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Stereoselective synthesis of hexahydro-3-methyl-1-arylchromeno[3,4-*b*]pyrrole and its annulated heterocycles as potent antimicrobial agents for human pathogens

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ABSTRACT

Synthesis of a series of novel hexahydrochromenopyrrole analogues has been accomplished through an intramolecular 1,3-dipolar cycloaddition (1,3-DC reaction) of azomethine ylides, generated by the aldehyde induced decarboxylation of secondary amino acids. These compounds were screened for antibacterial and antifungal activities against six human pathogenic bacteria and three human pathogenic fungi and found to have good antimicrobial properties against most of the microorganisms.

The synthesis of fused pyrrolidines, pyrrolizidines, indazolidines, pyranoquinolines and chromenopyrrole ring systems has received synthetic chemists attention over the years, since these heterocycles form the structural subunits of biologically important alkaloids[1] and pharmaceutically important compounds.[2] Instructively, a chromene-derived bisbenzopyran was reported[3] as a novel selective estrogen receptor modulators (SERM*a*) to alleviate hot flushes and effectively increase fluidity in rats. Pizzo et al. reported[4] the synthesis of chromene derivatives through [4+2] cycloaddition in high yields.

The [3+2] cycloaddition reaction is a powerful method for the synthesis of bicyclic saturated five-membered heterocycles, and consequently, it has been extensively studied by our research group.[5] The intramolecular version of this reaction generally occurs with high regio- and stereocontrol[6] and results in the formation of fused nitrogen containing bicyclic systems. Majority of examples reported in the literature pertain to the synthesis of chromeno[4,3-*b*]pyrrole fused skeletons and only limited reports are available for the synthesis of chromeno[3,4-*b*]pyrroles. Confalone and co-workers[7] first reported the synthesis of chromeno[4,3-*b*]pyrrole via deprotonation route. Similarly, Grigg et al.[8] also extensively studied the intramolecular azomethine ylide cycloaddition reaction for the synthesis of same type of compounds. Literature is abound with examples for the synthesis of chromeno[4,3-*b*]pyrrole fused ring system[9] through intramolecular cycloaddition reaction. Although Padwa[10] and DeShong et al.[11] reported the synthesis of furo/pyrano[3,4-*b*]pyrrole ring system through azomethine ylides derived from aziridines, there is no report for the synthesis of chromeno/furano/pyrano[3,4-*b*]pyrrole fused ring system via intramolecular [3+2] cycloaddition reaction.

Lamellarins[12] a marine natural product (Fig. 1) has a core unit of chromeno[3,4-*b*]pyrrole which is cytotoxic to a wide range of cancer cell lines[13] and selective inhibitor of HIV integrase both in vitro and in vivo.[14] With a need to develop simpler methods for the synthesis of chromeno[3,4-*b*]pyrrole annulated heterocycles, and in continuation of our interest in cycloaddition chemistry, herein we report the synthesis of hexahydro-3-methyl-1-arylchromeno[3,4-*b*]pyrrole and its analogues through intramolecular 1,3-DC reaction of *O*-alkyl aldehydes with suitably positioned dipolarophiles.

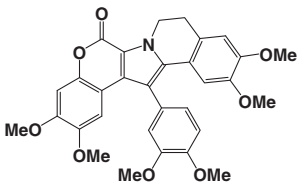

Figure 1. Lamellarin G trimethyl ether.

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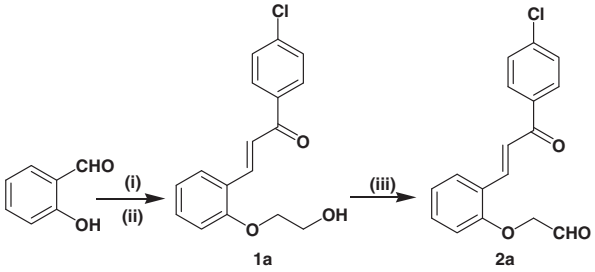
The required alkenyl aldehyde **2a** was prepared from salicylaldehyde in three steps in good yield (Scheme 1). Thus, 2-(2-hydroxyethoxy)benzaldehyde[15] on treatment with *p*-chloroacetophenone in presence of base furnished alkenyl alcohol **1a**, which on oxidation with iodoxybenzoic acid (IBX) in DMSO gave the alkenyl aldehyde **2a** in excellent yield. The structures of the alkenyl alcohol **1a** and alkenyl aldehyde **2a** were characterized by spectral analysis. The ^{1}H NMR spectrum of **2a** exhibited a doublet at δ 7.70 (J = 15.9 Hz) corresponding to one of the olefinic protons. Thus, the geometry of the olefinic double bond was found to be *E* isomer. The aldehydic proton resonated at δ 9.82 as a singlet. The carbonyl carbon of aldehyde was confirmed by the presence of a peak at 196.8 ppm in the ^{13}C NMR spectrum of **2a**.

The intramolecular 1,3-DC reaction was carried out by reacting the alkenyl aldehyde **2a** with sarcosine (**3a**) in refluxing toluene under Dean-Stark reaction condition. The azomethine ylide generated through decarboxylative condensation reaction, underwent [3+2] cycloaddition smoothly to give hexahydrochromeno[3,4-*b*]pyrrole **4** in good yield[16a] (Scheme 2).

The structure of the cycloadduct **4** was confirmed by spectral analysis. The ^{1}H NMR spectrum of **4** exhibited a singlet at δ 2.46 corresponding to *N*-methyl proton. A distorted doublet of triplet at δ 2.68 was observed for the *N*-CH (H_b) proton. The benzylic proton H_a resonated as a doublet of doublet at δ 3.92 (J = 2.1, 11.1 Hz). The coupling constant suggested a *cis* fusion at the ring junction. A multiplet in the region δ 3.83–3.91 was observed for H_c proton. The stereochemistry of the cycloadduct **4** was also deduced on the basis of 2D NOESY experiments. The strong NOESY between H_a and H_b of **4** clearly proved *cis* stereochemistry at the ring junction.

The presence of *N*-methyl and *N*-methylene group in **4** was confirmed by the two signals at 39.7 and 55.2 ppm respectively in ^{13}C NMR spectrum. The *O*-methylene carbon exhibited a peak at 65.7 ppm. The *N*-CH carbon of **4** resonated at 64.6 ppm and was confirmed by DEPT 135 spectrum. The carbonyl carbon exhibited a peak at 198.7 ppm. Moreover, the cycloadduct **4** exhibited a peak at *m/z* 328.33 (M^++1) in the mass spectrum. Finally, the regio and stereochemical outcome of the cycloaddition reaction was confirmed by a single crystal X-ray analysis[17] of the cycloadduct **4** (Fig. 2).



Scheme 1. Synthesis of alkenyl aldehyde **2a**. Reagents and conditions: (i) Chloroethanol, NaOH/H_2O, reflux, 16 h, 78%, (ii) *p*-chloroacetophenone, rt, 10% NaOH in EtOH, 6 h, 80% (**1a**), (iii) IBX, DMSO, rt, 8 h, 85% (**2a**).

The same reaction was carried with cyclic amino acids L-proline (**3b**), thiazolidine-4-carboxylic acid (**3c**) and tetrahydroisoquinoline-3-carboxylic acid (**3d**) to obtain the polycyclic *cis* fused cycloadducts **5**–**7** in good yields[16b] (Scheme 3). The structures of the products **5**–**7** were also confirmed by ^{1}H NMR, ^{13}C NMR, COSY and mass spectral analysis.

In the ^{1}H NMR of **5** the benzylic proton H_a resonated as a doublet of doublet at δ 5.17 (J = 3.0, 12 Hz) which clearly showed the stereochemistry of the ring junction. The ^{13}C NMR spectrum of **5** showed the benzoyl carbonyl peak at 198.4 ppm. Moreover, the cycloadduct **5** exhibited a peak at *m/z* 354.27 (M^++1) in the mass spectrum which confirmed the structure of the cycloadduct **5**.

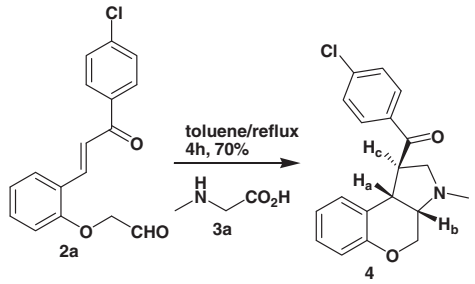
In order to extend the scope of the reaction, the alkenyl aldehyde **2b** (Scheme 4) was subjected to [3+2] cycloaddition reaction with various secondary amino acids (**3a–3d**). The reaction yielded a novel spirochromenopyrrole **8**, spiropyrrolizidine **9**, spirothiazolidine **10** and spiroindolizidine **11** (Scheme 5) in good yields.[16c,d] The structure of the cycloadducts **8–11** were also established by spectroscopic data. The ^{1}H NMR spectrum of **8** exhibited singlet at δ 2.45 corresponding to *N*-methyl group. The benzylic proton H_a resonated as a doublet at δ 4.75 (J = 10.5 Hz). The coupling constant suggested a *cis* fusion at the ring junction. The benzylic –CH– carbon resonated at 41.8 ppm and the carbonyl carbon exhibited a peak at 199.3 ppm.

Moreover, the cycloadduct **8** exhibited a peak at *m/z* 320.20 (M^++1) in the mass spectrum. Further, the regio- and stereochemical outcome of the cycloaddition reaction was confirmed by a single crystal X-ray analysis[18] of the cycloadduct **10** (Fig. 3).

In the present study, minimum inhibitory concentration of newly synthesized arylchromeno[3,4-*b*]pyrroles were evaluated against six human bacterial pathogens viz. *Staphylococcus aureus*, *Bacillus subtilis*, *Streptococcus pneumoniae*, *Escherichia coli*, *Shigella* sp., *Salmonella typhi* by well diffusion method[19] and three human fungal pathogens viz. *Trichoderma* sp., *Aspergillus* sp. and *Candida albicans*, by poison food technique.[20] The compounds at the concentration range 5–150 μg/mL in 0.25% DMSO was used in this study with tetracycline and carbendazim, respectively, for bacteria and fungi being used as control.

Effect of tested compounds on the growth of human bacterial pathogens: Antibacterial activity for the above cycloadducts **4–11** was evaluated against both positive and negative human pathogenic bacterial strains and was compared with the reference antibiotic tetracyclin as minimum inhibitory concentration (MIC).

All the eight compounds exhibited different levels of antibacterial activity. Further, the antibacterial activity of the tested compounds was found to be dose dependent and remarkable at higher concentrations. The minimum inhibitory concentration (MIC) of the compounds **4–11** against human pathogens determined by well diffusion method ranged between 10 and



Scheme 2. Synthesis of hexahydrochromeno[3,4-*b*]pyrrole **4**.

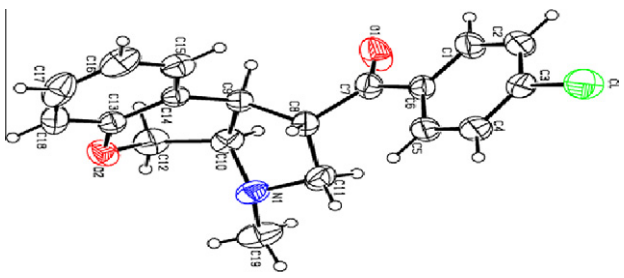
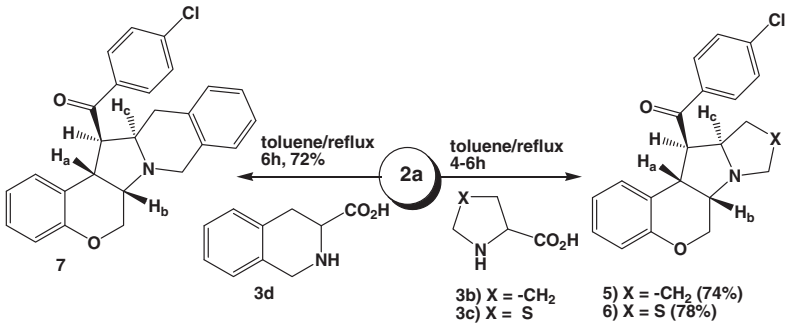
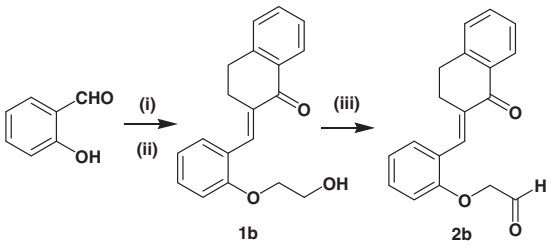


Figure 2. ORTEP diagram of **4**.



Scheme 3. Synthesis of spirochromenopyrrole annulated heterocycles **5**–**7**.



Scheme 4. Synthesis of alkenyl aldehyde **2b**. Reagents and conditions: (i) Chloroethanol, NaOH/H_2O, reflux, 16 h, 78%. (ii) α-tetralone, 0 °C to rt, 10% NaOH in EtOH, 5 h, 72% (**1b**). (iii) IBX, DMSO, rt, 10 h, 88% (**2b**).

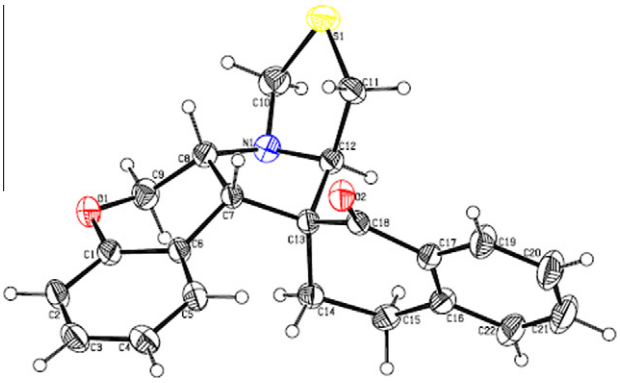
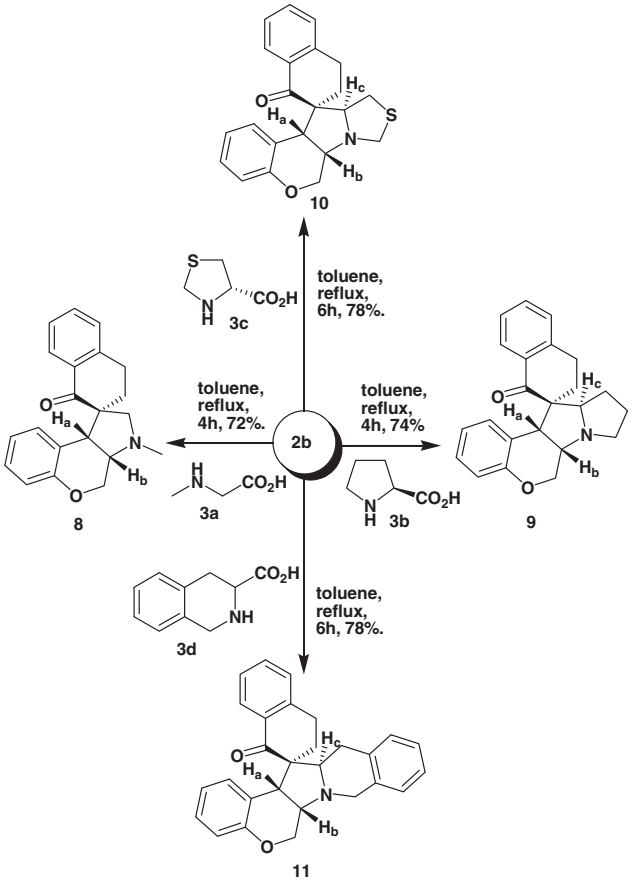


Figure 3. ORTEP diagram of **10**.



Scheme 5. Synthesis of spirochromenopyrrole annulated heterocycles **7**–**11**.

70 μg/mL. Significantly the compounds **5, 7** and **11** showed good antibacterial activity even at the lower concentration in the range of 7–25 μg/mL against all the tested pathogenic bacteria. Further the compounds **5** and **11** were found to be more active than the standard antibiotic tetracyclin. The high activity of the compounds 5, 7 and **8** against all the bacterial pathogens than the standard drug tetracycline indicated, that there is a possibility that these compounds might be developed as a drug. The compounds **4** and **6** were found to have moderate activity against all the pathogens with MIC ranging from 15 to 30 μg/mL while compounds **8**–**10** exhibited low anti bacterial activity against the tested pathogens with high MIC values (Table 1).

Effect of tested compounds on the growth of human fungal pathogens: All the eight compounds exhibited different levels of antifungal activity against the three tested fungal pathogens, *Trichoderma* sp., *Aspergillus* sp. and *C. albicans* with 10% DMSO as control. The antifungal activity of the test compounds was dose dependent and remarkable at higher concentrations. The minimum inhibitory concentrations (MICs) of all the compounds **4–11** against the pathogens ranged between 15 and 105 μg/mL and showed moderate activity against all the microorganisms compared to standard drug carbendazim. Among all the eight compounds tested, the compounds **4**, **5**, and **7** inhibited moderately all the three human fungal pathogens at low concentrations (20–45 μg/mL) as compared to compounds **6** and **8–10** which showed antifungal activity only at higher concentrations (70–110 μg/mL) (Table 2).

In conclusion, we have achieved the synthesis of a variety of novel chromeno[3,4-*b*]pyrrole and its analogues through intramolecular 1,3-DC reaction. All the synthesized compounds showed good antimicrobial activity against all the selected human bacterial and fungal pathogens. In particularly cycloadducts **5, 7** and **11** exhibited the best antibacterial activity even better than the antibiotic tetracycline against all the bacterial pathogens. The synthetic compounds also exhibited moderate activity against all the fungal pathogens.

Table 1
In vitro antibacterial activity against human pathogens

Cycloadducts	MIC of +Ve bacteria[a]		MIC of −Ve bacteria[a]			
	S. aureus	*B. subtilis*	*S. pneumoniae*	*E. coli*	*Shigella* sp.	*S. typhi*
4	20	15	25	10	25	10
5	5	5	10	10	5	15
6	25	20	30	15	30	25
7	5	5	15	10	20	15
8	20	35	60	25	45	55
9	65	70	55	50	75	60
10	45	55	40	65	70	60
11	5	5	10	5	5	5
Tetracyclin	15	10	20	10	15	25

[a] Minimum inhibitory concentration (MIC) in μg/mL.

Table 2
In vitro antifungal activity against human pathogens

Cycloadducts	MIC of fungus pathogens[a]		
	Trichoderma sp.	*Aspergillus* sp.	*C. albicans*
4	40	35	45
5	30	25	25
6	75	70	65
7	45	25	20
8	105	85	75
9	110	75	95
10	105	75	90
11	50	25	35
Carbendazim	15	15	10

[a] Minimum inhibitory concentration (MIC) in μg/mL.

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16. *General procedure for synthesis of cycloadducts*: The solution containing 1.0 mmol of alkenyl aldehyde (**2**) and 2.5 mmol of secondary amino acid was refluxed in dry toluene for 4–6 h at 110 °C using Dean-Stark apparatus. After completion of the reaction as indicated by TLC, toluene was evaporated under reduced pressure. The crude product was then purified by column chromatography using hexane/EtOAc (8:2) as eluent.
(a) *Synthesis of hexahydrochromeno[3,4-b]pyrrole* (**4**): Isolated yield: 70%. White solid. Mp 128 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.36 (t, J = 9.3 Hz, 3H); 2.46 (s, 3H); 2.68 (dt, J = 6.6, 2.1 Hz, 1Hb); 3.51 (t, J = 8.4 Hz, 1H); 3.83–3.91 (m, 1Hc); 3.92 (dd, J = 2.1, 11.1 Hz, 1Ha); 4.19–4.25 (m, 2H); 6.80–6.91 (m 3H); 7.04–7.10 (m, 1H); 7.40 (d, J = 8.4 Hz, 1H); 7.86 (d, J = 8.4, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.2, 39.7, 55.2, 61.1, 64.6, 65.7, 117.7, 122.0, 127.1, 127.2, 128.7, 129.1, 130.0, 134.9, 140.1, 154.8, 198.7. ESI Mass m/z 328.33 (M^++1). Anal. Calcd. for $C_{19}H_{18}ClNO_2$: C, 69.62; H, 5.53; N, 4.27. Found: C, 69.74; H, 5.62; N, 4.38.
(b) *Synthesis of octahydrochromeno[4,3-b]pyrrolizine* (**5**): Isolated yield: 74%. White solid. Mp 152–54 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.68–1.75 (m, 2H); 1.95–2.03 (m, 1H); 2.11–2.15 (m, 2H); 2.34–2.42 (m, 1H); 2.65–2.73 (m, 1H); 3.02–3.09 (m, 1H); 3.76–3.85 (m, 1H); 4.20–4.25 (m, 2H); 5.17 (dd, J = 3.0, 12 Hz, 1H); 6.82–6.81 (m, 2H); 7.11–7.15 (m, 2H); 7.18–7.22 (m, 2H); 7.32–7.34 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.9, 46.7, 50.8, 54.1, 82.1, 93.8, 97.0, 99.3, 109.9, 120.9, 124.1, 126.2, 128.2, 128.4, 132.1, 132.3, 143.7, 158.6, 198.4. ESI Mass m/z 354.27 (M^++1). Anal. Calcd. for $C_{21}H_{20}ClNO_2$: C, 71.28; H, 5.70; N, 3.96. Found: C, 71.42; H, 5.90; N, 3.86.
(c) *Synthesis of spiro hexahydrochromeno[3,4-b]pyrrole* (**8**): Yield: 72%. White soild. Mp 162–64 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.29 (d, J = 9 Hz, 1H); 2.40 (m, 2H); 2.45 (s, 3H); 2.69–2.76 (m, 1H); 2.98–3.09 (m, 2H); 3.21 (d, J = 9 Hz, 1H); 3.85 (dd, J = 12, 3.6 Hz, 1H); 4.05 (dd, J = 12,3.6 Hz, 1H); 4.75 (d, J = 10.5 Hz,1H); 6.75–6.76 (m, 1H); 6.79–6.83 (m, 2H); 6.88–6.92 (m, 1H); 7.04–7.10 (m, 1H); 7.15–7.31 (m, 1H); 7.33–7.48 (m,1H); 8.08 (d, J = 7.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 26.0, 27.5, 40.5, 41.8, 57.2, 61.4, 65.4, 68.2, 117.4, 121.8, 124.7, 126.5, 127.2, 128.0, 129.7, 132.5, 133.6, 143.6, 157.3, 199.3. ESI Mass m/z 320.20 (M^+ +1). Anal. Calcd. for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39. Found: C, 79.07; H, 6.72; N, 4.41.
(d) *Synthesis of spiro octahydrochromeno[4,3-b]pyrrolizine* (**9**): Yield: 74%. White solid. Mp 170–72 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42–1.62 (m, 2H); 1.79–1.93 (m, 3H); 2.03–2.14 (m, 3H); 2.19–2.26 (m, 1H); 2.83–2.89 (m, 1H); 3.01–3.07 (m, 1H); 3.16–3.18 (m, 1H); 4.04 (dd, J = 10.2, 7.5 Hz, 1H); 5.05 (d, J = 7.5 Hz, 1H); 5.09 (dd, J = 10.2,7.5 Hz, 1H); 6.58 (d, J = 8.1 Hz, 1H); 6.79 (t, J = 7.1 Hz, 1H); 6.84–6.81 (m, 1H); 7.00–7.15 (m, 4H); 7.48 (d, J = 7.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.4, 27.2, 29.7, 31.5, 46.8, 50.0, 55.0, 82.0, 95.9, 97.6, 109.4, 120.5, 125.8, 126.2, 126.5, 126.9, 127.7, 128.5, 129.3, 138.2, 139.1, 160.0, 198.5. ESI Mass m/z 346.22 (M^++1). Anal. Calcd. for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.05. Found: C, 80.12; H, 6.91; N, 4.02.
17. The detailed X-ray crystallographic data for **4** (CCDC numbers: 752538) is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
18. The detailed X-ray crystallographic data for **10** (CCDC numbers: 770455) is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
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