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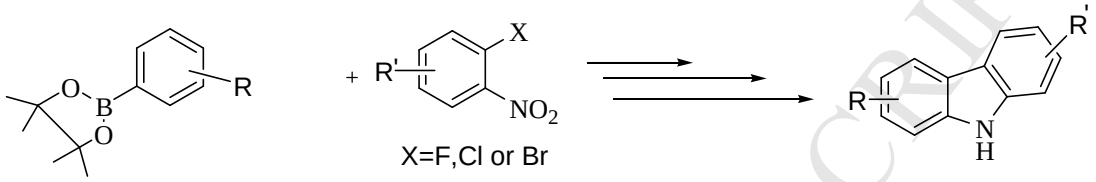

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Total synthesis of carbazole alkaloids

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ABSTRACT

A Suzuki-Miyaura cross coupling, followed by triphenylphosphine mediated Cadogan reductive cyclization sequence provided efficient access to a series of carbazole alkaloids.
In the present work, this approach was applied to the total synthesis of mukonine, clauszoline K, koenoline, murrayanine, murrayafoline A, mukoeic acid, glycoborine, glycozolicine, mukolidine, mukoline, glycozoline, 3-methoxy-9*H*-carbazole-1-carboxylic acid methyl ester, (3-methoxy-9*H*-carbazol-1-yl)-methanol, 3-methoxy-9*H*-carbazole-1-carbaldehyde, 3-methoxy-9*H*-carbazole-1-carboxylic acid, 2-methyl-9*H*-carbazole and nonsteroidal anti-inflammatory drug (NSAID) carprofen and its derivatives.

1. Introduction

Carbazole derivatives are well known for their pharmacological activities. Due to their biological and pharmacological activities,[1] carbazoles are important targets for natural product synthesis. Carbazole (Fig. 1) was isolated first from coal tar in 1872 by Graebe and Glazer.[2]

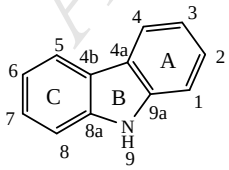

Fig. 1. Structure of Carbazole

Carbazole ring is present in a variety of naturally occurring medicinally active substances. A large number of biologically active carbazole alkaloids have been isolated from natural sources.[3-11]

Carbazole alkaloids and its derivatives are having extensive potential applications in the field of medicinal chemistry as anti-tumor,[4,12] antiplatelet aggregative,[13] antibiotic,[4,14,15] anti-viral,[16-18] anti-plasmodial,[19] anti-convulsant,[20] and sigma receptor antagonist[21,22] properties. Because of their importance, a large number of methodologies have been developed to construct the skeleton of substituted carbazole analogues. These include Fischer–Borsche synthesis,[23] Graebe–Ullmann synthesis,[24] and conversion of indole derivatives to carbazoles.[25] Although numerous synthetic approaches to substituted

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carbazoles have been reported, improvement is still needed to provide a step economic and regioselective method. In the synthesis of carbazoles, regioselective installation of appropriate substituents on the eight different available sites in the aromatic ring systems is a challenging task.

One of the most common methods for carbazole synthesis involves the reductive cyclization of 2-nitrobiphenyl derivatives in the presence of suitable organophosphorus reagents.[26] This method is commonly referred to as the Cadogan cyclization and has a number of advantages, which include increased substrate scope and functional group tolerance, and more precise regiocontrol of functional group placement within the product. Many substituents are tolerated in this reductive cyclization, which represents the best procedure for the cyclization of the 2-nitrobiphenyls to the carbazole derivatives. The starting materials 2-nitrobiphenyl derivatives are easily prepared by the Suzuki-Miyaura cross-coupling of haloarenes with arylboronic acids.

Suzuki-Miyaura reaction is a palladium catalyzed cross-coupling reaction between organic boron compounds and organic halides.[27-30] This is relatively simple and versatile C-C bond formation reaction can be extended to various substrates and therefore finds wide application for the synthesis of pharmaceuticals and total synthesis of complex natural products.

Herein, we report a concise and efficient total synthesis of carbazole alkaloids mukonine,[31] koenoline, murrayafoline A, murrayanine, mukoeic acid, clauszoline K,[32] glycoborine,[33,34] glycozolicine,[35] glycozoline,[34,36] mukolidine, mukoline, 3-methoxy-9*H*-carbazole-1-carboxylic acid methyl ester, (3-methoxy-9*H*-carbazol-1-yl)-methanol, 3-methoxy-9*H*-carbazole-1-carbaldehyde, 3-methoxy-9*H*-carbazole-1-carboxylic acid, 2-methyl-9*H*-carbazole and anti-inflammatory drug carprofen and its derivatives from commercially available simple starting materials utilizing a Suzuki-Miyaura cross coupling reaction, followed by Cadogan reductive cyclization in good to excellent yields (see Fig. 2). This methodology provides an efficient route to carprofen with no deschloro impurity and its derivatives.

The first carbazole alkaloid to be isolated from plant source was murrayanine (**5**) extracted from the stem bark of the small tree *Murraya Koenigii* (*Fam. Rutaceae*)[37] an Indian medicinal plant commonly known as “curry-leaf tree”. It exhibits antimicrobial properties against human pathogenic fungi.[38] Since then, the field has expanded enormously large due to the promising biological activities of many of the carbazole alkaloids.

Mukoeic acid (**6**), isolated from the bark of the Murraya koenigii. It represents the first carbazole carboxylic acid isolated from a plant source.[39] The corresponding methyl ester of mukoeic acid, mukonine (**2**) was isolated in 1978 by Chakraborty et al. from *Murraya koenigii*[40] and later also by Wu et al. from *Clausena excavata*.[13,41] The shrub *clausena excavata* is traditionally used in China for the treatment of snakebites, abdominal pain and as a detoxification agent.

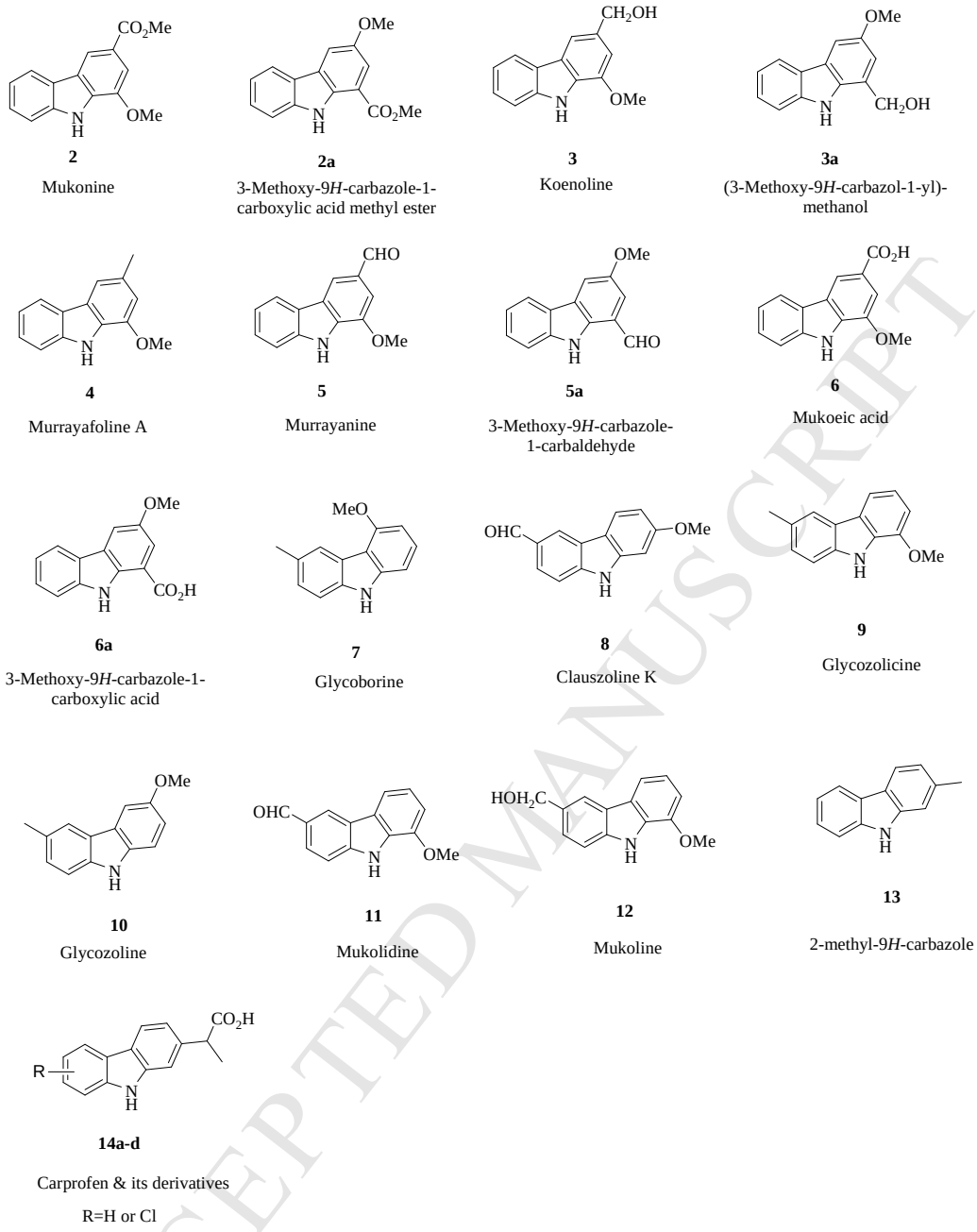


Fig. 2. Structures of carbazole alkaloids

Koenoline (**3)**, a carbazole alkaloid, has been isolated from the root bark of *Murraya koenigii* for the first time as a natural product by M.Fiebig et al.[42] Its structure was established as 1-methoxy-3-hydroxymethylcarbazole by analysis of spectroscopic data and was confirmed by partial synthesis from murrayanine isolated from *M. siamensis* roots. It shows the biological activities such as cytotoxic, antiproliferative activities against MCF-7 breast adenocarcinoma cell line.[43]

Murrayafoline A (**4)** exhibited strong fungicidal activity against *Cladosporium cucumerinum* which was isolated from the root of several species of the Murraya.[44,45]

Chakravarty and co-workers isolated glycoborine (**7**), from the root of *Glycosmis arborea*.[33] This was the first 5-oxygenated tricyclic natural carbazole ever isolated.[33]

In 1992, Bhattacharyya et al. isolated glycozolicine (**9**) from the roots of *Glycosmis pentaphylla*[46] and its structure assigned as the isomeric 5-methoxy-3-methyl-9*H*-carbazole, but in 2001, Chakravarty et al. reassigned its structure as 8-methoxy-3-methylcarbazole (**9**) on the basis of the total syntheses of both isomeric compounds and the comparison of spectroscopic data with those of the natural product.[33] This structural assignment was confirmed by synthesis via Fischer indolization of 2-methoxyphenylhydrazine and 4-methylcyclohexanone.[33] It exhibits moderate antimicrobial activity.[47]

Carbazoles Mukolidine (**11**) and mukoline (**12**) were isolated from the root, leaves, and fruit of *Murraya koenigii* Spreng,[48] whose extracts exhibit antibacterial activity.[49] Chakraborty et al. confirmed the structures for **11** and **12** by their total syntheses, which included a Fischer–Borsche cyclization as the key step. Tamariz et al. described the total syntheses of **11** and **12** by using a Diels–Alder cycloaddition of a 4,5-dimethylene oxazolidin-2-one and acrolein as the key step.[50]

A wide range of 6-oxygenated carbazole alkaloids has been isolated from natural sources. Glycozoline (**10**) was the first member of this class of alkaloids and originally isolated from the stem bark of *Glycosmis pentaphylla*[51] and later also by Chakravarty et al. from the roots of *G.arborea.*[52] It exhibits antibacterial, antifungal, antifeedant and antiinflammatory properties.[53]

The spectroscopic data confirmed that glycozoline is 6-methoxy-3-methylcarbazole.[52,54] Chemical support for this structural assignment was derived through transformation into known carbazole derivatives[54] and total synthesis.[55]

In 1997, Ito et al. described the isolation and structural elucidation of clauszoline K (**8**)[56] from the stem bark of the Chinese medicinal plant *Clausena excavata*.

Carprofen is a non-narcotic, non-steroidal anti inflammatory drug (NSAID) with characteristic analgesic and antipyretic activity.[57-59] NSAIDs are classified as arylpropionic acid derivates, with the characteristic of an iso-propionic acid group bound on an aromatic compound.

NSAIDs are commonly used to treat acute and chronic pain. NSAIDs produce their beneficial action by inhibiting the two isoforms of the cyclooxygenase (COX) enzyme, COX-1 and COX-2.[60,61] These enzymes convert arachidonic acid into prostaglandins and thromboxane, which are important physiological and pathological effectors.

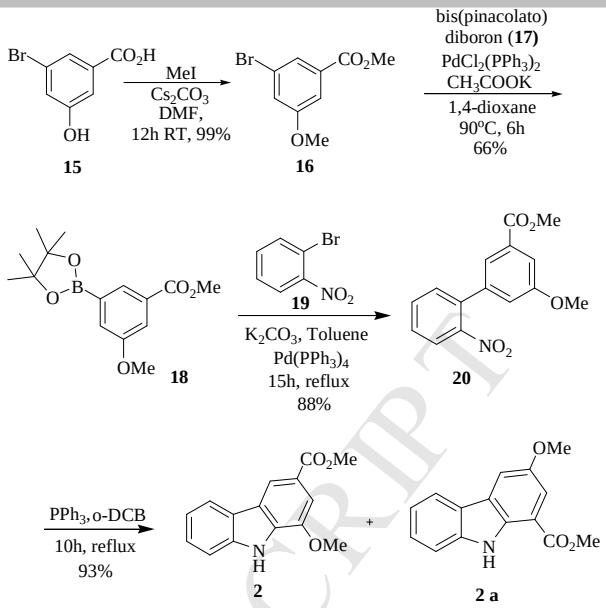
The anti-inflammatory effect of Carprofen is caused by an inhibition of the COX-2 activity. COX-2 is the second enzyme of the conversion of arachidonic acid to prostaglandin H2 (PGH2), which is the first step in the prostanoid synthesis that causes pain and inflammation.[62] Carprofen binds as a competitive inhibitor in the active site of COX-2.[63]

2. Results and discussion

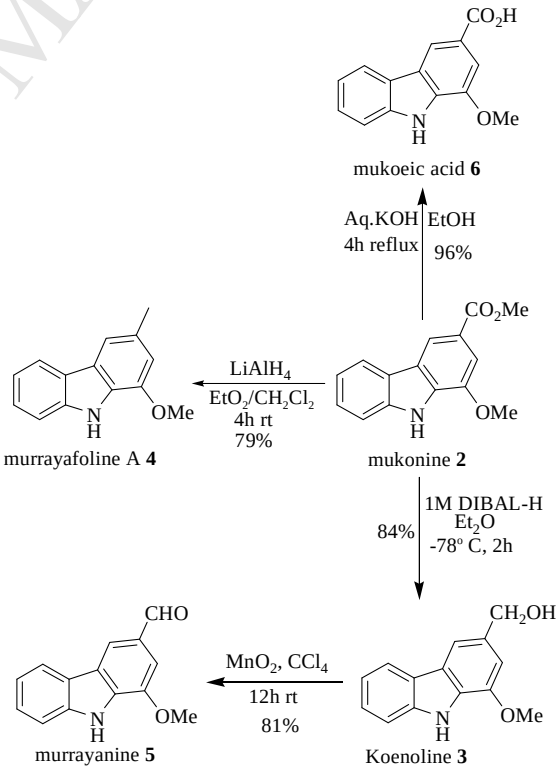
Carbazole natural product mukonine (**2**)[31,64-68] is an alkaloid from the Indian curry-leaf tree (*Murraya*

Koenigii).[7,8] We synthesize mukonine (**2**) starting from 3-bromo-5-hydroxybenzoic acid, which is converted into 3-bromo-5-methoxybenzoic acid methyl ester (**16**) in 99% yield. This ester **16** was treated with Bis(pinacolato)diboron (**17**) in 1,4-dioxane under nitrogen atmosphere to get 3-methoxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid methyl ester (**18**) in 66% yield. We carried out Suzuki-Miyaura cross-coupling reaction of compound **18** with commercially available *o*-bromonitrobenzene (**19**), followed by reductive cyclization of compound **20**, synthetic route is shown in Scheme 1. Two possibilities exist in **20**, which gives a mixture of **2** and its regioisomer 3-methoxy-9*H*-carbazole-1-carboxylic acid methyl ester **2a** (combined yields of 93%, 2/2a, 2.5:1); Mukonine (**2**) is the major product as a white, crystalline solid in 66% yield. The regioisomer **2a** is obtained in 27% yield as an off-white solid. The spectroscopic data of synthetic **2** are in full agreement with those reported for the natural product.[65] The structure of **2a** was assigned on the basis of HRMS, ^{1}H and ^{13}C NMR spectroscopic data.

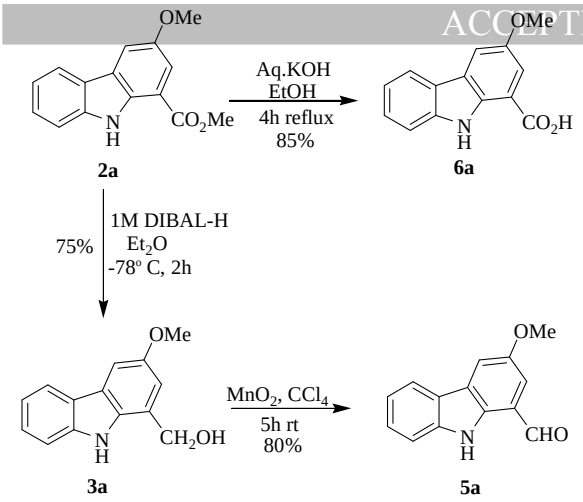
Starting from mukonine (**2**), the alkaloids **3-6** were synthesized in a few steps (Scheme 2). Reduction of **2** with diisobutylaluminum hydride[66c,69] provided Koenoline (**3**) in 84% yield. Reduction of ester **2** with lithium aluminum hydride in diethyl ether gave **4** in 79% yield. Murrayanine (**5**)[70] was obtained by oxidation of **3** with manganese dioxide. Saponification of **2** with potassium hydroxide in water and ethanol gave Mukoeic acid (**6**).[39,71] The spectroscopic data of synthetic **3-6** were identical with those reported in the literature.[42,36b,66c,72]



Scheme 1. Synthesis of mukonine and its regioisomer 3-methoxy-9*H*-carbazole-1-carboxylic acid methyl ester



Scheme 2. Synthesis of koenoline, murrayanine, mukoeic acid and murrayafoline A.

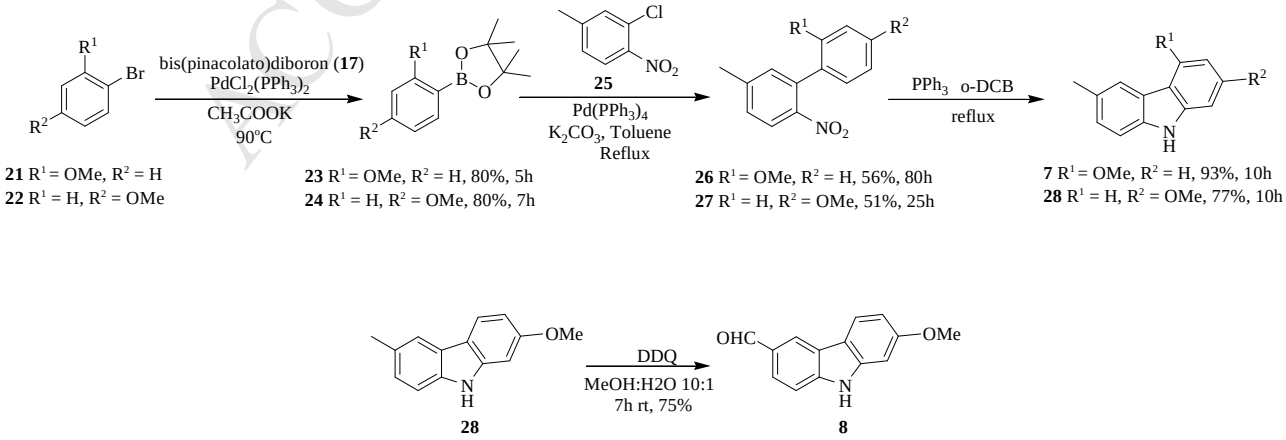


Scheme 3. Synthesis of **3a**, **5a** and **6a.**

Starting from regioisomer **2a**, the alkaloids **3a**, **5a** and **6a** were synthesized in a few steps (Scheme 3). Reduction of **2a** with the milder reducing agent diisobutylaluminum hydride gave (3-methoxy-9*H*-carbazol-1-yl)-methanol (**3a)** in 75% yield. Oxidation of **3a** with manganese dioxide provided 3-methoxy-9*H*-carbazole-1-carbaldehyde (**5a**) in 80% yield. Mukoeic acid (**6**) regioisomer **6a** was obtained by saponification of **2a** with potassium hydroxide in water and ethanol. The structures of **3a**, **5a** and **6a** were determined by Mass, ^{1}H and ^{13}C NMR spectroscopic data.

The glycoborine (**7**) was prepared by treating 2-bromoanisole (**21**) with bis(pinacolato)diboron (**17)** and bis(triphenylphospine)palladium(II)dichloride, potassium acetate in 1,4-dioxane to afford 2-(2-methoxyphenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**23**) in 80% yield. We carried out a Suzuki–Miyaura cross coupling of **23** and 2-chloro-4-methyl-1-nitrobenzene (**25)** by treatment with catalytic amounts of tetrakis(triphenyl phosphine)palladium in the presence of potassium carbonate in toluene afforded 2′-methoxy-5-methyl-2-nitrobiphenyl (**26**) in 56% yield. The reductive cyclization of **26** provided glycoborine (**7**) in 93% yield. The spectral data of **7** agree with those described for the natural[33,34] and synthetic[46,73] products.

For the synthesis of clauszoline K (**8**), we carried out a borlyation reaction of *p*-bromoanisole (**22**) with Bis(pinacolato)diboron (**17**), this reaction afforded 2-(4-methoxy-phenyl)-4,4,5,5-tetra methyl-[1,3,2]dioxaborolane (**24**) in 80% yield. The subsequent Suzuki–Miyaura reaction of **24** with 2-chloro-4-methyl-1-nitrobenzene (**25**) afforded 4′-methoxy-5-methyl-2-nitrobiphenyl (**27**) in 51% yield. The reductive cyclization of compound **27**, followed by oxidation of methyl group of 2-methoxy-6-methyl-9*H*-carbazole **(28**) at C-6 by treatment with DDQ in methanol-water mixture provided clauszoline K (**8**) in 75% yield.



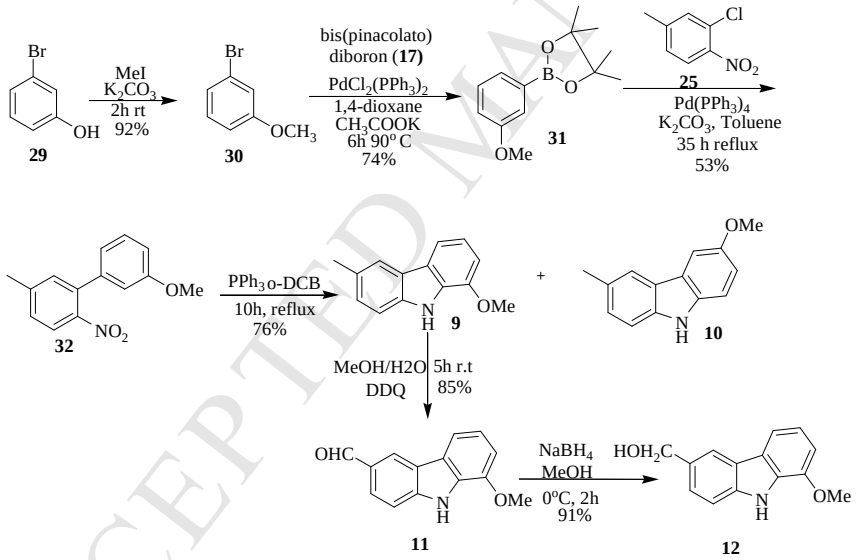
Scheme 4. Synthesis of glycoborine (**7**) and clauszoline K (**8**).

Synthetic route is shown in Scheme 4. The reductive cyclization of **32** provided two products glycozolicine (**9**) and glycozoline (**10**) in 76% yield (combined yield of 76%, 9/10, 1:1).

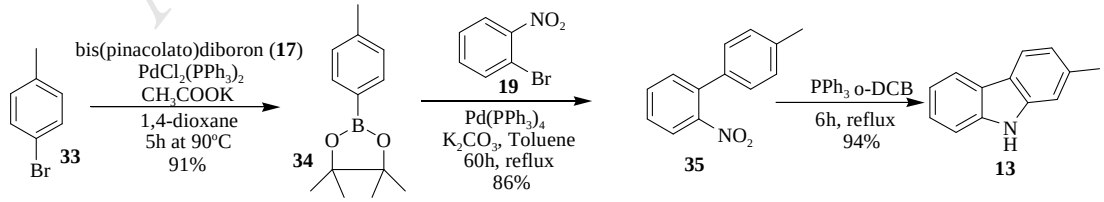
We found that the reaction of 3′-methoxy-5-methyl-2-nitro-biphenyl (**32**) provided two products **9** and **10** in equal amounts.

Starting from glycozolicine (**9**), the alkaloids mukolidine (**11**) and mukoline (**12**) were synthesized in a few steps[48,50] (Scheme 5). The oxidation of the methyl group at C-3 of glycozolicine (**9**) by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) provided mukolidine (**11**) in 85% yield. The reduction of **11** with sodium borohydride gave mukoline (**12**) in 91% yield.

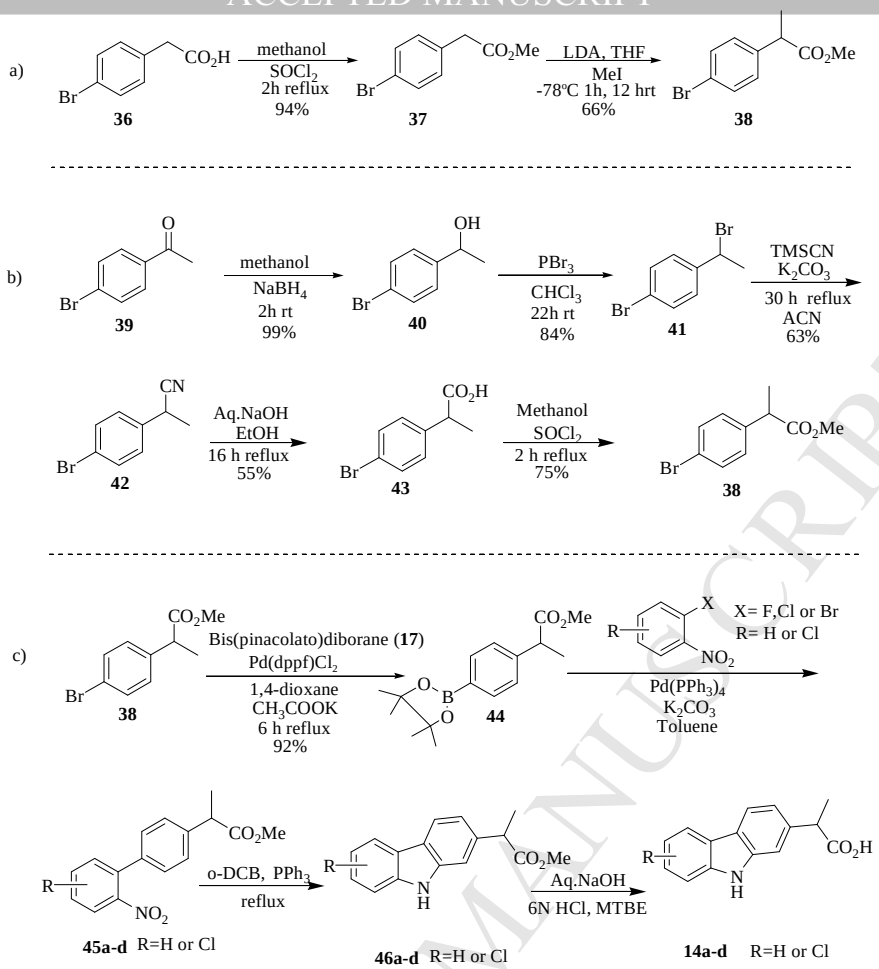
Our approach to the carbazole alkaloids glycozolicine (**9**), glycozoline (**10**), mukolidine (**11**), and mukoline (**12**) started with methylation of 3-bromophenol (**29**) (see Scheme 5). Methylation, followed by boronic acid pinacol ester synthesis provided **31** in 74% yield. The subsequent Suzuki–Miyaura cross coupling of **31** and 2-chloro-4-methyl-1-nitrobenzene (**25)** by treatment with catalytic amount of tetrakis(triphenylphosphine)palladium in the presence of potassium carbonate in toluene afforded 3′-methoxy-5-methyl-2-nitrobiphenyl (**32**) in 53% yield. The spectroscopic data of synthetic **8** are in full agreement with those reported for the natural product.[56,73]



Scheme 5. Synthesis of glycozolicine (**9**), glycozoline (**10**), mukolidine (**11**) and mukoline (**12**).



Scheme 6. Synthesis of 2-methyl-9*H*-carbazole (**13**)



Scheme 7. a) Synthesis of Methyl 2-(4-bromophenyl) propionate (**38**).
b) Synthesis of Methyl 2-(4-bromo phenyl) propionate (**38**) by an alternate route.
c) Synthesis of Carprofen and its analogues.

The spectroscopic data of the synthetic carbazoles **9**, **10**, **11** and **12** were in full agreement with those reported for the corresponding natural products.[33,48]

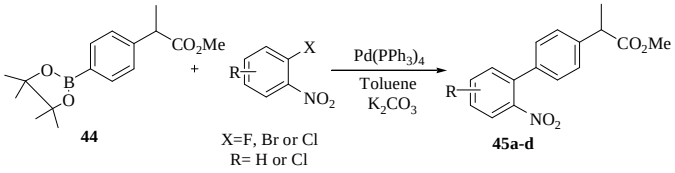
Synthesis of alkaloid 2-methyl-9*H*-carbazole (**13**) started with borylation of 4-bromotoluene (**33**). The palladium catalyzed boronic acid pinacol ester synthesis of 4-bromotoluene with bis(pinacolato)diboron (**17**) provided 4,4,5,5-tetramethyl-2-*p*-tolyl-[1,3,2]dioxa borolane (**34**) in 91% yield. The subsequent Suzuki–Miyaura reaction of **34** with 1-bromo-2-nitrobenzene (**19**) afforded 4′-methyl-2-nitrobiphenyl (**35**) in 86% yield. The reductive cyclization of **35** provided 2-methyl-9*H*-carbazole (**13**) in 94% yield.

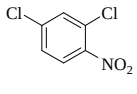
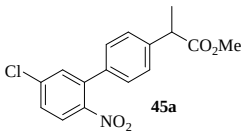
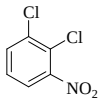
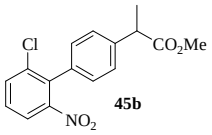
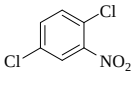
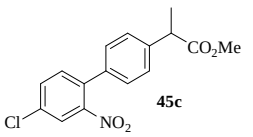
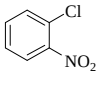
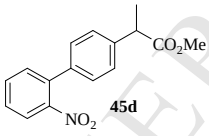
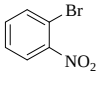
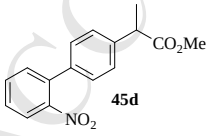
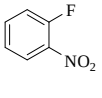
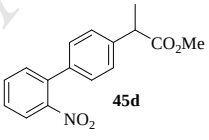
Carprofen was synthesized starting with readily available 4-bromophenyl acetic acid (**36**); the acid was converted to its methyl ester **37** with methanol and catalytic amount of thionyl chloride. Treatment of ester **37** with LDA and methyl iodide gave the methyl derivative **38**.[74]

Methyl derivative **38** was also prepared by an alternative route, starting from commercially available 4′-

bromoacetophenone (**39**). Reduction of the acetophenone The cyanation of compound **41** with TMS cyanide,[76] gave 1-(4-bromophenyl)ethanol (**40**), which was converted into 1-bromo-4-(1-bromoethyl)benzene (**41**) using PBr_3.[75] and hydrolysis of the resulting nitrile (**42**) provided 2-(4-bromo phenyl)propanoic acid (**43**). Esterification of **43** afforded Methyl 2-(4-bromophenyl)propionate (**38**).

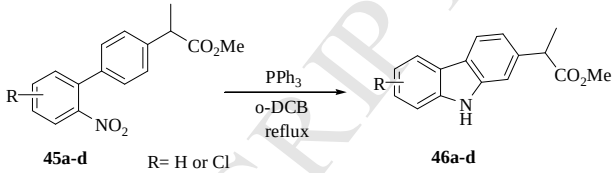
Table 1
2-Nitrobiphenyls prepared by Suzuki-Miyaura cross coupling

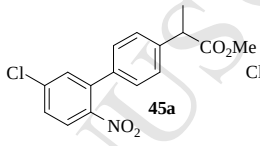
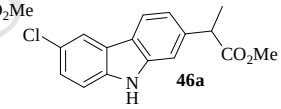
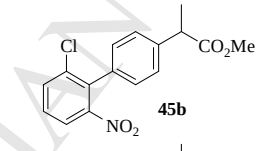
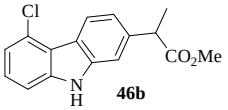
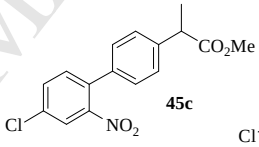
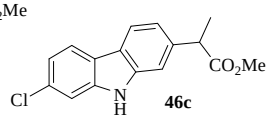
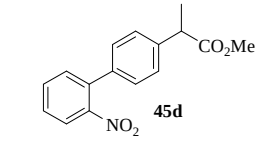
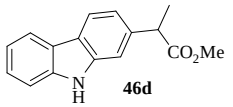


Entry	Halonitro benzne[a]	Nitrobiphenyl	Time (h)	Yield (%)[b]
1		 **45a**	28	54
2		 **45b**	20	56
3		 **45c**	20	58
4		 **45d**	100	71
5		 **45d**	40	81
6		 **45d**	120	10

[a]General conditions: Halonitrobenzene (1.0 eq), Methyl 2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaboralan-2-yl)phenyl] propionate (1.11 eq), $Pd(PPh_3)_4$ (0.011eq), potassium carbonate (2.24 eq), toluene (20 mL), water (2 mL), 100 °C, [b]Isolated yields.

Table 2
Reductive cyclization of nitrobiphenyls to carbazoles



Entry	Nitrobiphenyl[a]	Carbazole	Time (h)	Yield (%)[b]
1	 **45a**	 **46a**	9	89
2	 **45b**	 **46b**	6	77
3	 **45c**	 **46c**	10	88
4	 **45d**	 **46d**	9	81

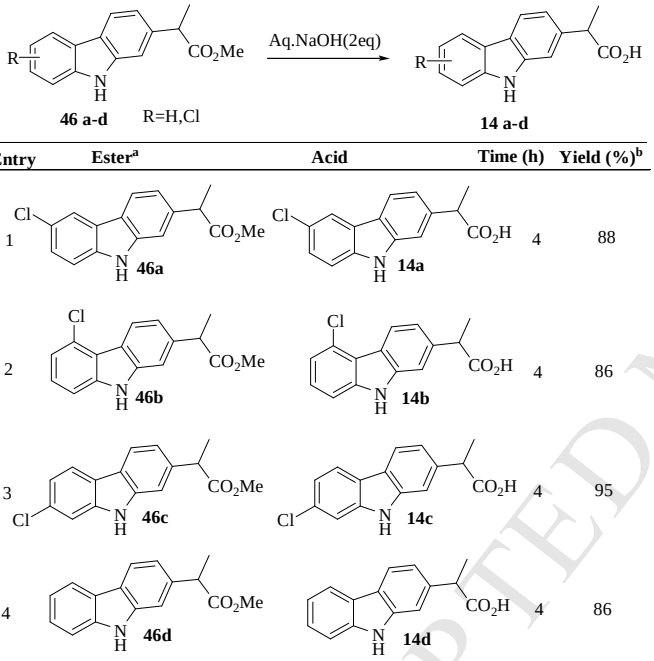
[a]General conditions: Substrate (**45a-d**, 1.0 eq), triphenylphosphine (2.5 eq)**,** o-dichlorobenzene (15 mL), 180–185 °C, 6–10 h, [b] Isolated yields.

Ester **38** was treated with bis(pinacolato)diboron and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium, potassium acetate in 1,4-dioxane to give phenyl dioxaborolane ester **44**.[77]

Nitrobiphenyls **45a-d** (Scheme 7 and Table 1) were synthesized via Suzuki-Miyaura cross coupling of phenyl dioxaborolane **44** and halonitrobenzenes.[78]

Reductive cyclization of the 2-nitro biphenyls **45a-d** using triphenylphosphine in *o*-dichlorobenzene gives carbazole esters **46a-d** (Scheme 7 and Table 2), which was hydrolyzed to carbazole acids **14a-d** in excellent yields by aqueous NaOH (Scheme 7 and Table 3). These conditions provided carprofen (**14a**) in high yield, with no deschloro impurity.

Table 3
Hydrolysis of carbazole ester to acid



Entry	Ester[a]	Acid	Time (h)	Yield (%)[b]
1	**46a**	**14a**	4	88
2	**46b**	**14b**	4	86
3	**46c**	**14c**	4	95
4	**46d**	**14d**	4	86

[a]General conditions: Substrate (**46 a-d**, 1.0 eq), aq.sodium hydroxide solution (2.0 eq), reflux, 4h
[b] Isolated yields.

3. Conclusion

In conclusion, we have reported a convenient method for the total synthesis of eleven natural carbazole alkaloids mukonine (**2**), koenoline (**3**), murrayafoline A (**4**), murrayanine (**5**), mukoeic acid (**6**), glycoborine (**7**), clauszoline K (**8**), glycozolicine (**9**), glycozoline (**10**), mukolidine (**11**), mukoline (**12**) and anti-inflammatory drug carprofen (**14a**) and its analogues via Suzuki-Miayura cross coupling, followed by Cadogan reaction. Our route also provided alkaloids, 2-methyl-9*H*-carbazole (**13**), 3-methoxy-9*H*-carbazole-1-carboxylic acid methyl ester (**2a**), (3-methoxy-9*H*-carbazol-1-yl)-methanol (**3a**), 3-methoxy-9*H*-carbazole-1-carbaldehyde (**5a**) and 3-methoxy-9*H*-carbazole-1-carboxylic acid (**6a**). These carbazole alkaloids (**2a**, **3a**, **5a** and **6a**) are regioisomers of mukonine (**2**), koenoline (**3**), murrayanine (**5**) and mukoeic acid (**6**).

4. Experimental section

4.1 General Description

Solvents and chemicals were purchased from commercial sources and used without further purification. Reverse-phase HPLC analysis was carried out using YMC pack C18 (5µm), 250x4.6 mm. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV 300 & 400-MHz instrument. Chemical shifts (δ) are reported in parts per million (ppm), and coupling constants (J) are reported in Hertz (Hz). Splitting pattern are described as follows; br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Column chromatography was performed on silica gel (100-200 mesh). IR spectra were recorded on a PerkinElmer Spectrum 100 FTIR spectrophotometer as KBr pellets or with the neat product. Mass spectra (MS) were recorded on an API 2000 LCMS/MS AB Sciex spectrometer. HRMS (ESI) were taken on an AB Sciex tripleTOF 5600+ and Bruker Daltonics MicrOTOF mass analyzers. Analytical thin-layer chromatography was carried out using E-Merck 60F254 aluminum-packed plates of silica gel (0.2mm).

Developed plates were visualized by using UV light or potassium permanganate solution.

4.2. 3-Bromo-5-methoxybenzoic acid methyl ester **(16).**

To a mixture of 3-Bromo-5-hydroxybenzoic acid (2.5 g, 11.52 mmol) and cesium carbonate (7.5 g, 23.04 mmol) in DMF (20 mL) was added methyl iodide (4.08 g, 28.8 mmol) at 0 °C. After 10 min. the ice bath was removed and the reaction allowed to warm to room temperature. The reaction mixture was stirred at room temperature for 12 h. The reaction was quenched with water (50 mL) and extracted with methyl *t*-butyl ether (30 mL x 3), combined organic layer was dried over sodium sulfate. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using hexane as an eluent gave the product **16** as a brown syrup (2.8 g, 99%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.48 (s, 1H), 7.23 (s, 1H), 3.91 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.69, 160.23, 132.69, 124.91, 122.70, 122.18, 113.47, 55.76, 52.48; IR (Neat) ν_{max} 2952.04, 1727.14, 1678.80, 1286.68, 1049.20, 766.94 cm^{-1}; MS: m/z 245.2 $(M + H)^+$.

4.3. 3-Methoxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan -2-yl)benzoic acid methyl ester **(18).**

To a stirred solution of **16** (2.5 g, 10.2 mmol) in 1,4-dioxane (30 mL) under nitrogen atmosphere was added bis(pinacolato)diboron (2.58 g, 10.2 mmol), $PdCl_2(PPh_3)_2$ (0.36 g, 0.51 mmol) and potassium acetate (2.0 g, 20.4 mmol) at room temperature, and the reaction mixture was stirred at 90 °C for 6 h under nitrogen atmosphere. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (50 mL). After the dilution, the mixture was filtered through a short pad of celite, and the filtrate was concentrated. The residue was purified by chromatography on a silica gel column (only hexane) provided compound **18**[79] as a white solid (2.0 g, 66%), mp 94.8–100.5 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.64 (s, 1H), 7.51 (d, *J* = 2.40 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 1.35 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.03, 159.16, 131.01, 128.13, 124.55, 117.56, 84.13, 55.53, 52.09, 24.86; IR (KBr) ν_{max} 2996.88, 2975.45, 1716.95, 1597.34, 950.98, 702.29 cm^{-1}; MS: m/z 293.1 $(M + H)^+$.

4.4. 5-Methoxy-2'-nitrobiphenyl-3-carboxylic acid methyl ester **(20).**

To a stirred solution of 1-bromo-2-nitrobenzene (**19**) (1.2 g, 5.94 mmol) in toluene (20 mL) was added $Pd(PPh_3)_4$ (343 mg, 0.297 mmol), **18** (1.73 g, 5.94 mmol) and potassium carbonate (1.64 g, 11.88 mmol), and the resulting mixture was refluxed for 15 h. under nitrogen atmosphere. After cooling to room temperature, the solvent was evaporated. Purification of the residue by column chromatography (silica gel, 2–3% ethyl acetate in hexane) provided **20** as a light green solid (1.5 g, 88%), mp 108.2–111.4 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.0 Hz, 1H), 7.63–7.52 (m, 4H), 7.44 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.03 (s, 1H), 3.91 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.47, 159.67, 148.98, 139.07, 135.43, 132.53, 131.91, 131.87, 128.72, 124.29, 121.59, 118.93,

113.85, 55.64, 52.34; IR (KBr) ν_{max} 2924.68, 1708.46, 1521.88, 1343.61 cm^{-1}; MS: m/z 287.9 $(M + H)^+$.

4.5. Mukonine **(2)** *and its regioisomer 3-methoxy-9H-carbazole-1-carboxylic acid methyl ester* **(2a).**

To a stirred solution of **20** (1.5 g, 5.22 mmol) in 1,2-dichlorobenzene (10 mL) was charged triphenylphosphine (2.74 g, 10.44 mmol) at room temperature, and the reaction mixture was refluxed for 10 h. The reaction mixture was concentrated in vacuo, and the obtained residue was purified by column chromatography to provide products **2a** (2% ethyl acetate in hexane) and **2**[40,66,80] (7–8% ethyl acetate in hexane).

4.5.1. Mukonine **(2).**

(887 mg, 66%), as a white solid, mp 192.4–196.8 °C (lit.[40] mp.198–200 °C), (lit.[80] 169–170 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.80 (s, 1H), 8.45 (s, 1H), 8.22 (d, *J* = 7.6 Hz, 1H), 7.54-7.52 (m, 2H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.21 (t, *J* = 7.4 Hz, 1H), 4.05 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.46, 145.62, 140.64, 133.27, 126.61, 123.43, 123.21, 121.09, 121.04, 120.04, 116.24, 112.26, 106.54, 56.00, 52.28; IR (KBr) ν_{max} 3319.28, 1697.73, 1351.49 cm^{-1}; MS: m/z 256.3 $(M + H)^+$.

4.5.2. 3-Methoxy-9H-carbazole-1-carboxylic acid methyl ester **(2a)**.

(350 mg, 27%), off-white solid, mp 163.8–164.1 °C: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.16 (s, 1H), 8.18 (d, *J* = 7.6 Hz, 1H), 8.08 (d, *J* = 2.8 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 2.4 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.18 (t, *J* = 7.4 Hz, 1H), 4.00 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.67, 152.62, 141.41, 134.36, 126.85, 125.71, 122.00, 120.94, 119.37, 114.38, 112.47, 112.26, 111.06, 56.46, 52.53; IR (KBr) ν_{max} 3415.11, 2925.43, 1681.89, 1485.93 cm^{-1}; MS: m/z 256.2 $(M + H)^+$; HRMS $(M)^+$ calcd for $C_{15}H_{13}NO_3$ 255.0893, found 255.0895.

4.6. Koenoline **(3).**

To a stirred solution of **2** (100 mg, 0.392 mmol) in diethylether (15 mL) under nitrogen was added DIBAL-H (25% in toluene) (335 mg, 0.587 mmol) at -78 °C, and the resulting solution was stirred for 2 h. at the same temperature. The reaction was quenched with water (30 mL), and extracted with dichloromethane (25 mL x 3). The combined organic layers dried over sodium sulfate, and the solvent was evaporated. The residue was purified by column chromatography (silica gel, hexane–ethyl acetate, 80:20) to give **3**[71,66a,c] as a white solid (75 mg, 84%), mp 127.8–129.4 °C (ref.[71] 127 °C), (ref.[66c] 142 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (br s, 1H, exchangeble with D_2O, NH), 8.04 (d, *J* = 8.0 Hz, 1H), 7.65 (s, 1H), 7.46–7.39 (m, 2H), 7.24-7.20 (m, 1H), 6.95 (s, 1H), 4.84 (d, *J* = 4.0 Hz, 2H), 4.02 (s, 3H), 1.69 (br s, 1H, exchangeble with D_2O, -OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.78, 139.46, 132.88, 129.46, 125.80, 124.08, 123.56, 120.51, 119.49, 111.70, 111.05, 105.69, 66.49, 55.57; IR (KBr) ν_{max} 3447.73, 3238.13, 2918.02, 1586.88, 1226.14, 735.13 cm^{-1}.

4.7. Murrayafoline A **(4).**

A mixture of **2** (40 mg, 0.156 mmol) and $LiAlH_4$ (18 mg, 0.47 mmol) in a mixture of CH_2Cl_2–diethylether (20 mL, 1:1) was stirred at 25 °C under nitrogen for 4 h. The reaction was quenched with 2N HCl (10 mL). The reaction mixture was extracted with dichloromethane (20 mL x 3), and combined organic layer was dried over sodium sulfate. The solvent was removed under vacuum and the residue was purified by column chromatography (silica gel, 2% ethyl acetate in hexane) to give **4**[81] (26 mg, 79%) as a pale yellow syrup, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (br s, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.38 (s, 1H), 7.33–7.27 (m, 2H), 7.14–7.08 (m, 1H), 6.64 (s, 1H), 3.89 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.29, 138.42, 128.40, 126.95, 124.45, 123.28, 122.49, 119.40, 118.10, 111.48, 109.86, 106.64, 54.42, 20.88; IR (Neat) ν_{max} 3037.36, 2978.16, 1605.85, 1030.91, 831.93 cm^{-1}; MS: *m/z* 212.0 $(M + H)^+$.

4.8. Murrayanine **(5).**

To a solution of **3** (50 mg, 0.22 mmol) in dry CCl_4 (20 mL) was added MnO_2 (382 mg, 4.4 mmol) at r.t., and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was filtered through celite, and the solvent was removed under vacuum. Purification of the residue by chromatography on a silica gel column (20% ethyl acetate in hexane) provided **5**[66,80] (40 mg, 81%), as a white solid, mp 169.7–171.3 °C (ref.[80] 154–156 °C): ^{1}H NMR (400 MHz, Acetone-d_6) δ 10.94 (br s, 1H), 10.08 (s, 1H), 8.37 (s, 1H), 8.25 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.51–7.47 (m, 2H), 7.32 (t, *J* = 7.4 Hz, 1H), 4.11 (s, 3H); ^{13}C NMR (100 MHz, Acetone-d_6) δ 190.93, 146.41, 140.40, 134.15, 130.29, 126.35, 123.65, 123.49, 120.48, 120.14, 119.54, 111.93, 103.34, 55.25; IR (KBr) ν_{max} 3149.46, 1659.05, 1342.26, 1136.97, 847.24 cm^{-1}; MS: *m/z* 226.0 $(M + H)^+$.

4.9. Mukoeic acid **(6).**

To a solution of **2** (100 mg, 0.391 mmol) in water (10 mL) and ethanol (2 mL) mixture was added potassium hydroxide (44 mg, 0.783 mmol) at 25 °C, and the reaction mixture was refluxed for 4 h. The reaction mixture was filtered through celite and concentrated in vacuo. Silica gel column chromatographic purification of the obtained residue using ethyl acetate-hexane (1:1) as an eluent provided product **6**[66a,c,80] as a light brown solid (90 mg, 96%), mp 226.5–228.8 °C (ref.[80] 215 °C), (ref.[4] 242 °C): ^{1}H NMR (400 MHz, Acetone-d_6) δ 10.77 (br s, 1H), 8.52 (s, 1H), 8.23 (d, *J* = 7.6 Hz, 1H), 7.65-7.63 (m, 2H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 4.09 (s, 3H); ^{13}C NMR (100 MHz, Acetone-d_6) δ 167.58, 145.45, 140.43, 133.14, 126.12, 123.47, 121.87, 120.42, 119.76, 116.03, 111.69, 106.58, 55.17; IR (KBr) ν_{max} 3418.95, 2928.28, 1685.61, 1585.88, 1384.81 cm^{-1}; MS: *m/z* 242.0 $(M + H)^+$.

4.10. (3-Methoxy-9H-carbazol-1-yl)-methanol **(3a).**

To a stirred solution of **2a** (107 mg, 0.419 mmol) in diethylether (20 mL) was added DIBAL-H (25% in toluene) (357 mg, 0.628 mmol) under nitrogen at -78 °C

and the resulting solution was stirred at same temperature for 2 h. The reaction was quenched with water (30 mL) and extracted with dichloromethane (25 mL x 3). The combined organic layers were dried over sodium sulfate and the solvent was removed under vacuum. The residue was purified by column chromatography (silica gel, hexane-ethyl acetate, 9:1) to give **3a** (72 mg, 75%) as a off-white solid, mp 139.2–140.4 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (br s, 1H), 8.02 (d, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 2.0 Hz, 1H), 7.42–7.36 (m, 2H), 7.21–7.17 (m, 1H), 6.87 (d, *J* = 2.0 Hz, 1H), 5.00 (s, 2H), 3.90 (s, 3H), 1.97 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.52, 140.25, 133.28, 125.88, 124.17, 123.51, 123.05, 120.24, 118.99, 113.21, 110.98, 102.56, 64.37, 56.15; IR (KBr) ν_{max} 3446.98, 3237.06, 2915.96, 1587.29, 1226.78, 1033.87, 735.99 cm^{-1}; MS: *m/z* 226.1 $(M - H)^-$; HRMS $(M + Na)^+$ calcd for $C_{14}H_{13}NNaO_2$ 250.0843, found 250.0841.

4.11. 3-Methoxy-9H-carbazole-1-carbaldehyde **(5a).**

To a stirred solution of **3a** (38 mg, 0.167 mmol) in dry CCl_4 (10 mL) was added MnO_2 (291 mg, 3.38 mmol) at 25 °C, and the reaction mixture was stirred for 5 h. at the same temperature. The reaction mixture was filtered through a short pad of celite and the filtrate was concentrated under vacuum. The residue was purified by chromatography on a silica gel column (3% ethyl acetate in hexane) to provide **5a** as a light green solid (30 mg, 80%), mp 178.3–180.9 °C: ^{1}H NMR (400 MHz, Acetone-d_6) δ 10.75 (br s, 1H), 10.06 (s, 1H), 8.05 (d, *J* = 7.6 Hz, 1H), 7.95 (d, *J* = 2.0 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 2.4 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.09 (t, *J* = 7.4 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, Acetone-d_6) δ 192.56, 153.41, 141.47, 132.73, 126.52, 125.51, 121.70, 120.36, 120.01, 119.56, 117.94, 112.04, 111.64, 55.75; IR (KBr) ν_{max} 3343.00, 1671.18, 1490.26, 1117.40 cm^{-1}; HRMS $(M + H)^+$ calcd for $C_{14}H_{12}NO_2$ 226.0868, found 226.0861.

4.12. 3-Methoxy-9H-carbazole-1-carboxylic acid **(6a).**

To a stirred solution of **2a** (30 mg, 0.117 mmol) in water (10 mL) and ethanol (2 mL) mixture was added potassium hydroxide (13 mg, 0.235 mmol) at 25 °C, and the resulting mixture was refluxed for 4 h. The reaction mixture was allowed to room temperature and concentrated in vacuo. The residue was purified by column chromatography (silica gel, ethyl acetate–hexane, 1:1) to give **6a** (24 mg, 85%) as a pale yellow solid, mp 201.2–202.8 °C: ^{1}H NMR (400 MHz, Acetone-d_6) δ 10.58 (br s, 1H), 8.17 (d, *J* = 7.6 Hz, 1H), 8.03 (s, 1H), 7.73-7.71 (m, 2H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.23 (t, *J* = 7.4 Hz, 1H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, Acetone-d_6) δ 152.96, 141.06, 135.15, 126.30, 125.38, 122.20, 120.25, 119.03, 114.74, 111.71, 111.66, 110.02, 55.62; IR (KBr) ν_{max} 3411.82, 2930.74, 1672.41, 1582.66, 1107.73 cm^{-1}; MS: *m/z* 240.2 $(M - H)^-$; HRMS $(M + H)^+$ calcd for $C_{14}H_{12}NO_3$ 242.0817, found 242.0812.

4.13. 2-(2-Methoxyphenyl)-4,4,5,5-tetramethyl-[1,3,2] dioxaborolane **(23).**

To a stirred solution of 1-Bromo-2-methoxybenzene (3.0 g, 16.04 mmol) in 1,4-dioxane (30 mL) was added bis(pinacolato)diboron (4.06 g, 16.04 mmol), $PdCl_2(PPh_3)_2$

(0.56 g, 0.802 mmol) and potassium acetate (3.14 g, 32.08 mmol) at room temperature, and the resulting mixture was stirred at 90 °C under nitrogen for 5 h. The reaction mixture was diluted with ethyl acetate (50 mL) and filtered through celite. The filtrate was concentrated under vacuum and the residue was purified by column chromatography on silica gel (hexane) to give **23**[82] (3.0 g, 80.0%) as a off-white solid, mp 76.5–77.8 °C (ref.[82] 80–81 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.39 (t, *J* = 7.2 Hz, 1H), 6.95 (t, *J* = 7.2 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 3.83 (s, 3H), 1.35 (s, 12H); IR (Neat) ν_{max} 2979.20, 1576.49, 1356.44, 1145.35 cm^{-1}.

4.14. 2'-Methoxy-5-methyl-2-nitrobiphenyl **(26).**

To a stirred solution of 3-chloro-4-nitrotoluene (1 g, 5.83 mmol) in toluene (20 mL) was added $Pd(PPh_3)_4$ (336 mg, 0.29 mmol), **23** (1.36 g, 5.83 mmol) and potassium carbonate (1.61 g, 11.65 mmol), and the reaction mixture was refluxed under nitrogen for 80 h. The reaction mixture was cooled to room temperature and filtered through celite. The filtrate was concentrated under vacuum followed by silica gel column purification of the obtained residue using ethyl acetate (0–1%) in hexane as an eluent provided product **26** as a yellow solid (0.8 g, 56%), mp 88.2–92.8 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.4 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.30 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 7.19 (s, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 3.69 (s, 3H), 2.45 (s, 3H); IR (KBr) ν_{max} 2930.22, 1609.77, 1522.7, 1354.94 cm^{-1}; MS: *m/z* 244.1 $(M + H)^+$.

To a stirred solution of **26** (0.5 g, 2.05 mmol) in 1,2-dichlorobenzene (10 mL) was added triphenylphosphine (1.35 g, 5.13 mmol) at room temperature, and the resulting mixture was refluxed for 10 h. The reaction mass was concentrated under vacuum and the residue purified by column chromatography (silica gel, 1% ethyl acetate in hexane) to give **7**[46] as a off-white solid (0.4 g, 93%), mp 133.4–137.9 °C (ref.[46] 135 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.94 (br s, 1H), 7.33–7.28 (m, 2H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 4.08 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.27, 141.24, 136.92, 128.92, 126.49, 126.23, 122.97, 122.85, 112.48, 109.61, 103.57, 100.19, 55.43, 21.50; IR (KBr) ν_{max} 3400.95, 2913.91, 1586.90, 1102.69 cm^{-1}; MS: *m/z* 212.0 $(M + H)^+$.

4.16. 2-(4-Methoxyphenyl)-4,4,5,5-tetramethyl-[1,3,2] dioxaborolane **(24).**

To a stirred solution of 1-Bromo-4-methoxybenzene (5.0 g, 26.73 mmol) in 1,4-dioxane (50 mL) was added bis(pinacolato)diboron (6.77 g, 26.73 mmol), $PdCl_2(PPh_3)_2$ (0.94 g, 1.33 mmol) and potassium acetate (5.2 g, 53.46 mmol) at room temperature, and the reaction mixture was stirred at 90 °C under nitrogen atmosphere for 7 h. The reaction mixture was diluted with ethyl acetate (75 mL) and filtered through celite. The filtrate was concentrated under vacuum and the residue was purified by column chromatography (silica gel, only hexane) to give **24** (5.0 gm, 80%) as a pale yellow syrup: ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.76 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 3.77 (s, 3H), 1.31 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.22, 136.56, 113.34, 83.52, 55.03, 24.89; IR (Neat) ν_{max} 2978.67, 1605.71, 1361.37, 1248.39, 1144.45 cm^{-1}; MS: *m/z* 235.2 $(M + H)^+$.

4.17. 4'-Methoxy-5-methyl-2-nitrobiphenyl **(27).**

To a stirred solution of 3-chloro-4-nitrotoluene (2 g, 11.65 mmol) in toluene (30 mL) were added $Pd(PPh_3)_4$ (0.67 g, 0.583 mmol), **24** (2.73 g, 11.65 mmol) and potassium carbonate (3.22 g, 23.3 mmol) at 25 °C under nitrogen, and the reaction mixture was refluxed for 25 h. The reaction mixture was allowed to reach room temperature and concentrated under vacuum to give **27** (crude) as light green syrup (1.45 g, 51%).

4.18. 2-Methoxy-6-methyl-9H-carbazole **(28).**

To a stirred solution of **27** (0.3 g, 1.23 mmol) in 1,2-dichlorobenzene (10 mL) was charged triphenylphosphine (0.81 g, 3.08 mmol) at room temperature, and the resulting mixture was refluxed for 10 h. The solvent was removed under vacuum and the residue was purified by column chromatography (silica gel, 1–2% ethyl acetate in hexane) to provide **28**[73,81,83] as a white solid (0.2 g, 77%), mp 226.8–228.0 °C (lit.[81] 228–229 °C), (lit.[83] 229–231 °C): ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.94 (s, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.77 (s, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 1.6 Hz, 1H), 6.74 (dd, *J* = 8.4, 2.0 Hz, 1H), 3.82 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.84, 141.81, 138.41, 127.57, 125.82, 123.29, 121.21, 119.59, 116.51, 110.76, 107.92, 94.86, 55.68, 21.58; IR (KBr) ν_{max} 3399.99, 2937.25, 1471.78, 1211.25, 808.56 cm^{-1}; MS: *m/z* 212.0 $(M + H)^+$.

4.19. Clauszoline K **(8).**

To a stirred solution of **28** (100 mg, 0.473 mmol) in methanol (10 mL), and water (1 mL) mixture was added DDQ (451 mg, 1.987 mmol) at 25 °C, and the reaction mixture was stirred for 7 h. at the same temperature. The solvent was removed under vacuum and the residue was purified by column chromatography (silica gel, 2% ethyl acetate in hexane) to give **8**[83] (80 mg, 75%) as a off-white solid, mp 169.3–174.3 °C (ref.[83] 170–171 °C), (ref.[73] 184–185 °C): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.70 (s, 1H), 10.02 (s, 1H), 8.60 (s, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.86 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 2.0 Hz, 1H), 6.89 (dd, *J* = 8.4, 2.0 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 192.43, 159.67, 144.09, 142.39, 128.75, 125.90, 123.40, 123.33, 122.02, 116.57, 111.50, 109.53, 95.56, 55.84; IR (KBr) ν_{max} 3288.53, 2925.00, 1673.56, 1161.66, 808.55 cm^{-1}; MS: *m/z* 226.0 $(M + H)^+$.

4.20. 2-(3-Methoxyphenyl)-4,4,5,5-tetramethyl-[1,3,2] dioxaborolane **(31).**

To a stirred solution of 1-Bromo-3-methoxybenzene (**30**) (3.0 g, 16.04 mmol) in 1,4-dioxane (30 mL) were added bis(pinacolato)diboron (4.06 g, 16.04 mmol), $PdCl_2(PPh_3)_2$ (0.563 g, 0.802 mmol) and potassium acetate (3.14 g, 32.08 mmol) at 25 °C, and the reaction mixture

was stirred at 90 °C under nitrogen atmosphere for 6 h. The reaction mixture was diluted with ethyl acetate (50 mL) and filtered through a short pad of celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, hexane) to give **31**[84] (2.8 g, 74%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.2 Hz, 1H), 7.32–7.25 (m, 2H), 7.01 (dd, *J* = 8.4, 2.6 Hz, 1H), 3.83 (s, 3H), 1.34 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.09, 134.76, 128.95, 127.71, 127.21, 118.81, 117.88, 83.82, 55.22, 24.88; IR (Neat) ν_{max} 2979.17, 1356.52, 1145.52, 706.51 cm^{-1}.

4.21. 3'-Methoxy-5-methyl-2-nitrobiphenyl **(32).**

To a stirred solution of 3-chloro-4-nitrotoluene (2 g, 11.65 mmol) in toluene (30 mL) were added $Pd(PPh_3)_4$ (673 mg, 0.582 mmol), **31** (2.73 g, 11.65 mmol) and potassium carbonate (3.22 g, 23.31 mmol), and the reaction mixture was refluxed for 35 h. under nitrogen atmosphere. The reaction mixture was allowed to reach room temperature and diluted with water (30 mL), stirred for 15 min. The reaction mixture was filtered through celite, the filtrate extracted with toluene (30 mL x 3), and the solvent removed under vacuum. The residue was purified by column chromatography on silica gel (0–0.5% ethyl acetate in hexane) to give **32** (1.5 g, 53%) as pale yellow syrup: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.26–7.22 (m, 2H), 6.93 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.87-6.83 (m, 2H), 3.82 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.58, 145.91, 142.29, 138.08, 135.28, 131.41, 128.56, 127.66, 123.20, 119.20, 112.56, 112.50, 54.21, 20.29; IR (Neat) ν_{max} 2958.89, 1599.49, 1519.98 cm^{-1}; MS: *m/z* 244.1 $(M + H)^+$.

4.22. Glycozolicine (8-methoxy-3-methylcarbazole) **(9)** *and Glycozoline* **(10).**

To a stirred solution of **32** (1.2 g, 4.933 mmol) in 1,2-dichlorobenzene (10 mL) was added triphenylphosphine (3.2 g, 12.33 mmol) at room temperature, and the reaction mass was refluxed for 10 h. The reaction mass was concentrated under vacuum and the residue was purified by column chromatography (silica gel, 0–0.5% ethyl acetate in hexane) to provide compound **9**[23d,50] and (1–2% ethyl acetate in hexane) **10**[23d,85] with 50:50 ratio.

4.22.1. Glycozolicine **(9).**

(400 mg, 38%), as a white solid, mp 130.8–132.7 °C (lit.[86] mp 145–146 °C), (lit.[33] mp 137–138 °C), (lit.[87] 129–130 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (br s, 1H), 7.84 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.35 (d, 8.4 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.13 (t, *J* = 7.8 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 4.00 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.69, 137.46, 130.14, 128.67, 127.08, 124.22, 123.86, 120.44, 119.50, 112.82, 110.59, 105.77, 55.51, 21.44; IR (KBr) ν_{max} 3414.12, 2931.15, 1577.33 cm^{-1}; MS: *m/z* 212.0 $(M + H)^+$; HRMS $(M)^+$ calcd for $C_{14}H_{13}NO$ 211.0992, found 211.0997.

4.22.2. Glycozoline **(10).**

(400 mg, 38%), as a off-white solid, mp 174.2–178.4 °C (lit.[85] 176–179 °C) (lit.[51] 181–182 °C): ^{1}H NMR (400

MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.79 (br s, 1H), 7.52 (d, *J* = 2.4 Hz, 1H), 7.31-7.28 (m, 2H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.05 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.92 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.77, 138.58, 134.78, 128.35, 127.20, 123.67, 123.55, 120.14, 114.89, 111.28, 110.43, 103.14, 56.09, 21.42; IR (KBr) ν_{max} 3399.91, 2937.99, 1458.93, 1211.08 cm^{-1}; MS: *m/z* 212.0 $(M + H)^+$.

4.23. Mukolidine (8-methoxycarbazole-3-carbaldehyde) **(11).**

To a stirred solution of **9** (100 mg, 0.473 mmol) in methanol (10 mL) and water (1 mL) mixture was added DDQ (451 mg, 1.987 mmol) and stirred for 5 h. at r.t. The reaction mass was diluted with ethyl acetate (50 mL) and the organic layer was washed with sat. sodium bicarbonate solution (30 mL x 2) and water (30 mL x 2) and dried over sodium sulfate. The solvent was removed under vacuum. Purification of the residue by column chromatography (silica gel, hexane-ethyl acetate, 92:8) provided **11**[50,87] (90 mg, 85%) as a off-white solid, mp 167.6–168.7 °C (ref.[87] 175–176 °C), (ref.[50] 148–150 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.09 (s, 1H), 8.60 (br s, 1H), 8.58 (s, 1H), 7.98 (dd, *J* = 8.8, 1.2 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.24 (t, *J* = 7.8 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 4.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.86, 145.86, 142.82, 130.31, 129.14, 127.05, 124.54, 124.27, 123.87, 121.22, 113.02, 111.26, 106.97, 55.63; IR (KBr) ν_{max} 3322.59, 2925.18, 1674.26, 1572.70, 1242.00, 1091.95, 817.15 cm^{-1}; MS: *m/z* 226.0 $(M + H)^+$.

4.24. Mukoline (3-hydroxymethyl-8-methoxy carbazole) **(12).**

To a stirred solution of **11** (60 mg, 0.266 mmol) in methanol (15 mL) was added sodium borohydride (30.2 mg, 0.799 mmol) at 0 °C and stirred for 2 h. at the same temperature. The solvent was removed under vacuum and the residue was purified by column chromatography (silica gel, hexane–ethyl acetate, 7:3) to give **12**[50,87] as a off-white solid (55 mg, 91%), mp 146.2–148.1 °C (ref.[87] 155–157 °C), (ref.[50] 125–126 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (br s, 1H), 8.03 (s, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.41 (s, 2H), 7.15 (t, *J* = 7.8 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 4.82 (s, 2H), 4.00 (s, 3H), 1.74 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.73, 138.86, 132.10, 130.22, 125.52, 124.24, 123.80, 119.88, 119.59, 112.88, 111.02, 106.08, 66.13, 55.54; IR (KBr) ν_{max} 3509.04, 3293.24, 2924.21, 1574.77, 1097.80, 821.55 cm^{-1}.

4.25. 4,4,5,5-Tetramethyl-2-p-tolyl-[1,3,2]dioxaborolane **(34).**

To a stirred solution of 4-bromotoluene (5 g, 29.23 mmol) in 1,4-dioxane (50 mL) were added bis(pinacolato)diboron (7.41 g, 29.23 mmol), $PdCl_2(PPh_3)_2$ (1.02 g, 1.56 mmol, 5 mol%) and potassium acetate (5.7 g, 58.46 mmol) at 25 °C, and the reaction mixture was stirred at 90 °C under nitrogen atmosphere for 5 h. The reaction mixture was diluted with ethyl acetate (50 mL) and filtered through celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, hexane) to give product **34** (5.8

g, 91%) as a light brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.6 Hz, 2H), 7.09 (d, *J* = 7.6 Hz, 2H), 2.26 (s, 3H), 1.23 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.38, 134.88, 128.55, 83.62, 24.90, 21.75; IR (Neat) ν_{max} 2979.33, 1613.77, 1361.25, 1145.86, 859.94 cm^{-1}.

4.26. 4′-Methyl-2-nitrobiphenyl **(35).**

To a solution of 1-bromo-2-nitrobenzene (0.2 g, 0.99 mmol) in toluene (10 mL) were added $Pd(PPh_3)_4$ (57 mg, 0.495 mmol), **34** (0.21 g, 0.99 mmol) and potassium carbonate (0.27 g, 1.98 mmol) at 25° C, and the resulting solution was refluxed for 60 h. under nitrogen atmosphere. The reaction mixture was allowed to reach r.t. and concentrated in vacuo. The obtained residue was purified by column chromatography on silica gel using 1% ethyl acetate in hexane to give **35** (0.18 g, 86%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.0 Hz, 1H), 7.61–7.57 (m, 1H), 7.47–7.42 (m, 2H), 7.25–7.20 (m, 4H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.42, 138.18, 136.29, 134.41, 132.20, 131.95, 129.47, 127.92, 127.77, 124.03, 21.25; IR (Neat) ν_{max} 2924.80, 1527.84, 1358.87, 818.93 cm^{-1}.

4.27. 2-Methyl-9H-carbazole **(13).**

To a stirred solution of 4'-methyl-2-nitrobiphenyl (**35**) (150 mg, 0.703 mmol) in o-dichlorobenzene (10 mL) was added triphenylphosphine (461 mg, 1.76 mmol) at 25 °C, and the reaction mixture was refluxed for 6 h. The reaction mixture was allowed to reach r.t. and concentrated under vacuum, followed by silica gel column purification of the obtained residue using 0–1% ethyl acetate-hexane as an eluent provided product **13** (120 mg, 94%) as a white solid, mp 256.7–259.7 °C (lit.[88] mp. 258–260 °C): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.08 (br s, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.26 (s, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 140.66, 140.17, 135.43, 125.39, 122.95, 120.63, 120.48, 120.30, 120.23, 118.81, 111.34, 111.25, 22.16; IR (KBr) ν_{max} 3399.96, 2914.05, 1439.51, 1327.31 cm^{-1}; MS: m/z 182.0 $(M + H)^+$.

4.28. Methyl 2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan -2-yl)phenyl]propionate **(44).**

A mixture of Methyl 2-(4-bromophenyl)propionate (**38**) (5 g, 20.56 mmol), potassium acetate (4.04 g, 41.11 mmol), Bis(pinacolato)diboron (10.45 g, 41.13 mmol) and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.84 g, 1.03 mmol) in 1,4-dioxane (100 mL) was refluxed for 6 h. under nitrogen atmosphere. The reaction mixture was cooled to 60 °C and concentrated under reduced pressure. Water (50 mL) and ethyl acetate (50 mL) were charged, stirred for 30 minutes and filtered through celite. Organic layer was separated, dried over sodium sulphate and concentrated. The residue was purified using column chromatography (silica gel, 3-5% ethyl acetate in hexane) to afford Methyl 2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaboralan-2-yl)phenyl]propionate (**44**) (5.5 g, 92%) as a colourless syrup: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.6 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 3.73 (q,

J = 6.8 Hz, 1H), 3.63 (s, 3H), 1.50 (d, *J* = 7.2 Hz, 3H), 1.32 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.72, 143.73, 135.18, 134.97, 126.89, 124.98, 83.76, 52.02, 45.61, 24.85, 18.50; IR (KBr) ν_{max} 2980.90, 1740.69 cm^{-1}; MS: m/z 291.1 $(M + H)^+$.

4.29. General procedure for the preparation of nitro biphenyls **45a-d**

To a stirred solution of Methyl 2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaboralan-2-yl)phenyl]propionate (**44**) (2 g, 6.89 mmol) in toluene (20 mL) under nitrogen atmosphere were added halonitrobenzene (6.2 mmol), potassium carbonate (1.92 g, 13.89 mmol), $Pd(PPh_3)_4$ (80 mg, 0.069 mmol) and water (2 mL). The reaction mixture was stirred for 20-100 h at 100 °C, until TLC had indicated complete consumption of the aryl halide. The reaction mixture was evaporated, and the residue was purified by column chromatography.

4.29.1. Methyl 2-{5'-chloro-2'-nitro-[1,1'-biphenyl]-4-yl} propionate **(45a).**

Yield: 1.08 g (54%) pale yellow syrup: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.4 Hz, 1H), 7.46 (d, *J* = 10.2 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.27-7.24 (m, 2H), 3.79 (q, *J* = 7.1 Hz, 1H), 3.69 (s, 3H), 1.54 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.68, 149.43, 140.95, 135.05, 134.38, 133.98, 133.02, 132.38, 128.14, 128.00, 124.22, 52.16, 45.13, 18.51; IR (Neat) ν_{max} 2982.71, 1738.60, 1732.74 cm^{-1}; MS: m/z 320 $(M + H)^+$.

4.29.2. Methyl 2-{2'-chloro-6'-nitro-[1,1'-biphenyl]-4yl} propionate **(45b).**

Yield: 1.12 g (56%), pale yellow syrup: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73-7.68 (m, 2H), 7.46-7.36 (m, 3H), 7.22 (d, *J* = 8.1 Hz, 2H), 3.77 (q, *J* = 7.1 Hz, 1H), 3.70 (s, 3H), 1.55 (d, *J* = 7.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.72, 151.26, 140.95, 135.82, 134.39, 133.28, 132.63, 129.04, 128.91, 128.80, 127.69, 127.54, 121.93, 52.14, 45.21, 18.55; IR (Neat) ν_{max} 3022.43, 1733.07, 1534.11, 758.14 cm^{-1}; MS: m/z 320.0 $(M + H)^+$.

4.29.3. Methyl 2-{4'-chloro-2'-nitro-[1,1'-biphenyl]-4yl} propionate **(45c).**

Yield: 1.16 g (58%) light green color liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 1.8 Hz, 1H), 7.60 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.39-7.35 (m, 3H), 7.26-7.23 (m, 2H), 3.78 (q, *J* = 7.0 Hz, 1H), 3.69 (s, 3H), 1.54 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.68, 149.43, 140.95, 135.05, 134.38, 133.98, 133.02, 132.38, 128.14, 128.00, 124.22, 52.16, 45.13, 18.51; IR (Neat) ν_{max} 2981.99, 1735.69, 1534.67, 738.15 cm^{-1}; MS: m/z 320.0 $(M + H)^+$.

4.29.4. Methyl 2-{2'-nitro-[1,1'-biphenyl]-4yl}propionate **(45d).**

Yield: 1.25 g (71%), pale yellow solid, mp 86.8–89.3 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.1 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.50-7.41 (m, 2H), 7.37 (d, *J* = 7.8 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 3.78 (q, *J* = 7.0 Hz, 1H), 3.69 (s, 3H), 1.54 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 174.90, 140.66, 136.29, 136.05, 132.39, 132.09, 128.31, 127.98, 126.19, 124.19, 52.27, 45.26, 18.66; IR (Neat) ν_{max} 2981.59, 1735.85, 1527.98 cm^{-1}; MS: *m/z* 286.1 $(M + H)^+$.

4.30. General procedure for the preparation of carbazole esters **46a-d**

To a stirred solution of compound **45** (2-nitrobiphenyl derivative) (0.01 mol) in *o*-dichlorobenzene (50 mL) was added triphenylphosphine (0.025 mol) under nitrogen atmosphere at room temperature, and the reaction mixture was refluxed for 6–10 h. The solvent was evaporated under reduced pressure at 75 °C, and the residue was purified by column chromatography (silica gel, hexane-ethyl acetate, 8.5:1.5).

4.30.1. Methyl 2-(6-chloro-9H-carbazol-2-yl)propionate **(46a).**

Yield: 2.55 g (89%), pale yellow solid, mp 97.5–99.2 °C; HPLC (239 nm) t_R 21.74 min, 96.20%: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (br s, 1H), 7.97 (s, 1H), 7.95 (d, *J* = 8.1 Hz, 1H), 7.35-7.28 (m, 3H), 7.18 (d, *J* = 8.1 Hz 1H), 3.89 (q, *J* = 7.1 Hz, 1H), 3.68 (s, 3H), 1.59 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.36, 139.32, 138.13, 137.03, 124.76, 123.86, 123.22, 120.60, 119.57, 118.89, 118.56, 110.53, 108.50, 51.13, 44.78, 17.91; IR (KBr) ν_{max} 3410.62, 1732.94 cm^{-1}.

4.30.2. Methyl 2-(5-chloro-9H-carbazol-2-yl)propionate **(46b).**

Yield: 2.2 g (77%), off-white solid, mp 112.4–113.7 °C; HPLC (239 nm), t_R 21.88 min, 97.03%: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, *J* = 8.1 Hz, 1H), 8.16 (br s, 1H), 7.39 (s, 1H), 7.32-7.30 (m, 2H), 7.23-7.18 (m, 2H), 3.91 (q, *J* = 7.0 Hz, 1H), 3.67 (s, 3H), 1.60 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.38, 140.82, 139.83, 139.02, 128.59, 126.08, 123.18, 121.47, 120.50, 120.23, 119.66, 109.08, 108.95, 52.17, 45.80, 18.94; IR (KBr) ν_{max} 3354.09, 1719.23 cm^{-1}; MS: m/z 288 $(M + H)^+$.

4.30.3. Methyl 2-(7-chloro-9H-carbazol-2-yl)propionate **(46c).**

Yield: 2.52 g (88%), off-white solid, mp 123.1–127.7 °C; HPLC (239 nm), t_R 21.88 min, 97.09%: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (br s, 1H), 7.97-7.91 (m, 2H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 3.89 (q, *J* = 7.05 Hz, 1H), 3.67 (s, 3H), 1.59 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.28, 140.24, 140.01, 138.86, 131.38, 121.95, 121.76, 121.06, 120.41, 120.11, 119.78, 110.68, 109.51, 52.17, 45.79, 19.01; IR (KBr) ν_{max} 3402.56, 1735.87 cm^{-1}; MS: m/z 287.9 $(M + H)^+$.

4.30.4. Methyl 2-(9H-carbazol-2-yl)propionate **(46d).**

Yield: 2.3 g (81%), white solid, mp 61.7–64.5 °C; HPLC (235 nm), t_R 13.99 min, 96.72%: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05-7.99 (m, 3H), 7.41-7.38 (m, 3H), 7.22-7.16 (m, 2H), 3.90 (q, *J* = 6.8 Hz, 1H), 3.67 (s, 3H), 1.60 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.51, 139.85, 138.46, 125.77, 123.11, 122.51, 120.44, 120.26, 119.47, 119.22, 110.65, 109.38, 52.14, 46.89, 19.04; IR (KBr) ν_{max} 3404.28, 1735.26 cm^{-1}; MS: m/z 254.1 $(M + H)^+$.

4.31. General procedure for the preparation of carbazole acids **14a-d**

To the sodium hydroxide solution (50 mL, 0.02 mol sodium hydroxide) was added carbazole ester **46** (0.01 mol), and the reaction mixture was refluxed for 4 h. Upon complete consumption of the ester starting material, the reaction was cooled to room temperature, and acidified by 6 N HCl (4 mL). The reaction mixture was extracted with methyl *t*-butyl ether (2 x 20 mL), and the combined organic layer was dried over sodium sulfate, and concentrated under vacuum. The product was purified by column chromatography (silica gel, hexane-ethyl acetate, 7:3).

4.31.1. 2-(6-Chloro-9H-carbazol-2-yl)propanoic acid (carprofen) **(14a).**

Yield: 2.34 g (88%), off-white solid, mp 186.3–189.5 °C; HPLC (239 nm), t_R 11.21 min, 99.29%: ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.34 (br s, 1H), 11.39 (s, 1H), 8.17 (s, 1H), 8.10 (d, *J* = 8.1 Hz, 1H), 7.49 (d, *J* = 8.7 Hz, 1H), 7.40-7.34 (m, 2H), 7.11 (d, *J* = 7.8 Hz, 1H), 3.84 (q, *J* = 6.9 Hz, 1H), 1.44 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.62, 139.65, 138.85, 137.43, 124.17, 122.69, 121.95, 119.70, 119.51, 118.73, 117.83, 111.43, 108.89, 44.21, 18.05; IR (KBr) ν_{max} 3425.24, 1696.92 cm^{-1}; MS: *m/z* 272.1 (M - H)$^-$.

4.31.2. 2-(5-Chloro-9H-carbazol-2-yl)propanoic acid **(14b).**

Yield: 2.28 g (86%), off-white solid, mp 179.5–182.5 °C; HPLC (239 nm), t_R 11.93 min, 98.38%: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.30 (br s, 1H), 11.56 (s, 1H), 8.34 (d, *J* = 8.4 Hz, 1H), 7.47-7.38 (m, 2H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.19–7.15 (m, 2H), 3.86 (q, *J* = 7.0 Hz, 1H), 1.46 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.97, 141.60, 140.56, 140.18, 127.34, 126.56, 122.41, 120.30, 119.62, 119.47, 119.35, 110.33, 110.19, 45.55, 19.40; IR (KBr) ν_{max} 3408.70, 1703.19 cm^{-1}; MS: *m/z* 272.1 (M - H)$^-$; HRMS (M + H)$^+$ calcd for $C_{15}H_{13}ClNO_2$ 274.0635, found 274.0658.

4.31.3. 2-(7-Chloro-9H-carbazol-2-yl)propanoic acid **(14c).**

Yield: 2.53 g (95%), white solid, mp 252.7–256.2 °C; HPLC (239 nm), t_R 11.79 min, 98.31%: ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.31 (s, 1H), 11.36 (s, 1H), 8.10-8.03 (m, 2H), 7.50 (s, 1H), 7.40 (s, 1H), 7.17-7.10 (m, 2H), 3.83 (q, *J* = 6.6 Hz, 1H), 1.44 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.00, 140.99, 140.80, 139.88, 130.16, 121.87, 121.66, 121.12, 120.71, 119.37, 119.18, 111.05, 110.31, 45.57, 19.43; IR (KBr) ν_{max} 3411.21, 1698.11 cm^{-1}; MS: *m/z* 272.1 (M - H)$^-$; HRMS (M+H)$^+$ calcd for $C_{15}H_{13}ClNO_2$ 274.0629, found 274.0641.

4.31.4. 2-(9H-carbazol-2-yl)propanoic acid **(14d).**

Yield: 2.27 g (86%), white solid, mp 238.4–242.7 °C; HPLC (239 nm), t_R 7.34 min, 99.53%: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.24 (br s, 1H), 11.16 (s, 1H), 8.07 (d, *J* = 7.6 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.38-7.33 (m, 2H), 7.13 (t, *J* = 7.4 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 3.82 (q, *J* = 7.2 Hz, 1H), 1.44 (d, *J* = 7.2

Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.12, 140.39, 139.32, 125.79, 122.70, 121.70, 120.52, 120.49, 118.98, 118.75, 111.34, 109.99, 45.58, 19.49; IR (KBr) ν_{max} 3413.46, 1697.91 cm^{-1}; MS: *m/z* 238.1 $(M - H)^-$; HRMS $(M + Na)^+$ calcd for $C_{15}H_{13}NNaO_2$ 262.0844, found 262.0860.

Supporting Information

Full experimental details, ^{1}H and ^{13}C NMR spectra, HRMS and HPLC traces can be found via the "Supplementary Content" section of this article's Webpage.

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