J. Chem. Sci. Vol. 126, No. 6, November 2014, pp. 1893–1902.

Synthesis of quinolino[2′,3′:8,7]cyclooct[*b*]indole

LEENA VAIRAVELU and K J RAJENDRA PRASAD*

Department of Chemistry, Bharathiar University, Coimbatore 641 046, India
e-mail: prasad_125@yahoo.com

MS received 21 November 2013; revised 17 February 2014; accepted 18 February 2014

Abstract. A rapid and efficient synthetic route for the synthesis of 7,8,9,10-tetrahydroquinolino[2′,3′:8,7]cyclooct[*b*]indole analogues has been developed by reaction of 1-oxo-1,2,3,4,5,6-hexahydrocyclooct[*b*]indole with anthranilic acid and 3-amino pyrazine acid under $POCl_3$ condition and the synthesis of 7,8,9,10-tetrahydroquinolino[2′,3′:8,7]cyclooct[*b*]indole-6-carboxylic acid has been designed by reaction of 1-oxo-1,2,3,4,5,6-hexahydrocyclooct[*b*]indole with isatin in the presence of NaOH via Pfitzinger reaction. These methods are more satisfactory in terms of the yield and simple one-pot operation. Structures of the products thus obtained were confirmed by spectral studies.

Keywords. 7,8,9,10-Tetrahydroquinolino[2′,3′:8,7]cyclooct[*b*]indole;1-oxo-1,2,3,4,5,6-hexahydrocyclooct[*b*]indole; Pfitzinger reaction.

1. Introduction

Among the nitrogen heterocycles, indole is an important structural components in alkaloids and many pharmaceutical agents. Indole exhibits a high degree of biological activities including antifungal, antibacterial, antitumour, anti-HIV and DNA interactions. Substituted indoles have been referred to as 'privileged structures' since they are capable of binding to many receptors with high affinity.[1] The structural diversity and biological importance of indole have made them attractive targets for synthesis over many years. Cyclooct[b]indoles, a sub-class of the indoles, represent an important part of many naturally occurring alkaloids, such as macroline (**1**), ajmaline (**2**), macrocarpamine (**3**), villalstonine (**4**), *O*-acetyl macralstonine (**5a**) and macralstonine (**5b**) with highly interesting pharmacological properties (figure 1). The biological activities of cyclooct[*b*]indoles cover wide spectrum which include antiamoebic, antiplasmodic, antiprotozol and antihypertensive activities.[2–5] The diverse biological activities of macrolines validates the cyclooct[*b*]indoles system as a promising scaffold for the generation of bioactive compounds (figure 1). The structure of cyclooct[b]indole core[6] is represented in figure 2.

Quinoline or 1-aza-napthalene or benzo[*b*]pyridine is nitrogen-containing heterocyclic aromatic compound. It is a system present in many classes of biologically active compounds. A number of quinoline related compounds have been clinically used as antifungal, antibacterial, and antiprotozoic drugs[7–10] as well as antituberculosis agents.[11–13] Some quinoline analogues also showed antineoplastics activity.[14] Recently, styrylquinoline derivatives have gained remarkable attention due to their activity as potential HIV integrase inhibitors.[15–19] The pyrazine ring is a part of many polycyclic compounds of biological and industrial significance. Examples are quinoxalines, phenazines, bioluminescent natural products, pteridines, flavins, and their derivatives. Pyrazino[3,2,1-*j*, *k*]carbazoles represent a new class of heterocyclic compounds possessing interesting pharmacological properties (figure 3). 3*H*-pyrazino[3,2,1-*j*, *k*]carbazoles possess neuroleptic properties and hence are of pharmacological interest.

Inspired by the wide range of useful activities possessed by cyclooct[*b*]indole, quinoline, and pyrazino pyrido derivatives and in continuation of our efforts in search of bioactive compounds, combination of cyclooct[*b*]indole, quinoline and pyrazino pyrido structures may therefore lead to play a vital role in biological as well as pharmaceutical systems. Considering these facts, our strategy is to couple quinoline and pyrazino pyrido moiety with cyclooct[*b*]indole nucleus to obtain a new class of compounds, the quinolino cyclooct[*b*]indole and pyrazino[2″,3″-e′]pyrido-[2′,3′:8,7]cyclooct[*b*]indole derivatives. In some cases, specific substitution patterns like quinolino cyclooct[*b*]indole and pyrazino[2″,3″-e′]pyrido-[2′,3′:8,7]cyclooct[*b*]indole are difficult to obtain by standard pyrazino pyrido forming or quinoline forming reactions, therefore, new methodologies

*For correspondence

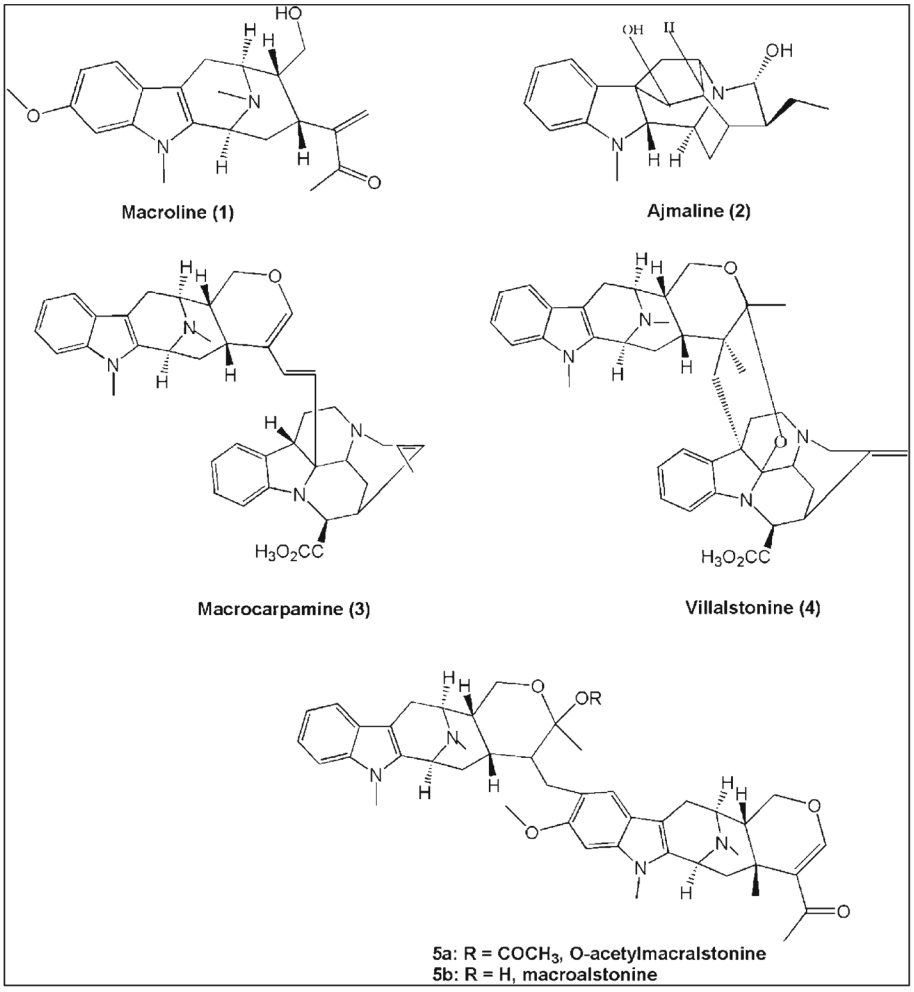


Figure 1. Structures of naturally occurring alkaloids having cyclooct[*b*]indole core.

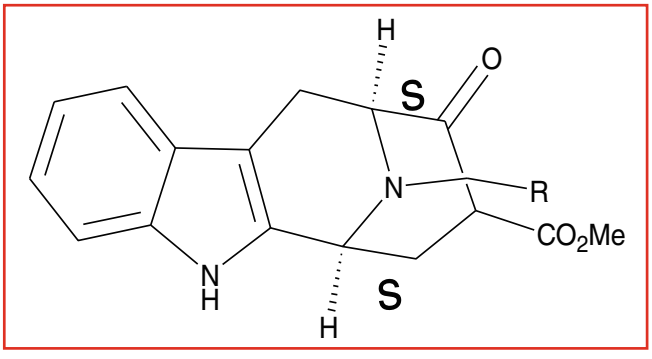


Figure 2. Structure of cyclooct[*b*]indole core.

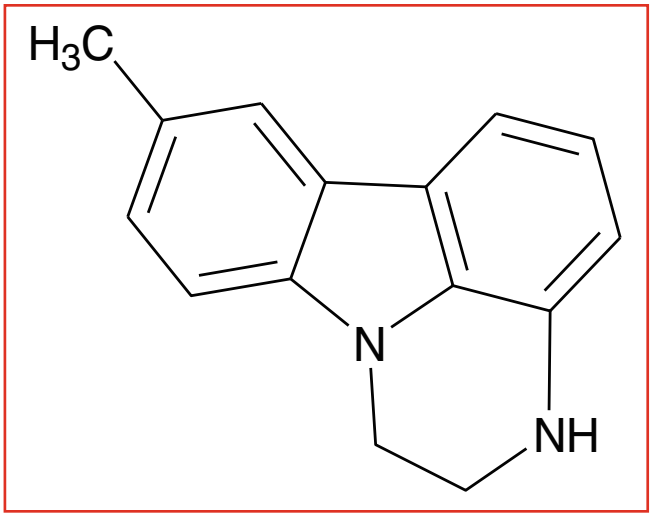


Figure 3. Structure of pyrazino[3,2,1-*j*, *k*]carbazole.

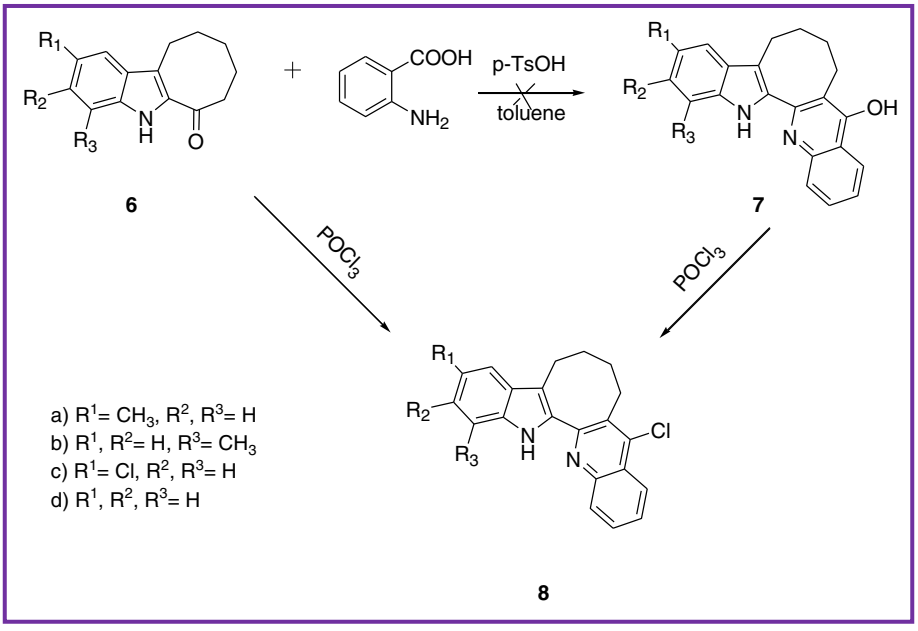
emerged. Prompted by all these observations, a simple strategy has been planned to synthesize a new class of cyclooct[*b*]indole derivatives possessing quinoline and pyrazino pyrido moiety in their structure with more potent activity. This manuscript represents the construction of quinolino cyclooct[*b*]indole and pyrazino[2″,3″-e′] pyrido-[2′,3′:8,7]cyclooct[*b*]indole derivatives, using 1-oxo-1,2,3,4,5,6-hexahydrocyclooct[*b*]indole **6** as the potential precursors.

The general synthetic methods shown in schemes 1, 2 and 3 are employed to prepare the quinolino-cyclooct[*b*]indole and pyrazino[2″,3″-e′]pyrido-[2′,3′:8,7]cyclooct[*b*]indole derivatives **8a–d, 10a–d** and **11a–d**. The synthesis of quinolino cyclooct[*b*]indole and pyrazino[2″,3″-e′]pyrido-[2′,3′:8,7]cyclooct[*b*]indole compounds were realized in $POCl_3$ in a single process and quinolino cyclooct[*b*]indole-6-carboxylic acid are prepared under Pfitzinger condition.

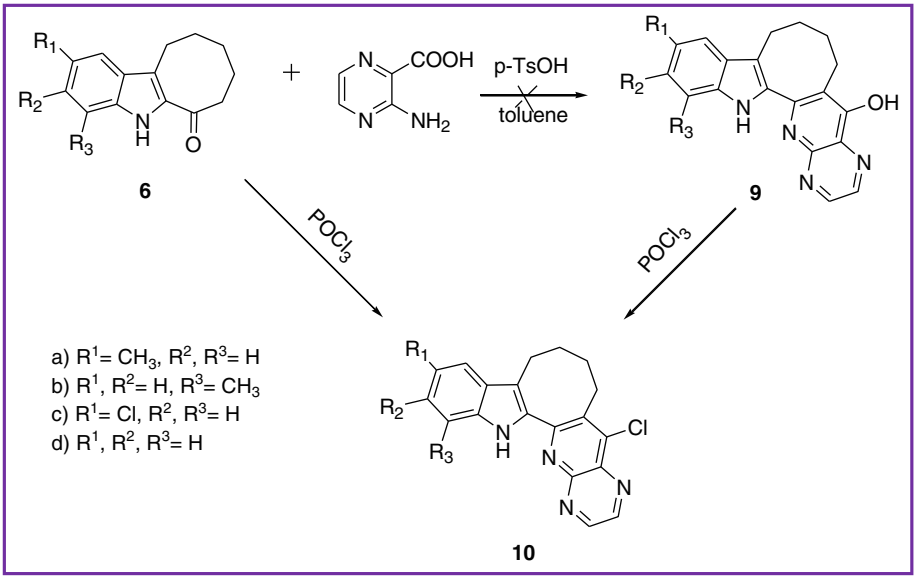
2. Experimental

2.1 *General*

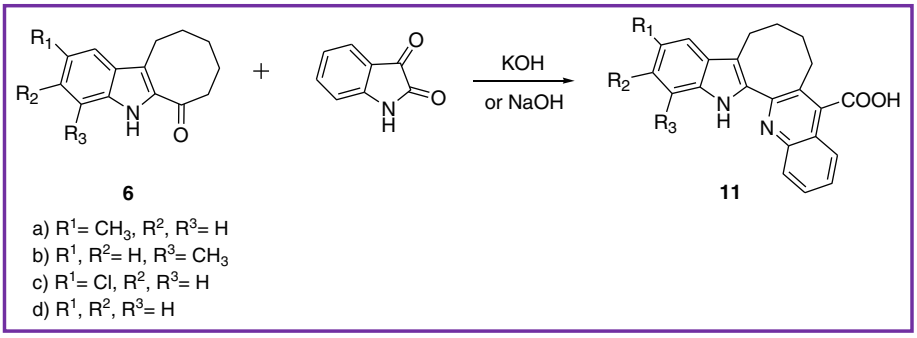
Melting points (m.p.) were determined on Mettler FP 51apparatus (Mettler Instruments, Switzerland) and are uncorrected. They are expressed in degree centigrade (°C). A Nicolet Avatar Model FT-IR spectrophotometer is used to record the IR spectra (4000–400 cm^{-1}).



Scheme 1. $POCl_3$ catalysed synthesis of 6-chloro-7,8,9,10-tetrahydroquinolino[2′,3′:8,7]cyclooct[*b*]indole.



Scheme 2. $POCl_3$ catalysed synthesis of 6-chloro-7,8,9,10-tetrahydro(pyrazino [2″,3″-e′]pyrido)-[2′,3′:8,7]cyclooct[*b*]indole.



Scheme 3. Synthesis of 7,8,9,10-tetrahydroquinolino[2′,3′:8,7]cyclooct[*b*]indole-6-carboxylic acid via Pfitzinger reaction.

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AV 500 (500 MHz (^{1}H) and 125 MHz (^{13}C)) spectrometer using tetramethylsilane (TMS) as an internal standard. The chemical shifts are expressed in parts per million (ppm). Mass spectra (MS), were recorded on Auto Spec EI+ shimadzu QP 2010 PLUS GC-MS mass spectrometer. Microanalyses were performed on a Vario EL III model CHNS analyzer (Vario, Germany) at the Department of Chemistry, Bharathiar University. Developing solvents were coated with silica Gel- G, petroleum ether and ethyl acetate.

2.2 *General procedure for the synthesis of 6-chloro-7,8,9,10-tetrahydroquinolino[2′,3′:8,7] cyclooct[b]indole (**8a–d**)*

A mixture of 1-oxo-1,2,3,4,5,6-hexahydrocyclooct[*b*] indole (**6**, 1 mmol), anthranilic acid (1 mmol) in 20 mL of phosphorous oxychloride was refluxed at 140°C for 16 h. The reaction was monitored by TLC. After the completion, the reaction mixture was poured into ice water with constant stirring and the pH was adjusted to 8 by adding 10% NaOH solution. The precipitate formed was filtered off and dried. The crude product thus obtained was purified by column chromatography over silica gel using petroleum ether:ethyl acetate mixture (99:1) and recrystallised from ethanol to yield the corresponding product 6-chloro-7,8,9,10-tetrahydroquinolino[2′,3′:8,7]cyclooct[*b*]indole **8**.

2.2a *6-Chloro-12-methyl-7,8,9,10-tetrahydroquinolino[2′,3′:8,7]cyclooct[b]indole (**8a**)*: Pale yellow solid; yield: 56%; M.p. 229–231°C IR (KBr, cm^{-1}) υ_{max} : 3458 (N-H), 1572 (C=N). ^{1}H NMR ($CDCl_3$) δ: 9.00 (b s, 1H, N_{15}-H), 8.30–7.15 (m, 7H, C_2, C_3, C_4, C_5, C_{11}, C_{13} and C_{14}-H), 3.50–1.00 (m, 8H, C_7, C_8, C_9 and C_{10}-CH_2), 2.50 (s, 3H, C_{12}-CH_3); ^{13}C NMR ($CDCl_3$) δ: 156.8 (C_{1a}), 142.3 (C_{2a}), 137.8 (C_6), 132.3 (C_3), 130.4 (C_{15a}), 130.2 (C_{1b}), 129.5 (C_{7a}), 128.7 (C_2), 128.2 (C_4), 127.3 (C_{11a}), 126.5 (C_5), 125.5 (C_{6a}), 124.4 (C_{12}), 123.8 (C_{11}), 123.5 (C_{1b}), 119.4 (C_{13}), 111.5 (C_{14}), 28.5 (C_7), 27.6 (C_8), 26.4 (C_9), 21.9 (C_{12}-CH_3), 19.6 (C_{10}).; MS : m/z (%) 346 (M^+ 100%), 348 (M+2, 18%) ; Anal. calcd. for $C_{22}H_{19}N_2Cl$: C, 76.18; H, 5.52, N, 8.08. Found: C, 76.20; H, 5.53 N, 8.10%.

2.2b *6-Chloro-14-methyl-7,8,9,10-tetrahydroquinolino[2′,3′:8,7]cyclooct[b]indole (**8b**)*: Yellow solid; yield: 43%; M.p. 225–227°C, IR (KBr, cm^{-1}) υ_{max} : 3288 (N-H), 1582 (C=N). ^{1}H NMR ($CDCl_3$) δ: 9.50 (b s, 1H, N_{15}-H), 7.80–6.90 (m, 7H, C_2, C_3, C_4, C_5, C_{11}, C_{12} and C_{13}-H), 3.40–3.60 (m, 4H, C_7, & C_{10}-CH2), 2.50 (s, 3H, C_{12}-CH_3), 2.10–1.20 (m, 4H, C_8 & C_9 – CH_2); ^{13}C NMR ($CDCl_3$) δ: 156.4 (C_{1a}), 142.3 (C_{2a}), 137.7 (C_6), 132.2 (C_3), 131.3 (C_{15a}), 130.3 (C_{1b}), 130.0 (C_{7a}), 128.9 (C_2), 128.8 (C_4), 127.5 (C_{11a}), 126.7 (C_5), 125.4 (C_{6a}), 124.6 (C_{12}), 123.7 (C_{11}), 123.6 (C_{11b}), 118.8 (C_{13}), 111.4 (C_{14}), 28.2 (C_7), 27.3 (C_8), 26.4 (C_9), 21.4 (C_{14}-CH_3), 19.4 (C_{10}).; MS : m/z (%) 346 (M^+ 100%), 348 (M+2, 18%); Anal. calcd.for $C_{22}H_{19}N_2Cl$: C, 76.18; H, 5.52, N, 8.08. Found: C, 76.20; H, 5.53 N, 8.10%.

2.2c *6,12-Dichloro-7,8,9,10-tetrahydroquinolino-[2′,3′:8,7]cyclooct[b]indole (**8c**)*: Orange yellow solid; yield: 42%; M.p. 241–242°C, IR (KBr, cm^{-1}) υ_{max} : 3297 (N-H), 1588 (C=N). ^{1}H NMR ($CDCl_3$) δ: 9.20 (b s, 1H, N_{15}-H), 7.70–7.10 (m, 7H, C_2, C_3, C_4, C_5, C_{11}, C_{13} and C_{14}-H), 3.00–1.20 (m, 8H, C_7, C_8, C_9 and C_{10}-CH_2); ^{13}C NMR ($CDCl_3$) δ: 156.1 (C_{1a}), 142.3 (C_{2a}), 137.5 (C_6), 132.2 (C_3), 131.3 (C_{15a}), 130.1 (C_{1b}), 129.7 (C_{7a}), 129.2 (C_2), 128.3 (C_4), 127.4 (C_{11a}), 126.7 (C_5), 125.6 (C_{6a}), 123.3 (C_{12}), 123.4 (C_{11}), 123.2 (C_{11b}), 119.2 (C_{13}), 112.1 (C_{14}),

28.5 (C_7), 27.3 (C_8), 26.9 (C_9), 19.7 (C_{10}).; MS : m/z (%) 366 (M^+ 100%), 368 (M+2, 18%); Anal. calcd. for $C_{21}H_{16}N_2Cl_2$: C,68.68; H, 4.39; N, 7.63. Found: C, 68.70; H, 4.38; N, 7.64%.

2.2d *6-Chloro-7,8,9,10-tetrahydroquinolino[2′,3′:8,7]cyclooct[b]indole (**8d**)*: Pale orange solid; yield: 47%; M.p. 190–192°C IR (KBr, cm^{-1}) υ_{max} : 3254 (N-H), 1588 (C=N). ^{1}H NMR ($CDCl_3$) δ: 9.24 (b s, 1H, N_{15}-H), 7.78–6.93 (m, 8H, C_2, C_3, C_4, C_5, C_{11}, C_{12}, C_{13} and C_{14}-H), 3.31–1.50 (m, 8H, C_7, C_8, C_9 and C_{10}-CH_2); ^{13}C NMR ($CDCl_3$) δ: 156.21 (C_{1a}), 142.26 (C_{2a}), 137.70 (C_6), 132.31 (C_3), 130.94 (C_{15a}), 130.02 (C_{1b}), 129.59 (C_{7a}), 128.86 (C_2), 128.10 (C_4), 127.35 (C_{11a}), 126.61 (C_5), 125.64 (C_{6a}), 123.54 (C_{11b}), 122.65 (C_{12}), 120.02 (C_{13}), 112.01 (C_{14}), 115.86 (C_{11}), 28.34 (C_7), 27.46 (C_8), 26.67 (C_9), 19.09 (C_{10}).; MS : m/z (%) 332 (M^+ 100%), 334 (M+2, 18%); Anal. calcd. for $C_{21}H_{17}N_2Cl$: C,75.78; H, 5.15; N, 8.62. Found: C, 75.76; H, 5.14; N, 8.63%.

2.3 *General procedure for the synthesis of 7,8,9,10-tetrahydro(pyrazino[2″,3″-e′]pyrido)-[2′,3′:8,7]cyclooct[b]indole (**10a–d**)*

A mixture of the appropriate 1-oxo-1,2,3,4,5,6-hexahydrocyclooct[*b*]indole (**6**, 1 mmol), and 3-aminopyrazine-2-carboxylic acid (1 mmol) 20 mL of phosphorous oxychloride was refluxed at 140°C for 16 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 (97:3) and recrystallised from ethanol to yield the respective 6-chloro-7,8,9,10-tetrahydro(pyrazino[2″,3″-′]pyrido)-[2′,3′:8,7]cyclooct[*b*]indole **10**.

2.3a *6-Chloro-12-methyl-7,8,9,10-tetrahydro(pyrazino[2″,3″-e′]pyrido)-[2′,3′:8,7] cyclooct[b]indole (**10a**)*: Pale yellow solid; yield: 65%; M.p. 184–186°C; IR (KBr, cm^{-1}) υ_{max} : 1613 (C=N); ^{1}H NMR ($CDCl_3$) δ: 9.00 (s, 1H, N_{15}-H), 7.69 (d, 1H, C_4-H J = 7.50 Hz), 7.58 (d, 1H, C_3-H J = 7.50 Hz), 7.50–6.95 (m, 3H, C_{11}, C_{13} and C_{14}-H), 3.25–2.80 (m, 4H, C_7, & C_{10}- CH_2), 2.50 (s, 3H, C_{12}-CH_3), 2.25–1.50 (m, 4H, C_8 & C_9−CH_2); ^{13}C NMR ($CDCl_3$) δ: 158.1 (C_{15b}), 148.3 (C_{1a}), 146.9 (C_{5a}), 145.2 (C_3), 145.2 (C_4), 143.3 (C_6), 137.7 (C_{6a}), 134.1 (C_{14a}), 132.5 (C_{10b}), 132.1 (C_{12}), 123.3 (C_{15a}), 121.5 (C_{11}), 119.2 (C_{13}), 113.3 (C_{10a}), 111.4 (C_{14}), 33.3 (C_9), 31.6 (C_8), 21.3 (C_{12}-CH_3), 22.9 (C_{10}). 19.6 (C_7),; MS : m/z (%) 348 (M^+ 100%), 350 (M+2, 18%); Anal. Calcd. for $C_{20}H_{17}ClN_4$: C, 68.86; H, 4.91; N, 16.06. Found: C, 68.87; H, 4.93; N, 16.05%.

2.3b *6-Chloro-14-methyl-7,8,9,10-tetrahydro(pyrazino[2″,3″-e′]pyrido)-[2′,3′:8,7] cyclooct[b]indole (**10b**)*: Yellow solid; yield: 65%; M.p. 184–187°C; IR (KBr, cm^{-1}) ν_{max}: 1624 (C=N); ^{1}H NMR ($CDCl_3$) δ: 9.00 (s, 1H, N_{15}-H), 7.45 (d, 1H, C_4-H J = 7.50 Hz), 7.38 (d, 1H, C_3-HJ = 7.50 Hz), 7.35–6.98 (m, 3H, C_{11}, C_{12} and C_{13}-H), 3.25–1.50 (m, 8H, C_7, C_8, C_9 and C_{10}- CH_2), 2.50 (s, 3H, C_{14}-CH_3); ^{13}C NMR ($CDCl_3$) δ: 158.34 (C_{15b}), 148.30 (C_{1a}), 146.79 (C_{5a}), 145.32 (C_3), 145.25 (C_4), 143.32 (C_6), 137.63 (C_{6a}), 134.12 (C_{14a}), 132.25 (C_{10b}), 132.14 (C_{12}), 123.40 (C_{15a}), 121.64 (C_{11}), 119.43 (C_{13}), 113.12 (C_{10a}), 111.49 (C_{14}), 33.39 (C_9), 31.50 (C_8), 22.30 (C_{14}-CH_3), 22.29 (C_{10}).; MS : m/z (%) 348 (M^+ 100%), 350 (M+2, 18%); Anal. Calcd. for $C_{20}H_{17}ClN_4$: C, 68.86; H, 4.91; N, 16.06. Found: C, 68.87; H, 4.93; N, 16.05%.

2.3c *6,12-Dichloro-7,8,9,10-tetrahydro(pyrazino[2″,3″-e′]pyrido)-[2′,3′:8,7]cyclooct[b]indole (**10c**)*: Brown yellow solid; yield: 65%; M.p. 189–191°C; IR (KBr, cm^{-1})ν_{max}: 1635 (C=N); ^{1}H NMR ($CDCl_3$)δ: 9.00 (s, 1H, N_{15}-H), 7.60 (d, 1H, C_4-H J = 7.50 Hz), 7.70 (d, 1H, C_3-H, J = 7.50 Hz), 6.95–7.45 (m, 3H, C_{11}, C_{13} and C_{14}-H), 3.35-1.50 (m, 8H, C_7, C_8, C_9 and C_{10}-CH_2); ^{13}C NMR ($CDCl_3$) δ: 157.2 (C_{15b}), 147.7 (C_{1a}), 146.4 (C_{5a}), 145.8 (C_3), 145.2 (C_4), 143.9 (C_6), 137.6 (C_{6a}), 134.2 (C_{14a}), 132.5 (C_{10b}), 132. 4 (C_{12}), 123.4 (C_{15a}), 121.6 (C_{11}), 119.4 (C_{13}), 113.2 (C_{10a}), 111.9 (C_{14}), 33.9 (C_9), 31.5 (C_8), 22.2 (C_{10}).; MS : m/z (%) 369 (M^+ 100%), 371 (M+2, 18%); Anal. Calcd. for $C_{19}H_{14}Cl_2N_4$: C, 61.80; H, 3.82; N, 15.17. Found: C, 61.82; H, 3.79; N, 15.15 %.

2.3d *6-Chloro-7,8,9,10-tetrahydro(pyrazino[2″,3″-e′]pyrido)-[2′,3′:8,7]cyclooct[b]indole (**10d**)*: Orange yellow solid; yield: 65%; M.p. 186–188°C; IR (KBr, cm^{-1}) ν_{max}: 1605 (C=N); ^{1}H NMR ($CDCl_3$) δ: 9.10 (s, 1H, N_{15}-H), 7.45 (d, 1H, C_4-H J = 7.00 Hz), 7.35 (d, 1H, C_3, J = 7.00 Hz), 6.90–7.35 (m, 4H, C_{11}, C_{12}, C_{13} and C_{14}-H), 3.40–2.98 (m, 4H, C_7 & C_{10}-CH_2), 2.25–1.45(m, 4H, C_8, & C_9−CH_2); ^{13}C NMR ($CDCl_3$) δ: 157.4(C_{15b}), 147.5 (C_{1a}), 146.7 (C_{5a}), 145.2 (C_3), 145.1 (C_4), 143.5 (C_6), 137.7 (C_{6a}), 134.5 (C_{14a}), 132.6 (C_{10b}), 132. 7 (C_{12}), 123.6 (C_{15a}), 121.2 (C_{11}), 119.1 (C_{13}), 113.6 (C_{10a}), 111.7 (C_{14}), 33.4 (C_9), 31.2 (C_8), 22.4 (C_{10}).; MS : m/z (%) 334 (M^+ 100%), 336

(M+2, 18%); Anal. Calcd. for $C_{19}H_{15}ClN_4$: C, 68.16; H, 4.52; N, 16.73. Found: C, 68.17; H, 4.50; N, 16.74%.

2.4 *General procedure for the synthesis of 7,8,9,10-tetrahydroquinolino[2′,3′:8,7] cyclooct[b]indole-6-carboxylic acid (**11a–d**)*

A mixture of the respective 1-oxo-1,2,3,4,5,6-hexahydrocyclooct[*b*]indole (**6**, 1 mmol), isatin (1 mmol) and NaOH (0.400 g) in ethanol (15 mL) was refluxed in a steam bath for 24 h. The reaction was monitored by TLC. After completion of the reaction, the excess solvent was removed and poured into ice and neutralized with dilute HCl. The crude solid obtained was filtered and purified with sodium bicarbonate treatment and neutralized with dilute HCl. The solid product was recrystalized from ethanol to yield the respective 7,8,9,10-tetrahydroquinolino[2′,3′:8,7]cyclooct[*b*]indole-6-carboxylic acid **11**.

2.4a *12-Methyl-7,8,9,10-tetrahydroquinolino[2′,3′:8,7]cyclooct[b]indole-6-carboxylic acid (**11a**)*: Orange solid; yield: 85% M.p. > 300°C IR (KBr, cm^{-1}) υ_{max}:, 3400 (O-H), 1712 (C=O), 1605 (C=N); ^{1}H NMR (DMSO) δ: 11.40 (b s, 1 H, acid OH), 9.20 (b s, 1 H, N_{15}-H). 8.00–7.70 (m, 2H, C_3 and C_4-H), 7.39–7.29 (m, 3H, C_2, C_5 and C_{11}-H), 7.20–6.95 (m, 2H, C_{13} and C_{14}-H) 3.30–3.10 (m, 4H, C_7 & C_{10}− CH_2), 2.50 (s, 3H, C_{14}-CH_3); 2.85–1.80 (m, 4H, C_8 & C_9-CH_2); ^{13}C NMR (DMSO) δ: 172.00 (C_6-COOH), 157.54 (C_{1a}), 152.67 (C_6), 146.76 (C_{2a}), 132.90 (C_{7a}), 130.21 (C_{1b}), 130.04 (C_{15a}), 128.78 (C_2), 127.47 (C_3), 126.95 (C_{11a}), 126.78 (C_4), 125.12 (C_{12}), 124.38 (C_5), 123.15 (C_{11}), 122.26 (C_{6a}), 120.05 (C_{13}), 114.87 (C_{11b}), 111.54 (C_{14}), 32.32 (C_9), 31.54 (C_8), 22.75 (C_{10}), 22.43 (C_7), 21.74 (C_{12}-CH_3). MS : m/z (%) 356 (M^+ 100%), 358 (M+2, 18%); Anal. calcd. for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86; Found: C, 77.49; H, 5.67; N, 7.88%.

2.4b *14-Methyl-7,8,9,10-tetrahydroquinolino[2′,3′:8,7]cyclooct[b]indole-6-carboxylic acid (**11b**)*: Yellow solid; yield: 80%; M.p. > 300°C IR (KBr, cm^{-1}) υ_{max} : 3449 (O-H), 1705 (C=O), 1614 (C=N); ^{1}H NMR (DMSO) δ: 11.23 (s, 1H, acid OH), 9.18 (b s, N_{15}-H). 7.85–7.78 (m, 2H, C_3 and C_4-H), 7.47–7.30 (m, 3H, C_2, C_5 and C_{11}-H), 7.10–7.05 (m, 2H, C_{12} & C_{13}-H), 3.30–3.05 (m, 4H, C_7 & C_{10}-CH2), 2.50 (s, 3H, C_{14}-CH_3), 2.15–1.80 (m, 4H, C_8 & C_9-CH_2); ^{13}C NMR (DMSO) δ: 173.12 (C_6-COOH), 157.56 (C_{1a}), 152.76 (C_6), 147.10(C_{2a}), 132.34 (C_{7a}), 131.06 (C_{1b}), 130.86 (C_{15a}), 128.57 (C_2), 127.68 (C_3), 126.86 (C_{4a}), 126.10 (C_4), 124.54 (C_5), 122.44 (C_{6a}), 122.18 (C_{11}), 121.11 (C_{12}), 120.89 (C_{13}), 115.05 (C_{11b}), 113.31 (C_{14}), 32.65 (C_9), 31.23 (C_8), 22.34 (C_{10}), 22.15 (C_7) 16.50 (C_{14}-CH_3). MS : m/z (%) 356 (M^+ 100%), 358 (M+2, 18%); Anal. calcd. for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86; Found: C, 77.49; H, 5.67; N, 7.88%.

2.4c *12-Chloro-7,8,9,10-tetrahydroquinolino[2′,3′:8,7]cyclooct[b]indole-6-carboxylic acid (**11c**)*: Brown solid; yield: 82%; M.p. > 300°C IR (KBr, cm^{-1}) υ_{max} : 3434 (O-H), 1720 (C=O), 1602 (C=N);. ^{1}H NMR (DMSO) δ: 11.15 (b s, 1H, acid OH), 9.20 (b s, 1H, N_{15}-H) 7.98–7.80 (m, 2H, C_3 and C_4-H), 7.52–7.29 (m, 3H, C_2, C_5 and C_{11}-H), 7.20–7.10 (m, 2H, C_{13} and C_{14}-H), 3.20–1.78 (m, 8H, C_7, C_8, C_9 and C_{10}-CH_2). ^{13}C NMR (DMSO) δ: 174.10 (C_6-COOH), 156.89 (C_{1a}), 152.14 (C_6), 147.64 (C_{2a}), 132.27 (C_{7a}), 132.14 (C_{1b}), 131.02 (C_{15a}), 128.89 (C_2), 127.98 (C_3), 127.12 (C_{11a}), 126.24 (C_4), 125.03 (C_5), 124.13 (C_{12}), 122.53 (C_{6a}), 122.54 (C_{11}), 120.11 (C_{13}), 115.50 (C_{11b}), 113.89 (C_{14}), 32.34 (C_9), 31.76 (C_8), 22.65 (C_{10}), 22.54 (C_7). MS : m/z (%) 375 (M^+ 100%), 377 (M+2, 18%); Anal. calcd. for $C_{22}H_{17}N_2O_2Cl$: C, 70.12; H, 4.55; N, 7.43; Found: C, 70.14; H, 4.53 N 7.45%.

2.4d *7,8,9,10-Tetrahydroquinolino[2′,3′:8,7]cyclooct[b]indole-6-carboxylic acid (**11d**)*: Pale yellow solid; yield: 78%; M.p. > 300°C IR (KBr, cm^{-1}) υ_{max} : 3272 (O-H), 1727 (C=O), 1632 (C=N);. ^{1}H NMR (DMSO) δ: 11.10 (s, 1H, acid-OH). 8.99 (b s, 1H, N_{15}-H), 7.80–7.69 (m, 2H, C_3 and C_4-H), 7.60–7.32 (m, 3H, C_2, C_5 and C_{11}-H), 7.20–7.00 (m, 3H, $C_{12,}$ C_{13} and C_{14}-H), 3.35–1.80 (m, 8H, C_7, C_8, C_9 and C_{10}-CH_2); ^{13}C NMR (DMSO) δ: 173.79 (C_6-COOH), 156.75 (C_{1a}), 152.27 (C_6), 147.29 (C_{2a}), 136.89 (C_{7a}), 132.89 (C_{1b}), 131.19 (C_{15a}), 128.90 (C_2), 127.65 (C_3), 127.18 (C_{11a}), 126.83 (C_4), 125.42 (C_5), 122.32 (C_{6a}), 121.72 (C_{11}), 119.67 (C_{12}), 118.68 (C_{13}), 115.64 (C_{11b}), 113.72 (C_{14}), 32.14 (C_9), 31.54 (C_7), 22.89 (C_{10}). 22.32 (C_7). MS : m/z (%) 342 (M^+ 100%), 344 (M+2, 18%); Anal. calcd. for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18; Found: C, 77.16; H, 5.31, N 8.21%.

3. Results and Discussion

In this paper we have have developed a facile process for a highly efficient assembly of cyclooct[*b*]indole with quinoline and pyrazino pyrido moiety under $POCl_3$ condition and via Pfitzinger reaction in which 1-oxo-1,2,3,4,5,6-hexahydrocyclooct[*b*]indoles **6** were used as a potential precursors.

In order to obtain 6-chloro-7,8,9,10-tetrahydroquinolino[2′,3′:8,7]cyclooct[*b*]indole **8**, 1-oxo-1,2,3,4,

5,6-hexahydrocyclooct[*b*]indole **6** was refluxed with anthranilic acid under toluene and *p*-TsOH/$POCl_3$ condition. The direct condensation of 1-oxo-1,2,3,4,5,6-hexahydrocyclooct[*b*]indole (**6**, 0.001 mol) with anthranilic acid (0.001 mol) under toluene and *p*-TsOH/$POCl_3$ did not lead to the expected quinolino[2′,3′:8,7]cyclooct[*b*]indole **8**. When the same reaction was carried under phosphorous oxychloride condition at 140°C for 16 h the targeted product 6-chloro-7,8,9,10-tetrahydroquinolino[2′,3′:8,7]cyclooct[*b*]indole **8** was obtained (scheme 1).

The disappearance of carbonyl stretching frequency and the presence of –C=N at 1572 cm^{-1} in its IR spectrum revealed the formation of **8**. In its ^{1}H-NMR spectrum the appearance of N_{15}-H signal at δ 9.00, seven protons in the aromatic region at δ 8.30–7.15, eight protons of four methylene group (C_7,C_8,C_9,C_{10}) at δ 3.50–1.00 and a singlet for C_{12} methyl proton at δ 2.50, respectively. Its ^{13}C spectrum revealed the presence of 22 carbon atoms. Spectral and analytical data of **8a** reported in experimental section of this paper fully support the structure assigned to it. From the spectral and analytical data, the obtained compounds was confirmed as 6-chloro-12-methyl-7,8,9,10-tetrahydroquinolino[2′,3′:8,7]cyclooct[*b*]indole (**8a**). A similar series of compounds were derived from **6b–d** to yield **8b–d**. Similarly, the yield, mp, spectral data and analytical data of **8b–d** are reported in experimental section of this paper, fully support the structures assigned to them.

3.1 *Mechanism for the formation of product 8*

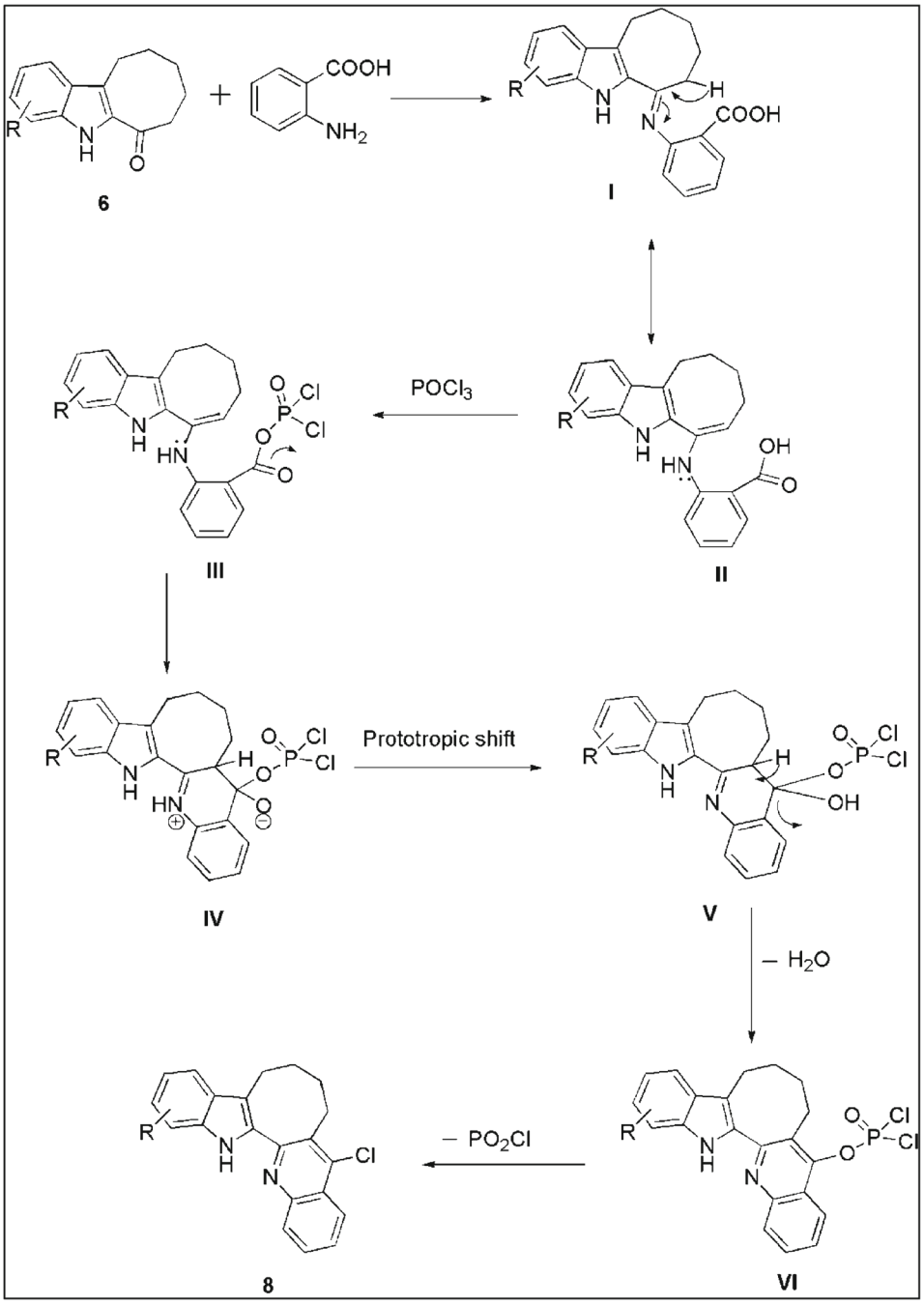
A plausible mechanism for the formation of product **8** is depicted in (scheme 4).[20] The compound 1-oxo-1,2,3,4,5,6-hexahydrocyclooct[*b*]indole **6** underwent phosphorous oxychloride acid catalysed condensation with anthranilic acid to give an intermediate (**I**) which was in equilibrium with the intermediate N-aryl enamine form (**II**). The reaction of excess phosphorous oxychloride with the intermediate **I** gave the mixed anhydride intermediate (**III**). The intramolecular electrophilic substitution reaction at the second position of the cyclooct[b]indole intermediate facilitated by the lone pair electron on nitrogen of the N-aryl moiety, with the aryl mixed anhydride carbonyl group afforded the intermediate (**IV**). On subsequent prototropic shift, dehydrogenation and chlorination followed by PO_2Cl elimination yielded the final product 6-chloro-7,8,9,10-tetrahydroquinolino[2′,3′:8,7]cyclooct[*b*]indole **8** (scheme 4).

In an attempt to extend this synthesis, 1-oxo-1,2,3,4,5,6-hexahydrocyclooct[*b*]indole **6** was reacted with 3-aminopyrazine-2-carboxylic acid under $POCl_3$ condition at 140°C for 16 h to afford 6-chloro-7,8,9,10-tetrahydro(pyrazino[2″,3″-e′]pyrido)-[2′,3′:8,7]cyclooct[*b*]indole **10**. A mixture of the appropriate 1-oxo-1,2,3,4,5,6-hexahydrocyclooct[*b*]indole (**6**, 0.001 mol) and 3-aminopyrazine-2-carboxylic acid (0.001 mol) in 20 mL of phosphorous oxychloride was refluxed at 140°C for 16 h.

In its IR spectrum C=N stretching was observed at 1613 cm^{-1}. The ^{1}H NMR spectrum exhibited a broad singlet at δ 9.00 corroborating the presence an indole NH moiety. The presence of C_3 and C_4 protons are indicated by two doublets in the region δ 7.69 and 7.58 with J = 8.00 Hz. A cluster of multiplets between δ 7.50–6.95 was due to $C_{11,}$ C_{13} and C_{14}-H. A cluster of multiplets between δ 3.25–1.50 was due to C_7, C_8, C_9 and C_{10}-H. A singlet at δ 2.50 indicates the presence of C_{12}-CH_3. Its ^{13}C NMR spectrum confirmed the presence of 17 carbons. From the spectral and analytical data, the obtained compounds were confirmed as 6-chloro-12-methyl-7,8,9,10-tetrahydro(pyrazino[2″,3″-e′]pyrido)-[2′,3′:8,7]cyclooct[*b*]indole (**10a**). A similar series of compounds were derived from **6b–d** to yield **10b–d**.

The synthesis of the targeted tetrahydroquinolino[2′,3′:8,7]cyclooct[*b*]indole-6-carboxylic acid **11** was carried out as outlined in scheme 5.[21] The versatile Pfitzinger reaction was utilized to synthesize the tetrahydroquinolino[2′,3′:8,7]cyclooct[*b*]indole-6-carboxylic acid **11** in satisfactory yields by reacting isatin with 1-oxo-1,2,3,4,5,6-hexahydrocyclooct[*b*]indole **6**. The Pfitzinger reaction (also known as the Pfitzinger–Borsche reaction) is the chemical reaction of isatin with base and a carbonyl compound to yield substituted carboxylic acids. The reaction proceeded in ethanol in the presence of KOH. The product was obtained only in moderate yield. The best result was obtained when the reaction was performed in the presence of NaOH instead of KOH. The yield of the products **11** thus obtained was compared in table 1. Inorder to get tetrahydroquinolino[2′,3′:8,7]cyclooct[*b*]indole-6-carboxylic acid **11**, a mixture of the respective 1-oxo-1,2,3,4,5,6-hexahydrocyclooct[*b*]indole (**6**, 1 mmol) was reacted with isatin (1 mmol) and NaOH (0.400 g) in ethanol (20 mL) was refluxed in a steam bath for 24 h.

Its IR spectrum shows absorptions at 3400, 1712 and 1605 cm^{-1} due to the presence of carboxylic acid OH, -C=O and -C=N, respectively. Its ^{1}H NMR spectrum showed the carboxylic acid OH at δ 11.40. A broad singlet at δ 9.20 was due to the presence of indole NH. A cluster of multiplet between δ 8.00–7.70 was due to the presence of C_3 and C_4-H. A multiplet between δ 7.39 and 7.29 was due to the presence of C_4, C_5 and C_{11}-H.



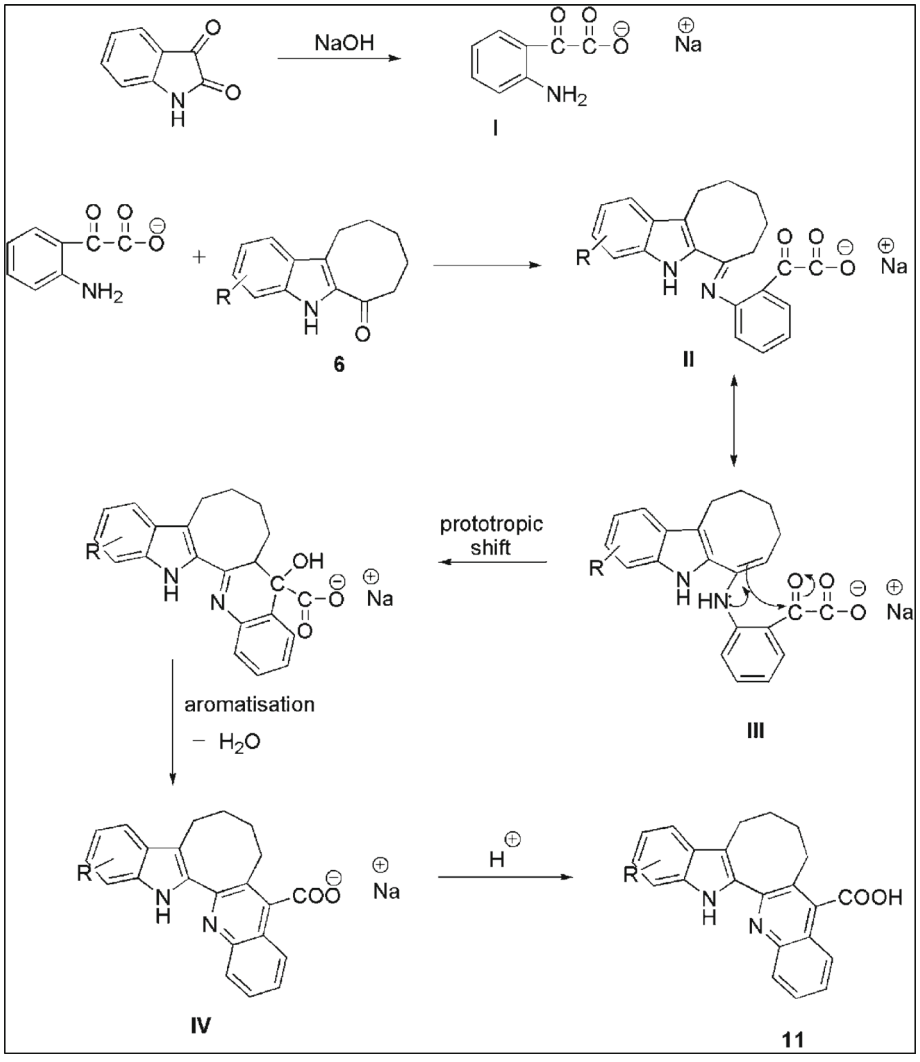
Scheme 4. Mechanism for the formation of product **8**.

A multiplet between δ 7.20 and 6.95 was due to the presence of C_{13} and C_{14}-H. A multiplet between δ 3.30 and 1.80 was due to the presence of C_7, C_8, C_9 and C_{10}-H. A singlet at δ 2.56 was due to the presence of C_{12}-CH_3, respectively. Its ^{13}C NMR spectrum confirmed the presence of 23 carbons.

From the spectral and analytical data, the obtained compounds were confirmed as 12-methyl-7,8,9,10-tetrahydroquinolino[2′,3′:8,7]cyclooct[*b*]indole-6-carboxylic acid (**11a**). A similar series of compounds were derived from **6a–d** to yield **11a–d**.

3.2 *Mechanism for the formation of product **11***

As shown in scheme 5, the isatin is converted by the action of sodium hydroxide into the salts of isotoic acid **I**. Isotoic acid **I** condenses with 1-oxo-1,2,3,4,5,6-hexahydrocyclooct[*b*]indole **6** releases water, forming the salt **II**. The salt **II** undergoes tautomerization followed by prototropic shift gave the intermediate **III**. The latter **III** undergo aromatization with the release of water gave salts of 7,8,9,10-tetrahydroquinolino[2′,3′:8,7]cyclooct[*b*]indole-6-car-



Scheme 5. Mechanism for the formation of product **11**.

Table 1. Comparison of the yield of the product **11**.

Compounds 3, 4, 5	R^1	R^2	R^3	Product **11** Yield using NaOH (%)	Product **11** Yield using KOH (%)
a	H	H	CH_3	**37**	**85**
b	CH_3	H	H	**32**	**80**
c	Cl	H	H	**27**	**82**
d	H	H	H	**41**	**78**

boxylic acid **IV**, the treatment of which with acid gives the required compound **11**.[22]

4. Conclusion

From the literature survey and to the best of our knowledge, first time we report here the rapid synthesis of 6-chloro-7,8,9,10-tetrahydroquinolino[2′,3′:8,7]cyclooct[*b*]indole, 6-chloro-7,8,9,10-tetrahydro(pyrazino[2″,3″-e′]pyrido)-[2′,3′:8,7]cyclooct[*b*]indole and 6-chloro-7,8,9,10-tetrahydroquinolino[2′,3′:8,7]cyclooct[*b*]indole-6-carboxylic acids. The methodology of the synthesis of a variety of novel bioactive cyclooct[*b*]indole incorporating quinoline and pyrazino pyrido moiety under $POCl_3$ conditions using 1-oxo-1,2,3,4,5,6-hexahydrocyclooct[*b*]indoles with anthranillic acid and 3-amino pyrazine acid and isatin has been developed and their structural features were identified. The present methodology gives significant advantages such as simple procedure, easy work-up, clean reaction profile and excellent percentage of yields.

Supplementary information

The ^{1}H and ^{13}C NMR spectra of all new compounds are included in the supplementary information (see www.ias.ac.in/chemsci).

Acknowledgements

We thank the Indian Institute of Technology (IIT) Madras, Chennai, and Indian Institute of Chemical Technology (IICT) Hyderabad, India for their support in spectral studies.

References

1. Humphrey G R and Kuethe J T 2006 *Chem. Rev.* **106** 2875
2. Keawpradub N, Eno-Amooquaye E, Burke P J and Houghton P 1999 *Planta Med.* **65** 311
3. Mayerl F and Hesse M 1978 *Helv. Chim. Acta* **61** 337
4. Keawpradub N, Kirby G C, Steele J C P and Houghton P J 1999 *Planta Med.* **65** 690
5. Wright C W, Allen D, Cai Y, Phillipson J D, Said J M, Kirby G C and Warhurst D C 1992 *Phytother. Res.* **6** 121
6. Edwankar C R, Edwankar R V, Deschamps J R and Cook J M 2012 *Angew. Chem. Int. Ed.* **51** 11762–11765.
7. Jampilek J, Dolezal M, Kunes J, Buchta V and Kralova, K 2005 *Med. Chem.* **1** 591
8. Roth H J, Fenner H. 2000 In *Arzneistoffe*, 3rd ed. In Deutscher Apotheker; Verlag: Stuttgart; pp 51–114
9. Musiol R, Jampilek J, Buchta V, Silva L, Niedbala, H, Podeszwa B, Palka A, Majerz-Maniecka K, Oleksyn B and Polanski J 2006 *Bioorg. Med. Chem.* **14** 3592
10. Harris C R and Thorarensen A 2004 *Curr. Med. Chem.* **11** 2213
11. Vangapandu S, Jain M, Jain R, Kaur S and Singh P P 2004 *Bioorg. Med. Chem.* **12** 2501
12. Andries K, Verhasselt P, Guillemont J, Gohlmann H W, Neefs J M, Winkler H, Van Gestel J, Timmerman P, Zhu M, Lee E, Williams P, de Chaffoy D, Huitric E, Hoffner S, Cambau E, Truffot-Pernot C, Lounis N and Jarlier V 2005 *Science* **307** 223
13. Vinsova J, Imramovsky A, Jampilek J, Monreal-Ferriz J and Dolezal M 2008 *Anti-infective Agents Med. Chem.* **7** 12
14. Sissi C and Palumbo M 2003 *Curr. Med. Chem. Anti-Canc. Agents* **3** 439
15. Mekouar K, Mouscadet J F, Desmaele D, Subra F, Leh, H, Savoure D, Auclair C and d'Angelo J 1998 *J. Med. Chem.* **41** 2846
16. Polanski J, Zouhiri F, Jeanson L, Desmaele D, d'Angelo J, Mouscadet J, Gieleciak R, Gasteiger J and Bret M L 2002 *J. Med. Chem.* **45** 4647
17. Polanski J, Niedbala H, Musiol R, Tabak D, Podeszwa B, Gieleciak R, Bak A, Palka A and Magdziarz T 2004 *Acta Poloniae Pharm. Drug Res.* **61** 3
18. Pommier Y, Johnson A A and Marchand C 2005 *Nat. Rev. Drug. Discov.* **4** 236
19. Zouhiri F, Danet M, Bernard C, Normand-Bayle M, Mouscadet J F, Leh H, Thomas C M, Mbemba G, d'Angelo J and Desmaele D 2005 *Tetrahedron Lett.* **46** 2201
20. Prabakaran K and Prasad K J R 2010 *Syn. Comm.* **40** 3528
21. Pfitzinger W 1886 *J. Prakt. Chem.* **33** 100
22. Prabakaran K 2009 *Synthetic Studies on Hetero-annulated Carbazoles*, Ph.D. Thesis, Bharathiar University, Coimbatore, Tamil Nadu, India