively (entries 5 and 6). Under the same conditions, the reaction of 6-aminocoumarin (**3c**) with **2a** and **2e** afforded the products **4g** and **4h** in 64 and 60% yield, respectively (entries 7 and 8). All the reactions were carried out in refluxing toluene for four hours and the structures of the products were determined from their spectroscopic data.

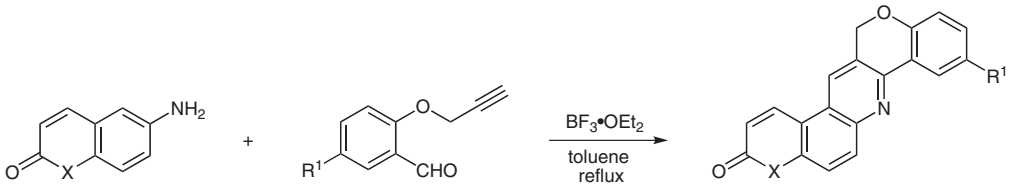
A probable mechanism of the aza-Diels–Alder reaction is depicted in Scheme 3. The intermediates **6** were not isol-



Scheme 3 Probable mechanism of aza-Diels–Alder reaction

able. Even then we can reasonably assume that initially imine formation occurs between **3** and **2** to give the hetero-diene intermediate, which then undergo Lewis acid induced intramolecular hetero-Diels–Alder reaction to give the cyclized products **4**. In some case we have isolated some uncyclized reduction product **5**.

Table 2 Aza-Diels–Alder Reaction of **3a–c** with **2a–e** in Refluxing Toluene[a]



3a X = NEt
3b X = NMe
3c X = O

2a–e

4a–h

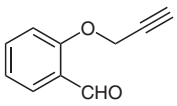
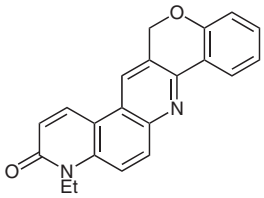
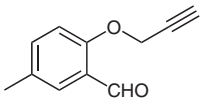
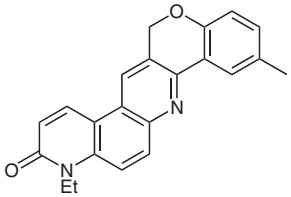
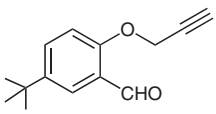
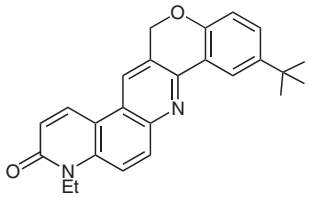
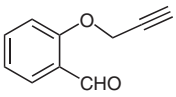
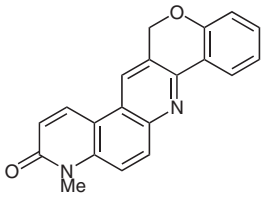
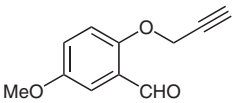
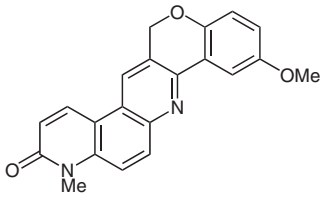
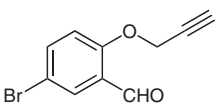
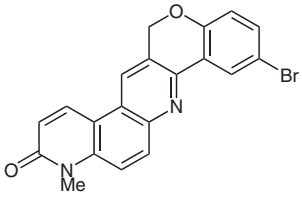
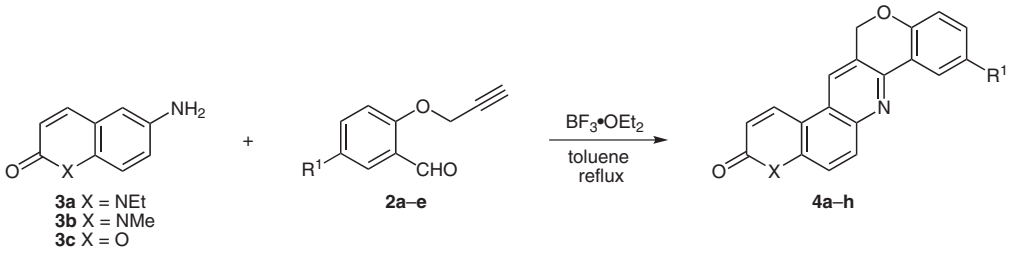
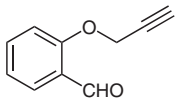
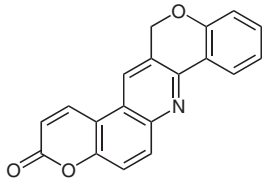
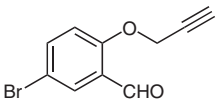
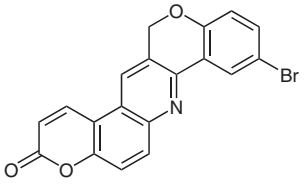
Entry	Aromatic aldehyde **2**	Substrate **3**	Product **4a–h**	Yield (%)[b]
1	**2a** 	**3a**	**4a** 	78
2	**2b** 	**3a**	**4b** 	72
3	**2c** 	**3a**	**4c** 	75
4	**2a** 	**3b**	**4d** 	77
5	**2d** 	**3b**	**4e** 	74
6	**2e** 	**3b**	**4f** 	70

Table 2 Aza-Diels–Alder Reaction of **3a–c** with **2a–e** in Refluxing Toluene[a] (continued)



Entry	Aromatic aldehyde **2**	Substrate **3**	Product **4a–h**	Yield (%)[b]
7	**2a** 	**3c**	**4g** 	64
8	**2e** 	**3c**	**4h** 	60

[a] All the reactions were carried out in refluxing toluene for 4 h.
[b] Isolated yields.

The hetero-Diels–Alder reaction represents one of the most powerful and efficient synthetic tools for the synthesis of heterocyclic compounds, including natural products.[13] There are several examples of intramolecular domino Knoevenagel–hetero-Diels–Alder reactions with alkenes and alkynes.[14] Despite the proven synthetic utility of the domino Knoevenagel– hetero-Diels–Alder reaction, the aza-analogue has been much less investigated.[15] Various heterocyclic moieties that constitute the structural skeletons of a large number of natural products and pharmacologically active compounds were synthesized by aza-Diels–Alder reaction.[16] Recently, Ramesh et al. have reported the synthesis of chromenoquinolines by copper/Lewis acid catalyzed aza-Diels–Alder reaction of unactivated alkynes.[17] In our laboratory, we have synthesized indole- and thiochromen-annulated [6,6]-fused thiopyrano chromene derivatives using domino Knoevenagel–hetero-Diels–Alder reaction of unactivated alkynes in the absence of copper(I) catalyst.[14b,c] However, our approach is solely copper(I) catalyst-free aza-Diels–Alder reaction.

In conclusion, we have developed a novel and efficient protocol for the synthesis of dihydro-3*H*-chromeno[3,4-*b*][4,7]phenanthrolin-3-one and chromeno[4,3-*b*]pyrano[3,2-*f*]quinolin-3(13*H*)-one derivatives by aza-Diels–Alder reaction of 6-aminoquinolones and 6-aminocoumarin with the unactivated alkynes. The copper(I)-catalyst-free reaction occurs in a single-step operation with the use of commercially available $BF_3{\cdot}OEt_2$ which makes the protocol simple, convenient, and practical.

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Perkin-Elmer L 120-000A spectrometer on KBr disks. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer in $CDCl_3$ with TMS as internal standard (chemical shift in δ). C,H,N-analyses were recorded on 2400 series II CHN Perkin-Elmer analyzer. MS were recorded on a Q-TOF micro™ instrument at the Indian Institute of Chemical Biology, Kolkata. Silica gel [(60–120, 230–400 mesh), Rankem, India] was used for chromatographic separation. Silica gel G [CDH (India)] was used for TLC.

Compounds 4a–h; General Procedure

A mixture of 6-aminocoumarin (**3c**; 0.621 mmol, 1 equiv) or 6-aminoquinolone **3a**,**b** (0.530 or 0.574 mmol, 1 equiv) and O-propargylated salicylaldehyde **2a–e** (0.530–0.621 mmol, 1 equiv) was stirred in toluene at r.t. for 30 min. Then, $BF_3{\cdot}OEt_2$ (10 mol%) was added and the reaction mixture was refluxed for 4 h. After completion of the reaction as monitored by TLC, the mixture was cooled, diluted with sat. aq $NaHCO_3$ (50 mL), and extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine (50 mL) and dried (Na_2SO_4). The solvent was removed by distillation. The resulting crude product was purified by column chromatography over silica gel (60–120 mesh) using hexane–EtOAc mixture as eluent to give the respective compounds **4a–h**.

4a

Yield: 78%; colorless solid; mp 224–226 °C.

IR (KBr): 1106, 1501, 1646, 2951 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.45 (t, *J* = 7.2 Hz, 3 H), 4.49 (q, *J* = 7.2 Hz, 2 H), 5.42 (s, 2 H), 6.89 (d, *J* = 10.0 Hz, 1 H), 7.03 (d, *J* = 8.0 Hz, 1 H), 7.18 (t, *J* = 7.2 Hz, 1 H), 7.39 (t, *J* = 7.6 Hz, 1 H), 7.79 (d, *J* = 9.6 Hz, 1 H), 8.26 (d, *J* = 9.6 Hz, 1 H), 8.32 (s, 1 H), 8.39 (d, *J* = 10.0 Hz, 1 H), 8.44 (d, *J* = 7.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.3, 38.0, 68.5, 114.4, 117.4, 117.9, 121.5, 122.6, 122.7, 124.3, 124.8, 125.2, 126.5, 132.0, 132.9, 137.9, 144.2, 148.1, 157.1, 161.6, 162.5.

MS: *m*/*z* = 351.31 (M^+ + Na).

Anal. Calcd for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found: C, 76.72; H, 4.99; N, 8.46.

4b

Yield: 72%; colorless solid; mp 234–236 °C.

IR (KBr): 1083, 1496, 1658, 2970 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (t, *J* = 7.2 Hz, 3 H), 2.43 (s, 3 H), 4.50 (dd, *J* = 7.2, 14.0 Hz, 2 H), 5.40 (s, 2 H), 6.90 (d, *J* = 10.0 Hz, 1 H), 6.94 (d, *J* = 8.0 Hz, 1 H), 7.19 (dd, *J* = 2.0, 8.4 Hz, 1 H), 7.80 (d, *J* = 9.6 Hz, 1 H), 8.26 (br s, 1 H), 8.29 (d, *J* = 9.6 Hz, 1 H), 8.35 (s, 1 H), 8.42 (d, *J* = 9.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.3, 20.8, 38.0, 68.5, 114.4, 117.1, 117.8, 121.5, 122.3, 124.3, 124.8, 125.1, 126.7, 132.0, 132.8, 132.9, 132.9, 137.8, 144.1, 148.3, 155.1, 161.6.

Anal. Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.01; H, 5.37; N, 8.15.

4c

Yield: 75%; colorless solid; mp >250 °C.

IR (KBr): 1106, 1501, 1647, 2951 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (s, 9 H), 1.46 (t, *J* = 7.2 Hz, 3 H), 4.52 (d, *J* = 6.8 Hz, 2 H), 5.40 (s, 2 H), 6.90 (d, *J* = 9.6 Hz, 1 H), 6.98 (d, *J* = 8.8 Hz, 1 H), 7.44 (d, *J* = 8.4 Hz, 1 H), 7.80 (d, *J* = 9.6 Hz, 1 H), 8.32 (d, *J* = 8.4 Hz, 2 H), 8.41 (d, *J* = 10.0 Hz, 1 H), 8.48 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.3, 31.5, 34.6, 38.0, 68.5, 114.5, 116.9, 117.8, 121.5, 121.6, 121.9, 124.3, 124.8, 126.8, 129.4, 133.0, 133.1, 137.9, 144.2, 145.5, 148.6, 155.0, 161.6.

Anal. Calcd for $C_{25}H_{24}N_2O_2$: C, 78.10; H, 6.29; N, 7.29. Found: C, 78.25; H, 6.23; N, 7.30.

4d

Yield: 77%; colorless solid; mp >250 °C.

IR (KBr): 1118, 1498, 1654, 2847 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.88 (s, 3 H), 5.40 (s, 2 H), 6.91 (d, *J* = 10.0 Hz, 1 H), 7.03 (d, *J* = 8.0 Hz, 1 H), 7.18 (t, *J* = 7.2 Hz, 1 H), 7.39 (t, *J* = 7.6 Hz, 1 H), 7.79 (d, *J* = 9.6 Hz, 1 H), 8.27 (d, *J* = 9.6 Hz, 1 H), 8.33 (s, 1 H), 8.39 (d, *J* = 9.6 Hz, 1 H), 8.44 (d, *J* = 7.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.7, 68.5, 114.4, 117.3, 117.9, 121.6, 122.6, 122.7, 124.3, 124.8, 125.2, 126.5, 132.0, 132.9, 132.9, 137.9, 144.2, 148.1, 157.1, 161.6.

Anal. Calcd for $C_{20}H_{14}N_2O_2$: C, 76.42; H, 4.49; N, 8.91. Found: C, 76.65; H, 4.45; N, 8.85.

4e

Yield: 74%; colorless solid; mp >250 °C.

IR (KBr): 1047, 1498, 1645, 2834 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.88 (s, 3 H), 3.94 (s, 3 H), 5.37 (s, 2 H), 6.90 (d, *J* = 9.6 Hz, 1 H), 6.97 (s, 2 H), 7.78 (d, *J* = 9.2 Hz, 1 H), 7.94 (s, 1 H), 8.28 (d, *J* = 9.2 Hz, 1 H), 8.32 (s, 1 H), 8.39 (d, *J* = 9.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.2, 55.9, 68.6, 107.8, 114.2, 118.0, 118.4, 119.5, 121.6, 123.1, 124.2, 124.9, 127.0, 133.0, 133.0, 138.8, 144.2, 148,3, 151.4, 155.2, 162.1.

Anal. Calcd for $C_{21}H_{16}N_2O_3$: C, 73.24; H, 4.68; N, 8.13. Found: C, 73.35; H, 4.71; N, 8.10.

4f

Yield: 70%; colorless solid; mp >250 °C.

IR(KBr): 1076, 1496, 1655, 2851 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.90 (s, 3 H), 5.44 (s, 2 H), 6.91 (d, *J* = 8.4 Hz, 1 H), 6.92 (d, *J* = 9.6 Hz, 1 H), 7.45 (dd, *J* = 2.4, 8.8 Hz, 1 H), 7.82 (d, *J* = 9.2 Hz, 1 H), 8.28 (d, *J* = 9.6 Hz, 1 H), 8.36 (s, 1 H), 8.40 (d, *J* = 9.6 Hz, 1 H), 8.56 (d, *J* = 2.4 Hz, 1 H).

Anal. Calcd for $C_{20}H_{13}BrN_2O_2$: C, 61.09; H, 3.33; N, 7.12. Found: C, 61.29; H, 3.26; N, 7.13.

4g

Yield: 64%; colorless solid; mp >250 °C.

IR (KBr): 1113, 1504, 1717, 2923 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.43 (s, 2 H), 6.62 (d, *J* = 9.6 Hz, 1 H), 7.03 (d, *J* = 8.0 Hz, 1 H), 7.19 (t, *J* = 7.2 Hz, 1 H), 7.41 (dt, *J* = 1.6, 7.6 Hz, 1 H), 7.67 (d, *J* = 9.2 Hz, 1 H), 8.23 (s, 1 H), 8.27 (d, *J* = 9.2 Hz, 1 H), 8.37 (d, *J* = 10.0 Hz, 1 H), 8.45 (dd, *J* = 1.2, 7.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 68.4, 107.9, 112.7, 116.4, 117.4, 120.5, 122.5, 122.8, 123.4, 124.8, 125.4, 126.8, 132.3, 134.3, 138.1, 148.6, 154.5, 157.3, 162.1.

Anal. Calcd for $C_{19}H_{11}NO_3$: C, 75.74; H, 3.68; N, 4.65. Found: C, 75.53; H, 3.67; N, 4.69.

4h

Yield: 60%; colorless solid; mp >250 °C.

IR (KBr): 1114, 1497, 1720, 2921 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.44 (s, 2 H), 6.62 (d, *J* = 9.6 Hz, 1 H), 6.92 (d, *J* = 8.4 Hz, 1 H), 7.47 (dd, *J* = 2.0, 8.4 Hz, 1 H), 7.69 (d, *J* = 9.2 Hz, 1 H), 8.25 (s, 1 H), 8.27 (d, *J* = 9.2 Hz, 1 H), 8.36 (d, *J* = 10.0 Hz, 1 H), 8.57 (d, *J* = 2.8 Hz, 1 H).

Anal. Calcd for $C_{19}H_{10}BrNO_3$: C, 60.02; H, 2.65; N, 3.68. Found: C, 60.15; H, 2.71; N, 3.56.

5

Yield: 30%; yellow colored solid; mp 74–76 °C.

IR (KBr): 1138, 1702, 2131, 3277 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.53 (d, *J* = 2.4 Hz, 1 H), 4.25 (s, 1 H), 4.37 (s, 2 H), 4.77 (d, *J* = 2.0 Hz, 2 H), 6.34 (d, *J* = 9.2 Hz, 1 H), 6.61 (d, *J* = 2.8 Hz, 1 H), 6.84 (dd, *J* = 2.8, 8.8 Hz, 1 H), 6.97 (t, *J* = 7.6 Hz, 1 H), 7.01 (d, *J* = 8.4 Hz, 1 H), 7.13 (d, *J* = 8.8 Hz, 1 H), 7.29 (t, *J* = 8.4 Hz, 2 H), 7.56 (d, *J* = 9.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 43.7, 56.0, 75.7, 78.5, 108.6, 112.0, 116.6, 117.4, 118.5, 119.3, 121.6, 127.3, 128.5, 128.9, 143.5, 145.0, 146.7, 155.3, 161.4.

MS: *m*/*z* = 306.0 $(M + H)^+$.

Anal. Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.95; H, 4.83; N, 4.66.

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