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An Expedient General Synthesis of Quinolino and Pyrrolocycloocta[b] Indoles

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Abstract

A one pot solvent free acid catalyzed Friedlander synthesis of quinolinocycloocta[*b*]indoles (2 and 3) and pyrrolocycloocta[*b*]indoles (4) has been accomplished through the condensation reaction of various 5,7,8,9,10,11-hex ahydrocycloocta[*b*]indole-6-ones (1) with amino benzophenones and glycine respectively. The reaction condition was optimized for the synthesis of quinolinocycloocta[*b*]indoles. This is the first general synthesis of pyrrolocycloocta[*b*] indoles.

Keywords: Quinolinocycloocta[*b*]indoles; Pyrrolocycloocta[*b*] indoles; Friedlander synthesis; Solvent free synthesis

Introduction

Nitrogen-containing heterocycles are a very important group of organic compounds because of their wide application in medicine, agriculture, and technology. Among these, indole and quinoline derivatives are of significant synthetic interest due to their diverse range of biological activities. Substituted indoles have been referred to as "privileged structures" since they are capable of binding to many receptors with high affinity [1]. Cycloocta[*b*]indoles, an emerging class of biologically relevant indole analogues that has been found in many naturally occurring alkaloids such as macroline, ajmaline, macrocarpamine, villalstonine, *O*-acetyl macralstonine and macralstonine (Figure 1) and known to exhibit wide range of pharmacological properties such as antiamoebic, antiplasmodic, antiprotozol and antihypertensive activities [2-5]. The cycloocta[*b*] indole framework has recently been a subject of biology-oriented synthesis (BIOS) [6] and their analogues are promising targets for developing a novel class of potent and selective Mycobacterium protein tyrosine phosphatase B (MptpB) inhibitors against Mycobacterium tuberculosis [7]. The diverse biological activities of these alkaloids validate the cycloocta[*b*]indole core (Figure 2) as a promising scaffold for the generation of bioactive compounds. Compounds containing a quinoline framework have been found applications as pharmaceuticals and agrochemicals, as well as being general synthetic building blocks [8-10]. Industrial, biological, and synthetic significance places this scaffold in a prestigious position. Studies on new quinoline derivatives appear frequently in the chemical literature. Therefore, significant effort continues to be directed toward the development of new quinolines. In particular, there is much current interest in the quinoline ring system especially in the area of medicinal chemistry, and moreover it is a ubiquitous sub-structure found in many biologically active natural products [11-15]. Recently, the pyrrolo[2,3-*c*]carbazole, the common core of the marine alkaloids known as the dictyodendrins was found to possess excellent anti-tumour properties [15]. In continuation of our ongoing interest in the development of general synthetic routes to potentially bioactive condensed nitrogen heterocycles, [16,17] we recently focused our attention on a relatively less studied class of heterocycles i.e., cycloocta[*b*]indole which incorporate both the quinoline and the pyrrolo moiety. Thus it was of interest to design a synthetic route to the hitherto unreported cycloocta[*b*]indole molecular systems possessing quiolino and pyrrolo moiety in order to get the respective quinolinocycloocta[*b*]indoles and pyrrolocycloocta[*b*] indoles which may therefore lead to a play vital role in biological as well as pharmaceutical systems. In this Letter, we report a high-yielding, versatile, and simple one pot method for the (i) solvent-free, *p*-TsOH assisted rapid synthesis of quinolinocycloocta[*b*]indoles *via* Friedlander annulation reaction of 5,7,8,9,10,11-hexahydrocycloocta[*b*]indole-6-ones with 2-amino-5-methyl-benzophenone, 2-amino-5-chloro-benzophenone and (ii) pyrrolo cycloocta[*b*]indoles by the condensation of 5,7,8,9,10,11-hexahydrocycloocta[*b*]indole-6-ones with glycine under $POCl_3$ condition.

Experimental section

General procedure for the synthesis of 4-chloro-/4-methyl-6-phenyl-7,8,9,10-tetrahydro-15*H*-quinolino[2',3':8,7]cycloocta[*b*] indole (2 and 3): A mixture of an appropriate 5,7,8,9,10,11-hexa hydrocycloocta[*b*]indol-6-one (**1**, 0.001 mol) and the respective benzophenones (2-amino-5-chlorobenzophenone and 2-amino-5-methylbenzophenone, 1 mmol) was refluxed at 100°C for 3 h in the presence of catalytic amount of *p*-TsOH. After the completion of the reaction, the reaction mixture was cooled to room temperature, diluted with water and it was extracted using ethyl acetate. The organic layer was thoroughly washed with water and dried over anhydrous sodium sulphate. Upon removal of the solvent a brown crude product was obtained. It was purified by column chromatography over silica gel using petroleum ether : ethyl acetate (99 : 1) mixture as an eluent to afford the corresponding 4-chloro-/4-methyl-6-phenyl-7,8,9,10-tetrahydro-15*H*-quinolino[2',3':8,7]cyclo octa[*b*]indole (**2** and **3**).

4-Chloro-12-methyl-6-phenyl-7,8,9,10-tetrahydro-15*H*-quinolino[2',3':8,7]cycloocta[*b*]indole (2a): Yellow solid; yield: 82%; m.p.245-247°C; IR (KBr, cm^{-1}) ν_{max}: 3308 (N-H), 1624 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) δ_H: 9.05 (b s, 1H, N_{15}-H), 8.09-7.20 (m, 11H, C_2, C_3, C_5, C_{11}, C_{13}, C_{14}, C_2', C_3', C_4', C_5' and C_6'-H), 3.23-3.02 (m, 4H, C_7 and C_{10}-H), 2.49 (s, 3H, C_{12}-CH_3), 1.95-1.81 (m, 4H, C_8 and C_9-H); ^{13}CNMR (100 MHz, $CDCl_3$) (ppm) δ_C: 152.5 (C_{15b}), 145.6 (C_6), 140.8

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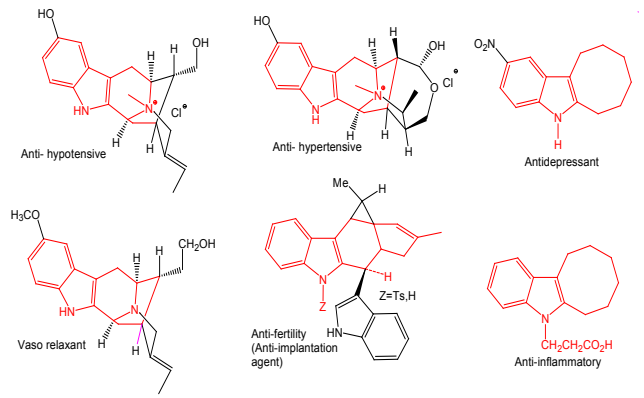


Figure 1: Representative naturally occurring biologically active cycloocta[*b*] indole alkaloids.

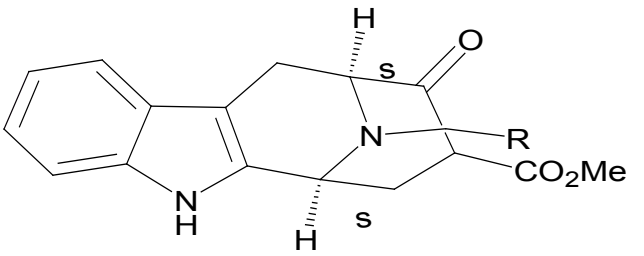


Figure 2: Cycloocta[*b*]indole core.

(C_{1a}), 137.9 (C_1'), 134.9 (C_{14a}), 132.0 (C_2), 131.2 (C_4), 130.0 (C_{12}), 129.3 (C_3', C_4' and C_5'), 128.2 (C_{10b}), 127.8 (C_{6a}), 127.1 (C_3), 126.7 (C_2' and C_6'), 125.4 (C_{15a}), 124.1 (C_5), 122.9 (C_{5a}), 121.5 (C_{11}), 120.2 (C_{13}), 115.1 (C_{10a}), 110.8 (C_{14}), 29.7 (C_9), 27.4 (C_8), 24.5 (C_7), 22.5 (C_{10}), 20.8 (C_{12}-CH_3); MS: *m/z* (M^+, 422); Anal. calcd. for: $C_{28}H_{23}ClN_2$: C, 79.51; H, 5.48; N, 6.62. Found: C, 79.56; H, 5.41; N, 6.57%.

4,12-Dichloro-6-phenyl-7,8,9,10-tetrahydro-15*H*-quinolino[2',3':8,7]cycloocta[*b*]indole (2b): Yellow solid; yield: 78%; m.p.214-216°C; IR (KBr, cm^{-1}) ν_{max}: 3329 (N-H), 1624 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) δ_H: 9.40 (b s, 1H, N_{15}-H), 8.00-6.96 (m, 11H, C_2, C_3, C_5, C_{11}, C_{13}, C_{14}, C_2', C_3', C_4', C_5' and C_6'-H), 3.31-2.29 (m, 8H, C_7, C_8, C_9 and C_{10}-H); ^{13}CNMR (100 MHz, $CDCl_3$) (ppm) δ_C: 151.1 (C_{15b}), 146.9 (C_6), 142.4 (C_{1a}), 136.5 (C_1'), 133.1 (C_{14a}), 132.5 (C_4), 131.8 (C_2), 129.9 (C_3', C_4' and C_5'), 128.0 (C_{12}), 127.5 (C_{10b}), 126.6 (C_{6a}), 127.1 (C_3), 126.9 (C_2' and C_6'), 125.0 (C_{15a}), 123.9 (C_5), 123.2 (C_{5a}), 122.5 (C_{11}), 121.3 (C_{13}), 114.2 (C_{10a}), 111.5 (C_{14}), 30.7 (C_9), 28.6 (C_8), 25.5 (C_7), 23.7 (C_{10}); MS: *m/z* (M^+, 442); Anal. calcd. for: $C_{27}H_{20}Cl_2N_2$: C, 73.14; H, 4.55; N, 6.32. Found: C, 73.09; H, 4.51; N, 6.37%.

4-Chloro-14-methyl-6-phenyl-7,8,9,10-tetrahydro-15*H*-quinolino[2',3':8,7]cycloocta[*b*] indole (2c): Yellow solid; yield: 70%; m.p.198-200°C; IR (KBr, cm^{-1}) ν_{max}: 3345 (N-H), 1609 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) δ_H: 9.55 (b s, 1H, N_{15}-H), 8.01-7.07 (m, 11H, C_2, C_3, C_5, C_{11}, C_{12}, C_{13}, C_2', C_3', C_4', C_5' and C_6'-H), 3.10-2.70 (m, 4H, C_7 and C_{10}-H), 2.47 (s, 3H, C_{14}-CH_3), 2.27-1.75 (m, 4H, C_8 and C_9-H); ^{13}CNMR (100 MHz, $CDCl_3$) (ppm) δ_C: 150.7 (C_{15b}), 147.6 (C_6), 143.4 (C_{1a}), 136.8 (C_1'), 134.8 (C_{14a}), 133.3 (C_2), 132.6 (C_4), 128.5 (C_3', C_4' and C_5'), 127.0 (C_{10b}), 126.7 (C_2' and C_6'), 126.3 (C_{6a}), 125.6 (C_3), 125.0 (C_{15a}), 123.6 (C_5), 122.7 (C_{12}), 121.8 (C_{5a}), 120.8 (C_{13}), 120.2 (C_{14}), 119.9 (C_{11}), 113.6 (C_{10a}), 31.5 (C_9), 29.6 (C_8), 25.5 (C_7), 23.7 (C_{10}), 18.8 (C_{14}-CH_3); MS: *m/z* (M^+, 422); Anal. calcd. for: $C_{28}H_{23}ClN_2$: C, 79.51; H, 5.48; N, 6.62. Found: C, 79.56; H, 5.41; N, 6.57%.

4-Chloro-6-phenyl-7,8,9,10-tetrahydro-15*H*-quinolino[2',3':8,7]cycloocta[*b*]indole (2d): Yellow solid; yield: 75%; m.p.210-212°C; IR (KBr, cm^{-1}) ν_{max}: 3331 (N-H), 1604 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) δ_H: 9.21 (b s, 1H, N_{15}-H), 8.05-7.00 (m, 12H, C_2, C_3, C_5, C_{11}, C_{12}, C_{13}, C_{14}, C_2', C_3', C_4', C_5' and C_6'-H), 3.25-1.67 (m, 8H, C_7, C_8, C_9 and C_{10}-H); ^{13}CNMR (100 MHz, $CDCl_3$) (ppm) δ_C: 155.0 (C_{15b}), 147.8 (C_6), 145.8 (C_{1a}), 135.8 (C_1'), 134.9 (C_{14a}), 133.5 (C_4), 132.7 (C_2), 129.5 (C_3', C_4' and C_5'), 127.5 (C_{10b}), 126.9 (C_2' and C_6'),126.6 (C_{6a}), 125.7 (C_3), 124.7 (C_{15a}), 123.5 (C_{12}), 122.9 (C_5), 122.6 (C_{5a}), 121.5 (C_{11}), 120.8 (C_{13}), 113.0 (C_{10a}), 112.2 (C_{14}), 32.3 (C_9), 31.6 (C_8), 27.5 (C_7), 25.7 (C_{10}); MS: *m/z* (M^+, 408); Anal. calcd. for: $C_{27}H_{21}ClN_2$: C, 79.30; H, 5.18; N, 6.85. Found: C, 79.36; H, 5.22; N, 6.90%.

4,12-Dimethyl-6-phenyl-7,8,9,10-tetrahydro-15*H*-quinolino[2',3':8,7]cycloocta[*b*]indole (3a): Yellow solid; yield: 80%; m.p.232-234°C; IR (KBr, cm^{-1}) ν_{max}: 3314 (N-H), 1596 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) δ_H: 9.55 (b s, 1H, N_{15}-H), 8.03-7.03 (m, 11H, C_2, C_3, C_5, C_{11}, C_{13}, C_{14}, C_2', C_3', C_4', C_5' and C_6'-H), 3.33-3.08 (m, 4H, C_7 and C_{10}-H), 2.47 (s, 3H, C_{12}-CH_3), 2.11 (s, 3H, C_4-CH_3), 1.38-1.29 (m, 4H, C_8 and C_9 -H); ^{13}CNMR (100 MHz, $CDCl_3$) (ppm) δ_C: 153.8 (C_{15b}), 142.7 (C_6), 140.6 (C_{1a}), 138.4 (C_1'), 133.7 (C_4), 132.3 (C_{14a}), 132.2 (C_{10b}), 131.6 (C_{12}), 131.2 (C_3), 129.2 (C_3', C_4' and C_5'), 128.6 (C_2), 127.9 (C_{6a}), 127.5 (C_2' and C_6'), 126.8 (C_5), 125.3 (C_{15a}), 125.0 (C_{5a}), 123.8 (C_{11}), 122.0 (C_{13}), 114.0 (C_{10a}), 113.1 (C_{14}), 29.8 (C_9), 27.7 (C_8), 26.2 (C_7), 23.5 (C_{10}), 21.8 (C_{12}-CH_3), 21.2 (C_4-CH_3); MS: *m/z* (M^+, 402); Anal. calcd. for: $C_{29}H_{26}N_2$: C, 86.53; H, 6.51; N, 6.96. Found: C, 86.58; H, 6.47; N, 7.00%.

12-Chloro-4-methyl-6-phenyl-7,8,9,10-tetrahydro-15*H*-quinolino[2',3':8,7]cycloocta[*b*]indole (3b): Yellow solid; yield: 77%; m.p.202-204°C; IR (KBr, cm^{-1}) ν_{max}: 3328 (N-H), 1589 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) δ_H: 9.33 (b s, 1H, N_{15}-H), 8.25-7.23 (m, 11H, C_2, C_3, C_5, C_{11}, C_{13}, C_{14}, C_2', C_3', C_4', C_5' and C_6'-H), 3.30-3.08 (m, 4H, C_7 and C_{10}-H), 2.38 (s, 3H, C_4-CH_3), 1.90-1.76 (m, 4H, C_8 and C_9-H); ^{13}CNMR (100 MHz, $CDCl_3$) (ppm) δ_C: 155.2 (C_{15b}), 143.4 (C_6), 142.1 (C_{1a}), 137.7 (C_1'), 135.1 (C_4), 134.2 (C_{14a}), 133.6 (C_{10b}), 131.7 (C_3), 129.6 (C_3', C_4' and C_5'), 128.2 (C_{12}), 127.9 (C_2), 127.2 (C_{6a}), 126.9 (C_2' and C_6'), 125.2 (C_5), 124.3 (C_{15a}), 123.0 (C_{5a}), 122.1 (C_{11}), 121.3 (C_{13}), 113.0 (C_{10a}), 112.1 (C_{14}), 30.1 (C_9), 28.3 (C_8), 25.6 (C_7), 24.1 (C_{10}), 20.5 (C_4-CH_3); MS: *m/z* (M^+, 422); Anal. calcd. for: $C_{28}H_{23}ClN_2$: C, 79.51; H, 5.48; N, 6.62. Found: C, 79.56; H, 5.41; N, 6.57%.

4,14-Dimethyl-6-phenyl-7,8,9,10-tetrahydro-15*H*-quinolino[2',3':8,7]cycloocta[*b*]indole (3c): Yellow solid; yield: 74%; m.p.206-208°C; IR (KBr, cm^{-1}) ν_{max}: 3345 (N-H) 1609 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) δ_H: 9.40 (b s, 1H, N_{15}-H), 8.06-7.23 (m, 11H, C_2, C_3, C_5, C_{11}, C_{12}, C_{13}, C_2', C_3', C_4', C_5' and C_6'-H), 3.26-2.87 (m, 4H, C_8 and C_9-H), 2.55 (s, 3H, C_{14}-CH_3), 2.15 (s, 3H, C_4-CH_3), 2.20-1.65 (m, 4H, C_7 and C_{10}-H);^{13}CNMR (100 MHz, $CDCl_3$) (ppm) δ_C: 154.2 (C_{15b}), 143.8 (C_6), 141.4 (C_{1a}), 137.9 (C_1'), 136.0 (C_4), 135.8 (C_{14a}), 133.1 (C_{10b}), 132.0 (C_3), 129.5 (C_3', C_4' and C_5'), 128.0 (C_2), 126.9 (C_{6a}), 126.5 (C_2' and C_6'), 126.0 (C_5), 124.2 (C_{15a}), 123.0 (C_{5a}), 123.1 (C_{12}), 121.0 (C_{13}), 120.1 (C_{14}), 119.8 (C_{11}), 113.0 (C_{10a}), 29.5 (C_9), 28.0 (C_8), 25.9 (C_7), 23.8 (C_{10}), 20.2 (C_4-CH_3), 19.5 (C_{14}-CH_3); MS: *m/z* (M^+, 402); Anal. calcd. for: $C_{29}H_{26}N_2$: C, 86.53; H, 6.51; N, 6.96. Found: C, 86.58; H, 6.47; N, 7.00%.

4-Methyl-6-phenyl-7,8,9,10-tetrahydro-15H-quinolino[2',3':8,7]cycloocta[b]indole (3d): Yellow solid; yield: 81%; m.p.218-220°C; IR (KBr, cm^{-1}) ν_{max}: 3362 (N-H), 1615 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) δ_H: 9.05 (b s, 1H, N_{15}-H), 8.00-7.00 (m, 12H, C_2, C_3, C_5, C_{11}, C_{12}, C_{13}, C_{14}, C_2', C_3', C_4', C_5' and C_6'-H), 3.24-3.08 (m,

4H, C_8 and C_9-H), 2.18 (s, 3H, C_4-CH_3), 1.90-1.72 (m, 4H, C_7 and C_{10}-H); ^{13}CNMR (100 MHz, $CDCl_3$) (ppm) δ_C: 152.5 (C_{15b}), 144.4 (C_6), 141.1 (C_{1a}), 138.2 (C_1'), 134.1 (C_4), 133.6 (C_{14a}), 132.6 (C_{10b}), 131.9 (C_3), 129.0 (C_3', C_4' and C_5'), 126.4 (C_2), 126.0 (C_2' and C_6'), 125.6 (C_{6a}), 125.1 (C_5), 123.3 (C_{15a}), 123.0 (C_{12}), 122.9 (C_{5a}), 122.1 (C_{11}), 120.9 (C_{13}), 112.6 (C_{10a}), 111.5 (C_{14}), 29.6 (C_9), 27.6 (C_8), 25.0 (C_7), 23.4 (C_{10}), 20.8 (C_4-CH_3); MS: *m/z* (M^+, 388); Anal. calcd. for: $C_{28}H_{24}N_2$: C, 86.56; H, 6.23; N, 7.21. Found: C, 86.51; H, 6.18; N, 7.27%.

General procedure for the synthesis of 3-chloro-4,5,6,7-tetrahydropyrrolo[2',3':8,7] cyclo octa[*b*]indole (4)

A mixture of the appropriate 5,7,8,9,10,11-hexahydrocycloocta[*b*] indol-6-one (**1**, 1 mmol) and glycine (1 mmol), 20 mL of phosphorous oxychloride was refluxed at 120°C for 5 h. The reaction was monitored by using TLC. After the completion of the reaction, it was poured into ice water and then neutralized with sodium bicarbonate solution, extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulphate. It was then purified by column chromatography over silica gel using petroleum ether:ethyl acetate mixture (95:5) and recrystallized from ethanol to yield the respective 3-chloro-4,5,6,7-tetrahydropyrrolo[2',3':8,7]cycloocta[*b*]indole (**4**).

3-Chloro-9-methyl-4,5,6,7-tetrahydropyrrolo[2′,3′:8,7] cycloocta[*b*]indole (4a): Brown solid; yield: 71%; m.p.145-147°C; IR (KBr, cm^{-1}) ν_{max}: 3386 (N-H), 1600 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) δ_H: 9.60 (s, 1H, N_{12}-H), 7.52-7.24 (m, 3H, C_8, C_{10} and C_{11}-H), 3.96 (s, 2H, C_2-H), 3.20-2.95 (m, 4H, C_4 and C_7-H), 2.46 (s, 3H, C_9-CH_3), 1.79-1.35 (m, 4H, C_5 and C_6-H); ^{13}CNMR (100 MHz, $CDCl_3$) (ppm) δ_C: 161.1 (C_{12b}), 134.9 (C_{11a}), 132.5 (C_{7b}), 132.0 (C_3), 131.5 (C_9), 128.6 (C_{3a}), 125.4 (C_{12a}), 124.4 (C_8), 122.0 (C_{10}), 113.6 (C_{7a}), 112.8 (C_{11}), 54.6 (C_2), 33.4 (C_6), 30.1 (C_5), 25.7 (C_7). 22.5 (C_4), 20.6 (C_9-CH_3); MS: *m/z* (M^+, 284); Anal. calcd. for: $C_{17}H_{17}ClN_2$: C, 71.70; H, 6.02; N, 9.84. Found: C, 71.75; H, 6.06; N, 9.90%.

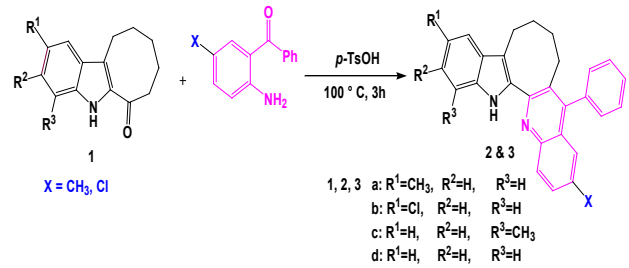
3,9-Dichloro-4,5,6,7-tetrahydropyrrolo[2′,3′:8,7]cycloocta[*b*] indole (4b): Brown yellow solid; yield: 67%; m.p.152-154°C; IR (KBr, cm^{-1}) ν_{max}: 3372 (N-H), 1592 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) δ_H: 9.39 (s, 1H, N_{12}-H), 7.48-7.07 (m, 3H, C_8, C_{10} and C_{11}-H), 4.00 (s, 2H, C_2-H), 3.05-1.20 (m, 8H, C_4, C_5, C_6 and C_7-H); ^{13}CNMR (100 MHz, $CDCl_3$) (ppm) δ_C: 159.5 (C_{12b}), 136.2 (C_{11a}), 134.2 (C_{7b}), 132.2 (C_3), 128.0 (C_9), 127.6 (C_{3a}), 124.2 (C_{12a}), 122.4 (C_8), 121.0 (C_{10}), 112.8 (C_{7a}), 111.7 (C_{11}), 56.5 (C_2), 32.5 (C_6), 29.6 (C_5), 26.1 (C_7). 23.2 (C_4); MS: *m/z* (M^+, 304); Anal. calcd. for: $C_{16}H_{14}Cl_2N_2$: C, 62.97; H, 4.62; N, 9.18. Found: C, 63.02; H, 4.57; N, 9.14%.

3-Chloro-11-methyl-4,5,6,7-tetrahydropyrrolo[2′,3′:8,7] cycloocta[*b*]indole (7c): Yellow solid; yield: 72%; m.p.184-186°C; IR (KBr, cm^{-1}) ν_{max}: 3364 (N-H), 1624 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) δ_H: 9.19 (s, 1H, N_{12}-H), 7.68-7.18 (m, 3H, C_8, C_9 and C_{10}-H), 4.03 (s, 2H, C_2-H), 3.18-2.96 (m, 4H, C_4 and C_7-H), 2.44 (s, 3H, C_{11}-CH_3), 1.99-1.68 (m, 4H, C_5 and C_6-H); ^{13}CNMR (100 MHz, $CDCl_3$) (ppm) δ_C: 158.6 (C_{12b}), 138.2 (C_{11a}), 133.0 (C_{7b}), 131.2 (C_3), 127.9 (C_{3a}), 124.1 (C_{12a}), 123.2 (C_9), 121.0 (C_{10}), 120.9 (C_{11}), 120.4 (C_8), 112.6 (C_{7a}), 54.6 (C_2), 31.7 (C_6), 28.1 (C_5), 26.7 (C_7). 24.5 (C_4), 19.6 (C_{11}-CH_3); MS: *m/z* (M^+, 284); Anal. calcd. for: $C_{17}H_{17}ClN_2$: C, 71.70; H, 6.02; N, 9.84. Found: C, 71.75; H, 6.06; N, 9.90%.

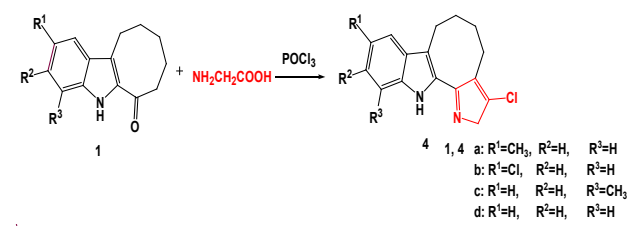
3-Chloro-4,5,6,7-tetrahydropyrrolo[2′,3′:8,7]cycloocta[*b*] indole (7d): Orange yellow solid; yield: 60%; m.p. 164-166°C; IR (KBr, cm^{-1}) ν_{max}: 3364 (N-H), 1605 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) δ_H: 9.11 (s, 1H, N_{12}-H), 7.60-7.25 (m, 4H, C_8, C_9, C_{10} and C_{11}-H), 3.95 (s, 2H, C_2-H), 3.21-1.69 (m, 8H, C_4, C_5, C_6 and C_7-H); ^{13}CNMR (100 MHz, $CDCl_3$) (ppm) δ_C: 157.8 (C_{12b}), 139.1 (C_{11a}), 131.2 (C_{7b}), 131.0 (C_3), 128.8 (C_{3a}), 124.5 (C_{12a}), 123.0 (C_9), 122.4 (C_8), 121.0 (C_{10}), 113.6 (C_{7a}), 112.7 (C_{11}), 57.1 (C_2), 30.5 (C_6), 28.6 (C_5), 25.1 (C_7). 22.2 (C_4); MS: *m/z* (M^+, 270); Anal. calcd. for: $C_{16}H_{15}ClN_2$: C, 70.98; H, 5.58; N, 10.35. Found: C, 71.03; H, 5.52; N, 10.40%.

Results and Discussion

Despite numerous methods reported such as Skrup, the Dobner-von Miller, or the Combes syntheses [18], the Friedlander and Pfitzinger annulations is still the most simple and straightforward approach for the synthesis of poly substituted quinolines and related azaheterocycles. Hence our plan was to utilize the Friedlander annulations protocol for the construction of quinoline ring on cycloocta[*b*]indole frame work. The synthesis of the envisaged title molecules, shown in Schemes 1 and 2 involved various 5,7,8,9,10,11-hexahydrocycloocta[*b*]indole-6-ones (**1**) as the starting precursor. Accordingly synthesis of the desired quinolinocycloocta[*b*]indoles (**2**) / (**3**) was achieved through the acid catalyzed condensation of 5,7,8,9,10,11-hexahydrocycloocta[*b*] indole-6-one (**1**) with 2-amino-5-chloro-benzophenone / 2-amino-5-methyl-benzophenone. The choice of an appropriate reaction medium is crucial for successful synthesis. To accelerate the acid catalyzed condensation of 5,7,8,9,10,11-hexahydrocycloocta[*b*]indole-6-ones (**1**) with 2-amino benzophenones, various catalysts and solvents such as H^+/AcOH, CF_3COOH, *p*-TsOH/toluene and *p*-TsOH/neat were examined and were shown to have a significant impact on the yield of the reaction. The desired product was obtained in fairly good yields with high purity up to 85–88% when the reaction was carried out under *p*-TsOH/neat condition. Moderate yields were observed when CF_3COOH, *p*-TsOH/toluene were used. The yield decreased when H^+/AcOH was used. Consequently *p*-TsOH was used as the catalyst of the choice. With the optimized reaction condition in hand the acid catalyzed condensation of 5,7,8,9,10,11-hexahydrocycloocta[*b*]indole-6-ones (**1**) with 2-amino benzophenones was carried out. The products (**2**) and (**3**) were purified by column chromatography. The structures of all the products are in good agreement with their IR and ^{1}H NMR and ^{13}C NMR spectroscopic data. For instance the absence of carbonyl group stretching and the presence of C=N stretching at 1624 cm^{-1} in the IR spectrum revealed the formation of **2a**. The ^{1}H NMR spectrum



Scheme 1: Solvent free synthesis of quinolinocycloocta[*b*]indoles **(2a-3d)**.



Scheme 2: Synthesis of pyrrolocycloocta[*b*]indoles **(4a-4d)**.

Entry	Catalyst/Solvent	Temperature	Time (h)	Yield (%)
1	Neat	170	2	25
2	H^+/AcOH	120	10	32
3	CF_3COOH	100	7	47
4	*p*-TsOH/toluene	120	8	56
5	*p*-TsOH/neat	100	3	82

Table 1: Optimization of the reaction conditions for the synthesis of Quinolinocycloocta[*b*]indoles **(2a-3d)**.

of **2a** furnished multiplets of signals between δ 8.09-7.20 attributed to aromatic protons. The broad singlet at δ 9.05 was due to NH function of indole core. The remaining protons appeared in the corresponding region. The proposed structure has also been established by their ^{13}C NMR and mass spectral analysis. Similarly the ^1H-NMR spectrum of **3a** furnished a broad singlet at δ 9.55 accountable for indole N-H and a multiplet between δ 8.03-7.03 was due to aromatic protons and two singlets at δ 2.47 and 2.11 attributed to C_{12} and C_4 methyl protons which strongly support the structure of the obtained product as **3**. Furthermore, the ^{13}C NMR gave strong evidence for the formation of compound **3**. The identities of the other compounds **2b** to **3d** were established in the same way with all spectroscopic data readily assignable (Table 1). To explore further the synthetic potential of this tandem protocol, 5,7,8,9,10,11-hexahydrocycloocta[*b*]indole-6-one (**1**) was treated with glycine under $POCl_3$ condition. The structure of **4** is fully supported by spectral and analytical data. The structure of **4** was confirmed by the infrared absorption band of the C=N group at 1600 cm^{-1} and C_2 proton signal at δ 3.96 in the ^1H-NMR and the sharp signal at δ 54.6 in the ^{13}C NMR spectrum. The four compounds **4a** to **4d** are based on the same chemical scaffold and are distinguished from each other only by the presence, absence, or position of a methyl group at the indole phenyl ring [19-21].

Conclusion

In summary, an efficient, general synthesis of quinolinocycloocta[*b*] indoles has been developed by the *p*-TsOH assisted reaction of 5,7,8,9,10,11-hexahydrocycloocta[*b*]indole-6-one (**1**) with 2-amino benzophenones using Friedlander annulations reactions under solvent free condition and the synthesis of pyrrolocycloocta[*b*]indole by the condensation of 7,8,9,10,11-hexahydrocycloocta[*b*]indole-6-one (**1**) with glycine. To the best of our knowledge, this is the first general synthesis of this class of compounds. The overall procedure is simple, the yields are consistently high thereby rendering our method even more useful. Pertinently we anticipate that the protocol described here could be explored further to have interesting implications in the fields of combinatorial chemistry and chemistry-driven drug discovery.

Appendix: Supplementary Data

Experimental procedures, ^1H NMR and ^{13}C NMR spectra of key compounds are given in Supplementary data.

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