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The first total synthesis of potent antitumoral (±)-mafaicheenamine A, unnatural 6-fluoromafaicheenamine A and expedient synthesis of clausine E

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Abstract

The first total synthesis of potent antitumoral mafaicheenamine A (**1**) and its unnatural analogue, 6-fluoromafaicheenamine A (**2**) have been accomplished. An expedient synthesis of clausine E, a key intermediate in the course of synthesis of **1** and **2**, was achieved in three steps from commercially available methyl 4-amino-3-(benzyloxy)benzoate (**10**) by copper-catalyzed N-arylation with aryllead triacetate followed by cyclodehydrogenation of the resultant diarylamine under palladium(II) acetate catalysis. Moreover, palladium-catalyzed O-prenylation of clausine E and subsequent o-Claisen rearrangement under microwave irradiation rendered the advanced intermediate, C-prenylated phenol, which was eventually subjected to oxidative cyclization to construct the dihydroisocoumarin unit, leading to the synthesis of **1** and **2** in 12% and 15% overall yield, respectively, from **10**.

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Keywords Carbazole alkaloids, natural products, Claisen rearrangement, cyclodehydrogenation, oxidative cyclization, antitumoral agents

Introduction

Cancer is one of the most leading causes of mortality. Despite of enormous efforts devoted to its prevention and treatment, it remains the second leading cause of death. As such discovery and development of anticancer agents has attracted a great deal of attention by several pharmaceutical companies as well as non-profit organizations [1]. A recent study has revealed that since 1940s to date 48.6% approved anticancer agents were either natural products or directly derived there from. The study concluded that natural products as sources of novel structures are indispensable in anticancer lead-finding research [2].

Naturally occurring carbazole alkaloids are known to exhibit numerous pharmacological activities including anti-bacterial [3], anti-malarial [4], anti-tuberculosis [4] and anti-HIV [5]. In addition, they have shown potent cytotoxic activity against several cancer cell lines such as prostate cancer [6], breast cancer [7], oral cavity cancer and small-cell lung cancer [8, 7b] and human leukemia [9]. Owing to the great utility of carbazoles, considerable efforts have been devoted to their isolation from natural sources [10] as well as on the development of methods for their synthesis [11].

In an effort towards to discover new bioactive compounds, phytochemical investigation of twigs of *Clausena lansium* has led the isolation and characterization of a new carbazole alkaloid, mafaicheenamine A (**1**) (Fig. 1) [12]. Compound **1** was evaluated for its antitumor activity against three human cancer cell lines namely: breast cancer (MCF7), oral cavity cancer (KB), and small lung cancer (NCI-H187). While exhibiting moderate activity against KB ($1C_{50}$ = 7.68 μg/mL) and

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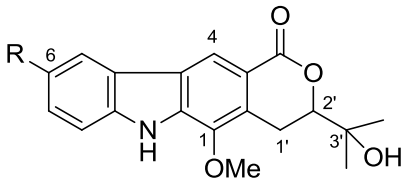
NCI-H187 ($1C_{50}$ = 13.27 μg/mL), compound **1** showed potent activity against MCF7 ($1C_{50}$ = 2.96 μg/mL).

Substitution of aromatic and heteroaromatic rings with fluorine substituent is a common practice in drug discovery. The incorporation of fluorine into a molecule can improve drug potency [13], target selectivity [14] and also can address issues associated with drug metabolism [15]. In a previous study, the effect of aromatic fluorine substitution in a series of thrombin inhibitors was investigated. The study revealed that incorporation of fluorine at C-4 of phenyl ring significantly enhanced the activity compared to when it was introduced at other positions of the phenyl ring. The high potency of 4-fluorophenyl derivative was rationalized due to the dipolar C–F…H–Cα and C–F…C=O interactions between the 4-fluorophenyl ring and the enzyme's active site [16]. In our continuing interest in the synthesis of bioactive natural products [17], we now wish to disclose the first total synthesis of **1** and its unnatural analogue, 6-fluoromafaicheenamine A **2** (Fig. 1). An expedient synthesis of clausine E, a key intermediate in the course of synthesis of **1** and **2**, was also accomplished and describe herein.



R = H (**1**)
R = F (**2**)

Fig. 1 Chemical structures of mafaicheenamine A (**1**) and 6-fluoromafaicheenamine A (**2**)

Results and discussion

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The synthesis of compound **1** was envisioned from intermediate **9** which was to be transformed to **1** by the operations of olefin metathesis followed by oxidative cyclization. To this end, ester **3** was reacted with allyl bromide in DMF, using K_2CO_3 as a base, to produce the known ester **4** [18]. The Claisen rearrangement of **4** to the corresponding C-allyl phenol in ortho-dichlorobenzene, N,N-dimethylaniline or DMF either by conventional heating or under microwaves was very low yielding (32%), requiring prolonged heating and higher reaction temperature (> 150 ^oC). In all attempts the reaction led to the recovery of either hydrolyzed acid (in case of N,N-dimethylaniline) or starting material (in case of ortho-dichlorobenzene and DMF). Consequently, the nitro group of **4** was reduced with iron powder in a mixture of ethanol, acetic acid and water promoted by ultrasonic irradiation, generating **5** in high yield (90%) [19]. The initial attempts of Claisen rearrangement of intermediate **5** in N,N-dimethylaniline under conventional heating or microwave irradiation were very sluggish, resulting the formation of only 10% of the desired product. However, with an optimized condition the reaction in DMF under microwave irradiation at 180 ^oC for 2 h gave the desired rearranged phenol **6** in high yield (85%). The chemoselective methylation on the phenolic OH of **6** with diazomethane in diethyl ether did not go to the completion even with the use excess of diazomethane; the desired **7** was formed in a low yield (15%) along with the recovery of **6**. In the second attempt, methylation was realized by stirring the solution of **6** in DMF with 1.3 equivalent of K_2CO_3 for 0.5 h followed by the addition of 1.2 equivalent of iodomethane. The amount of K_2CO_3 and short reaction time (1.5 h) was critical to obtain the desired **7** in high yield (73%). The N-arylation of ester **7** with bromobenzene under Buchwald-Hartwig conditions ($Pd(dba)_2$, BINAP) rendered the desired **8** in a very low yield (16%). The reaction become relatively cleaner when the combination of $Pd(OAc)_2$ and JohnPhos were used as catalyst and ligand, respectively but column chromatography purifications turned out to be tedious and the

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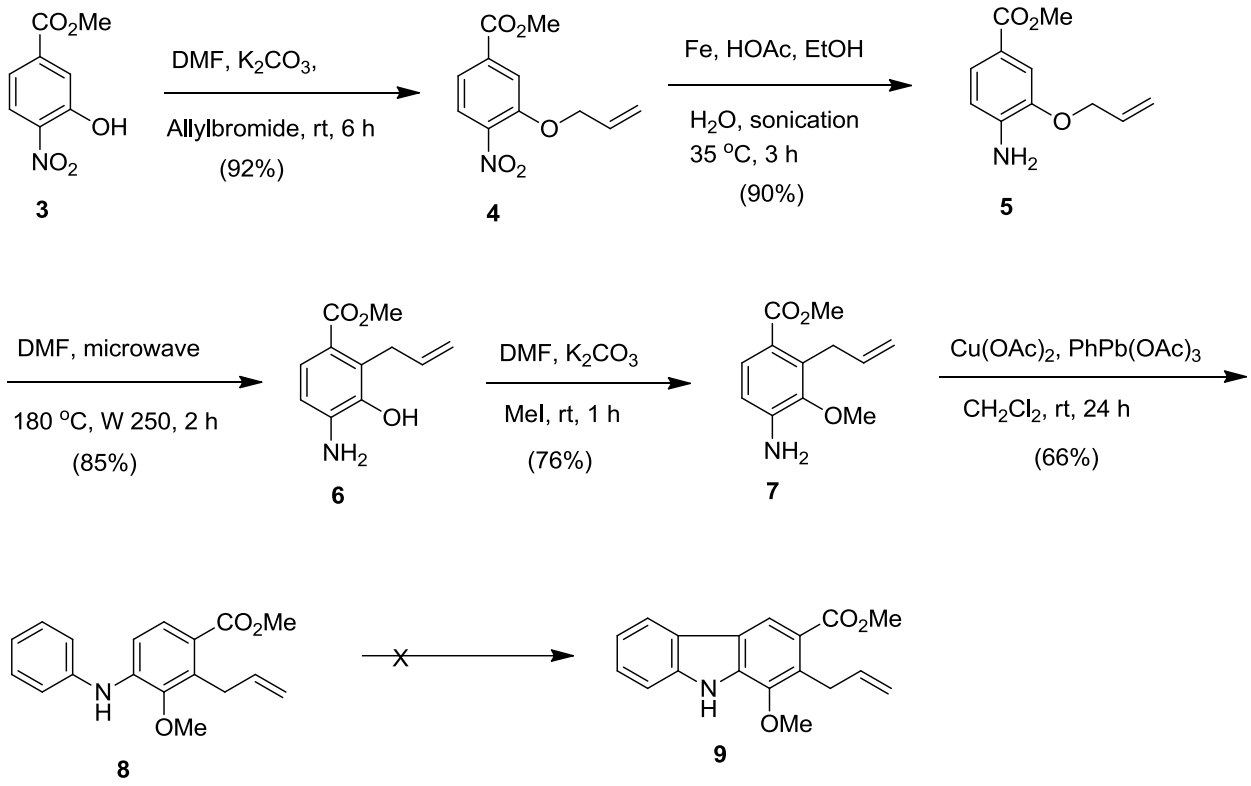
desired **8** was obtained in 20% yield. Consequently, N-arylation of ester **7** was realized under Barton conditions [20], using phenylead triacetate and copper(II) acetate as a catalyst to furnish the desired **8** in good yield (66%). Cyclodehydrogenation of **8** in acetic acid or DMF with catalytic or stoichiometric amounts of palladium(II) acetate and copper(II) acetate using either thermal induction [21] or microwave heating [22] at elevated temperatures did not yield the desired **9**, the decomposition of **8** was observed in all cases (Scheme 1).



Scheme 1: Synthesis of intermediate **9**

Failure in cyclodehydrogenation of **8** led us revised our synthetic strategy as outlined in scheme 2. N-arylation of commercially available ester **10** with phenylead triacetate under Barton conditions furnished the desired **11** in good yield (67%). The key step of cyclodehydrogenation on **11** was performed in acetic acid at 100 °C, using palladium(II) acetate as a catalyst to furnish the desired **13** in good yield (60%). Removal of O-benzyl protection of **13** with catalytic hydrogenation

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produced **15** (clausine E) in 34% overall yield from **10**. Despite the fact that six procedures for the synthesis of clausine E are known [23], our synthetic method provide an efficient access to the synthesis of clausine E in an overall high yielding reactions sequence from a commercially available starting material [24]. Next, Pd-catalyzed allylation of **15** at room temperature proceeded to give, after filtration, **17** which in turn was subjected as is to Claisen rearrangement under the optimized condition in DMF, using microwave irradiation at 180 ^{o}C for 2 h to afford the desired C-prenylated phenol **19** in 82% yield (over two steps). The chemoselective methylation on the phenolic OH of **19** was realized with iodomethane in DMF followed by the hydrolysis of the ester function under basic condition produced the desired **23** in 57% overall yield from **19** (Scheme 2). With compound **23** in hand, we next moved towards the construction of the dihydroisocoumarin unit of **1** [25]. To this end, acid **23** was treated with *m*-CPBA in CH_2Cl_2 followed by work-up with saturated $NaHCO_3$ readily generated the desired **1** in 78% yield (Scheme 2). All the spectral data of **1** matched with those of natural mafaicheenamine A [12].

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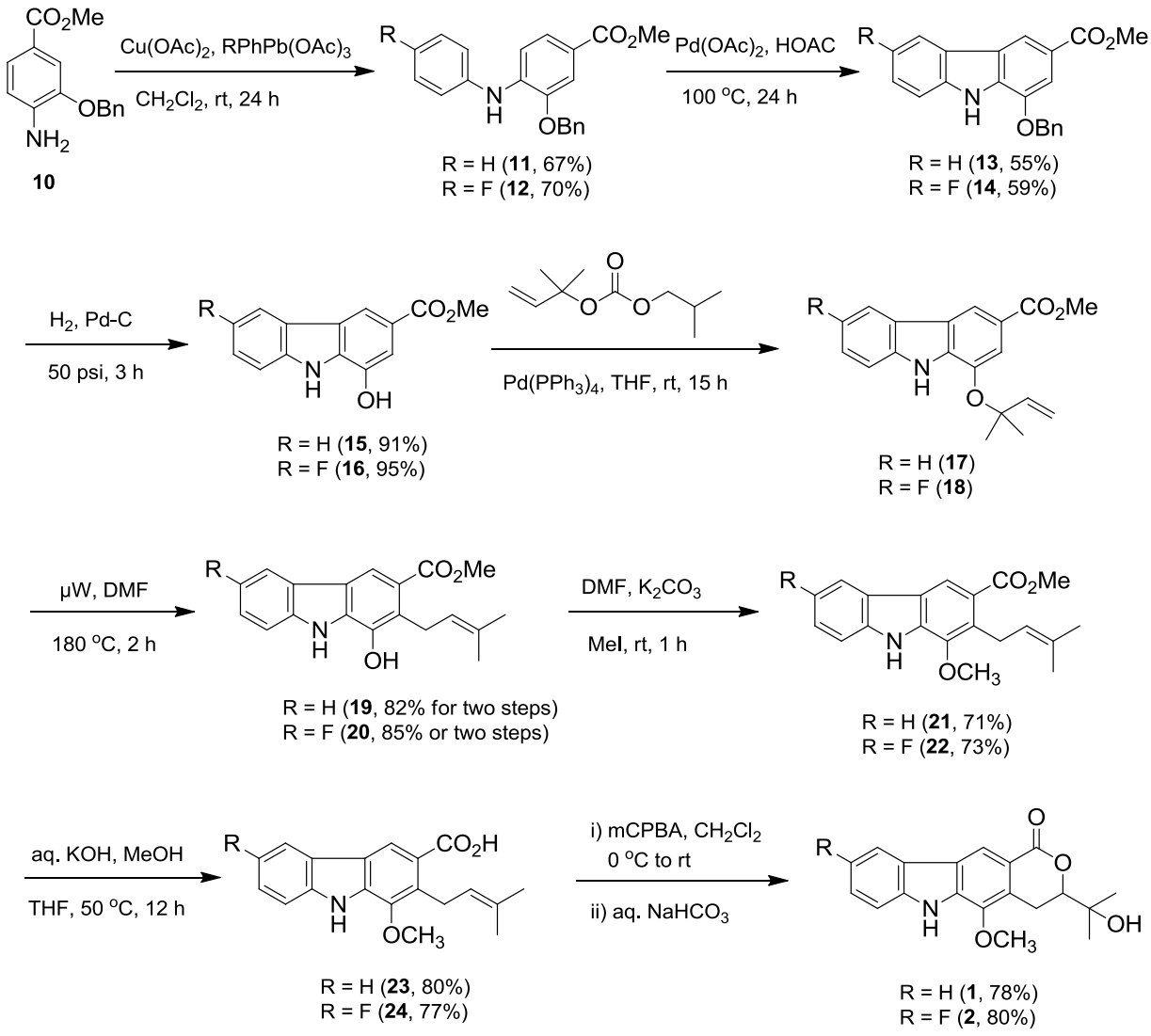

Scheme 2: Synthesis of mafaicheenamine A (**1**) and 6-fluoromafaicheenamine A (**2**)

Keeping in view the aforementioned importance and utility of fluorine substituents in drug discovery, the usefulness of our synthetic approach was extended towards the synthesis of 6-fluoromafaicheenamine A (**2**), an unnatural analogue of **1**. As depicted in Scheme 2, 6-fluoroclausine E (**16**) was synthesized from **10** by the reaction sequence of N-arylation with 4-fluorophenylead triacetate, palladium(II) acetate mediated cyclodehydrogenation and removal of benzyl protection with catalytic hydrogenation. Likewise intermediate **22** was originated from **16** by the operations of Pd-catalyzed allylation, Claisen rearrangement and O-methylation. Finally

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basic hydrolysis of ester function of **22** followed by oxidative cyclization furnished the desired **2** in 15% overall yield from **10** in eight steps (Scheme 2).

Experimental

General. Melting Points were determined on a Büchi apparatus (Büchi Labortechnik AG, Switzerland) and are uncorrected. Elemental analysis was carried out on a Perkin Elmer Elemental Analyzer Series 11 Model 2400 (PerkinElmer Inc. USA). IR spectra were recorded on a Perkin Elmer 16F PC FTIR spectrophotometer (PerkinElmer Inc. USA). ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ and d_6-DMSO using TMS as internal standard on a JEOL JNM-LA 500 MHz spectrometer (JEOL USA Inc.). Analytical TLC was carried out on silica gel 60 F_{254} plates (E. Merck); column chromatography was carried out on silica gel (200-400 mesh, E. Merck).

Synthesis of Methyl 3-(allyloxy)-4-aminobenzoate (**5**)

To a suspension of **4** (0.3 g, 1.3 mmol) in a mixture of glacial acetic acid (4 mL), ethanol (4 mL) and water (2 mL) was added reduced iron powder (0.37 g, 6.6 mmol). The resulting suspension was exposed to ultrasonic irradiation at 30 °C for 3 h and the mixture was filtered to remove the iron residue, which was washed with ethyl acetate (30 mL). The filtrate was added 2M KOH (20 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed with brine (2 x 30 mL) and water (3 x 50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was resolved on silica column, eluting with hexanes:ethyl acetate (80:20) to afford the title compound **5** as a bright yellow oil. Yield: 0.25 g, 90%; IR (neat): 3373, 3312, 3025, 2946, 1682, 1608, 1573, 1571, 1426, 1363, 1302, 1208, 1136, 1101 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.85 (s 3H, OCH_3), 4.28 (br. s, 2H, NH_2), 4.60 (d, *J* =

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5.5 Hz, 2H, O*CH*$_2$CH=CH$_2$), 5.30 (dd, *J* = 1.5, 10.3 Hz, 1H, OCH$_2$CH=*CH*$_2$), 5.41 (dd, *J* = 1.5, 17.1 Hz, 1H, OCH$_2$CH=*CH*$_2$), 6.07 (m, 1H, OCH$_2$*CH*=CH$_2$), 6.67 (d, J = 8.2 Hz, 1H, H-5), 7.45 (d, J = 1.8 Hz, 1H, H-2), 7.54 (dd, *J* = 1.7, 8.2 Hz, 1H, H-6); ^{13}C-NMR (125.7 MHz, CDCl$_3$): δ 51.66 (OCH$_3$), 69.23 (O*CH*$_2$CH=CH$_2$), 112.59, 113.27, 117.86, 119.39, 124.21, 132.98, 141.32, 144.95, 167.22 (C=O). Anal. Calcd for C$_{11}$H$_{13}$NO$_3$: C, 63.76; H, 6.32; N, 6.76%. Found: C, 63.72; H, 6.35; N, 6.71.

Synthesis of Methyl 2-allyl-4-amino-3-hydroxybenzoate (**6**)

In a microwave reaction vessel, through a solution of **5** (2 g, 9.7 mmol) in DMF (4 ml) was bubbled nitrogen for 1 min and vessel was then placed inside CEM Discover S-Class microwave synthesizer where it was exposed to microwaves at 180 ºC (260 W) for 2 h. After completion of the reaction, the mixture was diluted with ethyl acetate (50 mL), washed with water (10 mL) and then washed with brine (5 x 10 mL), dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under vacuum. Column chromatography purifications of the yellow oily material, eluting with hexanes:ethyl acetate (50:50) to obtain compound **6** as an off white solid. Yield: 1.7 g, 85%; m.p. 91-92 ºC; IR (neat): 3408, 3313, 3002, 2947, 1693, 1601, 1493, 1441, 1277, 1191, 1100, 1015 cm^{-1}; ^{1}H-NMR (500 MHz, CDCl$_3$): δ 3.82 (s, 3H, OCH$_3$), 3.89 (d, *J* = 6.1 Hz, 2H, Ar*CH*$_2$CH=CH$_2$), 4.12 (br. s, 2H, NH$_2$), 5.15-5.19 (m, 2H, OCH$_2$CH=*CH*$_2$), 6.06 (m, 1H, OCH$_2$*CH*=CH$_2$), 6.60 (d, *J* = 8.2 Hz, 1H, H-5), 7.50 (d, J = 8.2 Hz, 1H, H-6); ^{13}C-NMR (125.7 MHz, CDCl$_3$): δ 31.64 (Ar*CH*$_2$CH=CH$_2$), 51.57 (OCH$_3$), 112.44, 116.13, 119.13, 125.49, 126.88 136.45, 139.87, 142.00, 167.82 (C=O). Anal. Calcd for C$_{11}$H$_{13}$NO$_3$: C, 63.76; H, 6.32; N, 6.76%. Found: C, 63.71; H, 6.34; N, 6.72.

Synthesis of Methyl 2-allyl-4-amino-3-methoxybenzoate (**7**)

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In a solution of **6** (0.2 g, 0.97 mmol) in DMF (5 mL) was added K_2CO_3 (0.27 g, 1.93 mmol) and after being stirred for 30 minutes at room temperature, iodomethane (0.1 mL, 1.45 mmol) was added and the reaction mixture was further stirred for 1 h at room temperature. The mixture was diluted with water (30 mL) and then extracted with ethyl ether (2 x 15 mL). The combined organic layers was washed with water (10 mL) and brine (10 mL) and then dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Column chromatography of the light yellow oily material on silica gel eluting with petroleum ether:ethyl acetate (90:10) gave the title compound **7** as a dark pink crystalline solid. Yield: 0.16 g, 76%; m.p. 89-90 ºC; IR (neat): 3505, 3374, 3026, 2938, 1687, 1612, 1427, 1335, 1261, 1029 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.75 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.85 (d, J = 5.8 Hz, 2H, Ar*CH*$_2$CH=CH_2), 4.95-5.00 (m, 2H, $ArCH_2CH$=*CH*$_2$), 6.05 (m, 1H, $ArCH_2$*CH*=CH_2), 6.62 (d, *J* = 8.2 Hz, 1H, H-5), 7.64 (d, *J* = 8.2 Hz, 1H, H-6); ^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 30.73 (Ar*CH*$_2$CH=CH_2), 51.47 (OCH_3), 59.92 (OCH_3), 112.59, 114.52, 119.49, 128.60, 135.98 137.88, 143.89, 145.10, 167.42 (C=O). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33%. Found: C, 65.10; H, 6.86; N, 6.28.

Synthesis of Methyl 2-allyl-3-methoxy-4-(phenylamino)benzoate (**8**)

To a solution of compound **7** (0.25 g, 1.12 mmol) in dry CH_2Cl_2 (15 mL) was added phenyllead triacetate (0.67 g, 1.47 mmol) followed by the addition of copper(II) acetate (0.04 g, 0.22 mmol) and the reaction was stirred at room temperature for 24 h until the reaction was completed (TLC analysis). The mixture was filtered through a pad of celite and the filtrate was concentrated under reduced pressure. The residues was resolved on silica column, eluting with petroleum ether:ethyl acetate (90:10) to get the title compound **8** as a pale yellow oil. Yield: 0.22 g, 66%; IR (neat): 3345, 3075, 2996, 1707, 1588, 1497, 1430, 1254, 1135, 1036 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.82 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.91 (d, *J* = 5.6 Hz, 2H,

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Ar*CH*$_2$CH=CH$_2$), 5.00-5.04 (m, 2H, ArCH$_2$CH=*CH*$_2$), 6.07 (m, 1H, ArCH$_2$*CH*=CH$_2$), 6.47 (br. s, 1H, NH), 7.09 (t, *J* = 5.6 Hz, 1H, Ar-H), 7.14 (d, *J* = 8.6 Hz, 1H, Ar-H), 7.22 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.36 (m, 2H, Ar-H), 7.68 (d, *J* = 8.6 Hz, 1H, Ar-H); ^{13}C-NMR (125.7 MHz, CDCl$_3$): δ 30.90 (Ar*CH*$_2$CH=CH$_2$), 51.54 (OCH$_3$), 60.65 (OCH$_3$), 110.70, 114.67, 120.54, 120.64, 122.99, 126.04, 128.33, 128.39, 129.46, 135.72, 137.78, 140.71, 141.06, 146.21, 167.32 (C=O). Anal. Calcd for C$_{18}$H$_{19}$NO$_3$: C, 72.71; H, 6.44; N, 4.71%. Found: C, 72.66; H, 6.49; N, 4.65.

*Synthesis of Methyl 3-(benzyloxy)-4-(phenylamino)benzoate (**11**)*

Following the same procedure adopted for the synthesis of **8**, the reaction of compound **10** with phenyllead triacetate gave the title compound **11** as colorless crystalline solid. Yield: 0.26 g, 67%; m.p. 119-120 ^{o}C; IR (neat): 3399, 3024, 2946, 1692, 1587, 1515, 1493, 1440, 1418, 1380, 1347, 1268, 1221, 1101 cm^{-1}; ^{1}H-NMR (500 MHz, CDCl$_3$): δ 3.90 (s, 3H, OCH$_3$), 5.19 (s, 2H, O*CH*$_2$Ph), 6.56 (br. s, 1H, NH), 7.08 (t, *J* = 7.3 Hz, 1H, Ar-H), 7.21-7.24 (m, 3H, Ar-H), 7.33-7.36 (m, 2H, Ar-H), 7.39 (m, 1H, Ar-H), 7.42-7.45 (m, 2H, Ar-H), 7.48 (d, *J* = 7.0 Hz, 1H, Ar-H), 7.62 (dd, *J* = 1.8, 8.2 Hz, 1H, Ar-H), 7.65 (d, *J* = 1.6 Hz, 1H, Ar-H); ^{13}C-NMR (125.7 MHz, CDCl$_3$): δ 51.81 (OCH$_3$), 70.90 (O*CH*$_2$Ph), 111.02, 112.46, 115.35, 119.85, 120.36, 121.14, 123.19, 124.19, 127.96, 128.37, 128.71, 129.41. 129.57, 136.34, 138.64 140.53, 145.68, 156.03, 167.18 (C=O). Anal. Calcd for C$_{21}$H$_{19}$NO$_3$: C, 75.66; H, 5.74; N, 4.20%. Found: C, 75.61; H, 5.78; N, 4.15.

Synthesis of Methyl 3-(benzyloxy)-4-((4-fluorophenyl)amino)benzoate (**12**)

Following the same procedure adopted for the synthesis of **8**, the reaction of compound **10** with 4-fluorophenyllead triacetate gave the title compound **12** as a brown thick oil. Yield: 0.29 g, 70%; IR (neat): 3408, 3033, 2947, 1890, 1706, 1593, 1559, 1525, 1501, 1432, 1351, 1268, 1204, 1155, 1124, 1097 cm^{-1}; ^{1}H-NMR (500 MHz, CDCl$_3$): δ 3.88 (s, 3H, OCH$_3$), 5.17 (s, 2H, O*CH*$_2$Ph), 6.44 (br. s, 1H, NH), 7.01-7.05 (m, 3H, Ar-H), 7.11-7.17 (m, 2H, Ar-H), 7.38-7.49 (m, 5H, Ar-H),

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7.42 (t, *J* = 7.3 Hz, 2H), 7.62 (dd, *J* = 1.8, 8.2 Hz, 1H, Ar-H), 7.65 (d, *J* = 1.6 Hz, 1H, Ar-H); ^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 51.79 (OCH_3), 70.89 (O*CH*$_2$Ph), 110.38, 112.38, 116.02, 116.21, 119.73, 123.86, 124.24, 128.03, 128.41, 128.72, 136.29, 136.40 139.27, 145.41, 159.19 (d, *J* = 243.0 Hz, C-6), 167.11 (C=O). Anal. Calcd for $C_{21}H_{18}FNO_3$: C, 71.78; H, 5.16; N, 3.99%. Found: C, 71.73; H, 5.19; N, 3.93.

*Synthesis of methyl 1-(benzyloxy)-9H-carbazole-3-carboxylate (**13**)*

Under nitrogen atmosphere, to a solution of **8** (0.95 g, 2.85 mmol) in glacial acetic acid (60 mL) was added palladium(II) acetate (1.3 g, 5.7 mmol) and the mixture was heated at 100 ^{o}C for 24 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel, eluting with petroleum ether:ethyl acetate (80:20) to afford **13** as a colorless crystalline solid. Yield: 0.5 g, 55%; m.p. 149-150 ^{o}C; IR (neat): 3358, 3032, 2946, 1678, 1629, 1583, 1495, 1406, 1344, 1309, 1230, 1149, 1092 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.99 (s, 3H, OCH_3), 5.31 (s, 2H, O*CH*$_2$Ph), 7.27 (m, 1H, Ar-H), 7.39 (d, *J* =7.3 Hz, 1H, Ar-H), 7.42-7.47 (m, 4H, Ar-H), 7.53 (d, *J* = 7.3 Hz, 2H, Ar-H), 7.72 (d, *J* = 1.6 Hz, 1H, Ar-H), 8.11 (d, *J* =7.9 Hz, 1H, Ar-H), 8.51 (d, *J* = 1.6 Hz, 1H, Ar-H), 8.53 (br. s, 1H, NH); ^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 52.06 (OCH_3), 70.71 (O*CH*$_2$Ph), 107.86, 111.23, 116.48, 120.30, 120.77, 121.89, 123.75, 123.79, 126.41, 128.16, 128.44, 128.72, 136.44, 139.53, 144.29, 167.92 (C=O). Anal. Calcd for $C_{21}H_{17}NO_3$: C, 76.12; H, 5.17; N, 4.23%. Found: C, 76.08; H, 5.21; N, 4.17.

*Synthesis of Methyl 1-(benzyloxy)-6-fluoro-9H-carbazole-3-carboxylate (**14**)*

Following the same procedure adopted for the synthesis of **13**, the cyclodehydrogenation of compound **12** in acetic acid gave the title compound **14** as a colorless solid. Yield: 0.09 g, 59%; m.p. 172-176 ^{o}C; IR (neat): 3325, 2939, 1687, 1608, 1582, 1480, 1455, 1433, 1407, 1325, 1300, 1275, 1249, 1167, 1095, 1017 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.97 (s, 3H, OCH_3), 5.27 (s,

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2H, O*CH*$_2$Ph), 7.17 (td, *J* = 2.4, 9.1 Hz, 1H), 7.35-7.45 (m, 4H, Ar-H), 7.51 (d, *J* = 7.0 Hz, 2H, Ar-H), 7.69 (d, *J* = 1.3, 1H, Ar-H), 7.72 (dd, *J* = 8.2, 1.6 Hz, 1H, Ar-H), 8.42 (d, *J* = 1.2, 1H, Ar-H), 8.51 (br. s, 1H, NH); ^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 52.11 (OCH_3), 70.69 (O*CH*$_2$Ph), 106.31, 106.50, 108.04, 111.81, 111.90, 114.23, 114.44, 116.58, 121.89, 123.39, 124.34, 128.16, 128.47, 128.73, 134.08, 135.78, 136.28, 144.36, 159.42 (d, *J* = 249.0 Hz, C-6), 167.76 (C=O). Anal. Calcd for $C_{21}H_{16}FNO_3$: C, 72.20; H, 4.62; N, 4.01%. Found: C, 72.17; H, 4.65; N, 3.96.

*Synthesis of Methyl 1-hydroxy-9H-carbazole-3-carboxylate (**15**)*

To a suspension of **13** (0.48 g, 1.44 mmol) in a mixture of THF (20 mL) and ethanol (20 mL) was added palladium on activated carbon (0.05 g, 10% wet basis) and the reaction mixture was subjected to hydrogenation in a Parr apparatus at 50 psi for 5 h. The mixture was filtered through a pad of celite, and the filtrate was concentrated under vacuum and loaded on a silica column, eluting petroleum ether:ethyl acetate (66:33) afforded **15** as a white solid. Yield: 0.32 g, 91%. The spectral data of **15** matched with those of earlier values [23].

*Synthesis of Methyl 6-fluoro-1-hydroxy-9H-carbazole-3-carboxylate (**16**)*

Following the same procedure adopted for the synthesis of **15**, the title compound **16** was obtained as a white solid from the O-debenzylation of **14**. Yield: 0.2 g, 95%; m.p. 220-221; IR (neat): 3388, 3078, 2952, 1711, 1664, 1634, 1496, 1292, 1252, 1169 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6): δ 3.91 (s, 3H, OCH_3), 7.31 (td, *J* = 1.6, 8.8 Hz, 1H, Ar-H), 7.52 (d, *J* = 1.3 Hz, 1H, Ar-H), 7.55 (dd, *J* = 4.2, 8.8 Hz, 1H, Ar-H), 8.10 (d, *J* = 7.9 Hz, 1H, Ar-H), 8.38 (d, *J* = 1.3 Hz, 1H, Ar-H), 10.35 (br. s, 1H, NH), 11.64 (s, 1H, OH); ^{13}C-NMR (125.7 MHz, DMSO-d_6): δ 51.75 (OCH_3), 106.33, 110.29, 112.56, 112.63, 113.72, 113.92, 114.63, 120.58, 123.10, 124.34, 136.63, 142.99, 159.12 (d, *J* = 247.0 Hz, C-6), 166.98 (C=O). Anal. Calcd for $C_{14}H_{10}FNO_3$: C, 64.86; H, 3.89; N, 5.40%. Found: C, 64.82; H, 3.94; N, 5.35.

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*Synthesis of methyl 1-hydroxy-2-(3-methylbut-2-en-1-yl)-9H-carbazole-3-carboxylate (**19**)*

To a solution of compound **15** (0.45 g, 1.87 mmol) and isobutyl 2-methylbut-3-en-2-yl carbonate (0.61 g, 2.76 mmol) in THF (12 mL) at room temperature was added tetrakis(triphenylphosphine)palladium (0.036 g, 0.03 mmol) and the mixture was stirred at room temperature for 6 h. The reaction mixture was diluted with ethyl acetate (20 mL) and the whole was washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluting with petroleum ether:ethyl acetate (80:20) to give O-allyl ether **17**, which was used as is in the next reaction. In a microwave reaction vessel, a solution of **17** in DMF (2 ml) was bubble through nitrogen for 1 min and vessel was then placed inside CEM Discover S-Class microwave synthesizer where it was exposed to microwaves at 180^{o}C (260 W) for 2 h. After completion of the reaction and work up the residue was purified on silica gel column chromatography, eluting with hexanes:ethyl acetate (66:33) to get the title compound **19** as a white crystalline solid. Yield: 0.47 g, 82%; m.p. 131-132 ^{o}C; IR (neat): 3482, 3313, 2928, 1701, 1646, 1608, 1490, 1443, 1347, 1288, 1253, 1226, 1160, 1039 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.68 (s, 3H, CH_3), 1.83 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 3.97 (d, *J* = 5.8 Hz, 2H, Ar*CH*$_2$-), 5.29 (m, 1H, ArCH$_2$*CH*=C(CH$_3$)$_2$), 5.66 (br. s, 1H, OH), 7.25 (m, 1H, Ar-H), 7.41-7.46 (m, 2H, Ar-H), 8.04 (d, *J* =7.6 Hz, 1H, Ar-H), 8.37 (d, *J* = 1.2 Hz, 1H, Ar-H), 8.43 (br. s, 1H, NH); ^{13}C-NMR (125.7 MHz, $CDCl_3$): 18.10 (CH_3), 25.75 (CH_3), 25.96 (CH_2), 51.95 (OCH_3), 111.12, 115.36, 116.88, 119.96, 120.51, 121.76, 122.37, 122.51, 123.70, 126.15, 131.90, 132.24, 137.23, 139.82, 140.37, 168.95 (C=O). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53%. Found: C, 73.72; H, 6.24; N, 4.48.

*Synthesis of Methyl 6-fluoro-1-hydroxy-2-(3-methylbut-2-en-1-yl)-9H-carbazole-3-carboxylate (**20**)*

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Following the same procedure adopted for the synthesis of **19**, O-allylation of **16** followed by Claisen rearrangement in DMF under microwave irradiation gave the title compound **20** a white solid. Yield: 0.35 g, 85%; m.p. 121-122 ^{o}C; IR (neat): 3486, 3383, 2922, 1708, 1661, 1609, 1494, 1453, 1433, 1347, 1288, 1253, 1220, 1166, 1031 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6): δ 1.69 (s, 3H, CH_3), 1.81 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 3.92 (d, *J* = 5.8 Hz, 2H, Ar*CH*$_2$-), 5.26 (m, 1H, $ArCH_2$*CH*=$C(CH_3)_2$), 7.23 (td, *J* = 2.1, 8.8 Hz, 1H, Ar-H), 7.53 (dd, *J* = 4.3, 8.5 Hz, 1H, Ar-H), 7.95 (dd, *J* = 2.1, 9.7 Hz, 1H, Ar-H), 8.22 (s, 1H, Ar-H), 9.20 (br. s, 1H, NH), 11.09 (s, 1H, OH); ^{13}C-NMR (125.7 MHz, DMSO-d_6): δ 18.12 (CH_3), 25.77 (CH_3), 25.95 (CH_2), 51.97 (OCH_3), 106.03 (d, *J* = 23.86 Hz), 112.53, 113.53 (d, *J* = 24.89 Hz), 114.36, 116.13, 120.83, 121.55, 123.76, 131.95, 134.08, 136.43, 137.61, 140.34, 159.32 (d, *J* = 245 Hz, C-4), 168.16 (C=O). Anal. Calcd for $C_{19}H_{18}FNO_3$: C, 69.71; H, 5.54; N, 4.28%. Found: C, 69.65; H, 5.59; N, 4.22.

Synthesis of Methyl 1-methoxy-2-(3-methylbut-2-en-1-yl)-9H-carbazole-3-carboxylate ***(21)***

Following the same procedure adopted for the synthesis of **7**, the reaction of compound **19** with iodomethane gave the title compound **21** as colorless crystalline solid. Yield: 0.20 g, 71%; m.p. 129-133 ^{o}C; IR (neat): 3334, 2936, 1707, 1685, 1626, 1605, 1568, 1494, 1430, 1389, 1342, 1242, 1097 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.69 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 3.91-3.96 (m, 8H, 2 x OCH_3, Ar*CH*$_2$-), 5.24 (m, 1H, $ArCH_2$*CH*=$C(CH_3)_2$), 7.25 (m, 1H, Ar-H), 7.42-7.45 (m, 2H, Ar-H), 8.07 (d, *J* = 7.9 Hz, 1H, Ar-H), 8.58 (br. s, 1H, NH), 8.46 (s, 1H, Ar-H); ^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 18.10 (CH_3), 25.74 (CH_3), 25.96 (CH_2), 51.96 (OCH_3), 61.08 (OCH_3), 111.12, 120.16, 120.20, 120.46, 122.37, 122.66, 123.91, 124.19, 126.28, 131.28, 133.21, 135.57, 139.95, 143.22, 168.80 (C=O). Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33%. Found: C, 74.23; H, 6.60; N, 4.27.

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*Synthesis of Methyl 6-fluoro-1-methoxy-2-(3-methylbut-2-en-1-yl)-9H-carbazole-3-carboxylate (**22**)*

Following the same procedure adopted for the synthesis of **7**, the reaction of compound **20** with iodomethane gave the title compound **22** as a white solid. Yield: 0.15 g, 84%; m.p. 115-116 ºC; IR (neat): 3395, 2967, 1692, 1631, 1609, 1587, 1485, 1434, 1377, 1345, 1320, 1274, 1230, 1187, 1167, 1040 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.69 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 3.91-3.96 (m, 8H, 2 x OCH_3, Ar*CH_2*-), 5.22 (m, 1H, $ArCH_2$*CH*=$C(CH_3)_2$), 7.17 (td, *J* = 2.4, 8.8 Hz, 1H, Ar-H), 7.37 (dd, *J* = 4.2, 8.8 Hz, 1H, Ar-H), 7.68 (dd, *J* = 2.4, 8.8 Hz, 1H, Ar-H), 8.25 (br. s, 1H, NH), 8.40 (s, 1H, Ar-H); ^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 18.12 (CH_3), 25.77 (CH_3), 25.94 (CH_2), 52.00 (OCH_3), 61.17 (OCH_3), 106.35 (d, *J* = 24.90), 111.66 (d, *J* = 9.34), 114.13 (d, *J* = 24.90), 120.33, 122.28, 122.68, 123.93, 124.61, 124.68, 131.52, 133.81, 136.07, 136.55, 143.29, 157.89 (d, *J* = 236.54, C-6), 168.47 (C=O). Anal. Calcd for $C_{20}H_{20}FNO_3$: C, 70.37; H, 5.91; N, 4.10%. Found: C, 70.33; H, 5.95; N, 4.06.

Synthesis of 1-Methoxy-2-(3-methylbut-2-en-1-yl)-9H-carbazole-3-carboxylic acid (**23**)

To a solution of **21** (0.01 g, 0.30 mmol) in a mixture of MeOH (2 mL) and THF (1 mL) was added a solution of KOH (15 mL, 30% in H_2O) and the mixture was heated overnight at 50 ºC. The reaction was cooled to room temperature, acidified to pH 4 with 2M HCl and then extracted with ethyl acetate (2 x 30 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was passed through a pad of silica, eluting with hexanes:ethyl acetate (50:50) to afford compound **23** as a white crystalline solid. Yield: 80%, m.p. 176-177 ºC; IR (neat): 3337, 3062, 2925, 1675, 1610, 1448, 1406, 1278, 1236, 1031 cm^{-1}; ^{1}H-NMR (500 MHz, CD_3OD): δ 1.57 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 3.85 (d, *J* = 5.5 Hz, 1H, Ar*CH_2*-), 5.14 (m, 1H, $ArCH_2$*CH*=$C(CH_3)_2$), 7.08 (td, *J* = 1.1, 7.95 Hz, 1H, Ar-H), 7.28 (td, *J* =

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1.2, 7.35 Hz, 1H, Ar-H), 7.39 (d, *J* = 7.9 Hz, 1H, Ar-H), 7.93 (d, *J* = 7.95 Hz, 1H, Ar-H), 8.37 (s, 1H, Ar-H); ^{13}C-NMR (125.7 MHz, CD_3OD): δ 18.20 (CH_3), 25.94 (CH_3), 26.65 (CH_2), 61.35 (OCH_3), 120.62, 120.95, 121.00, 123.13, 123.73, 124.79, 125.65, 127.08, 131.50, 133.87, 137.05, 142.10, 144.72, 172.09 (C=O). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53%. Found: C, 73.72; H, 6.24; N, 4.48.

*Synthesis of 6-Fluoro-1-methoxy-2-(3-methylbut-2-en-1-yl)-9H-carbazole-3-carboxylic acid (**24**)*

Following the same procedure adopted for the synthesis of **23**, the basic hydrolysis of **22** gave the title compound **24** as a white crystalline solid from. Yield: 0.084 g, 77%; m.p. 196-197 ºC; IR (neat): 3455, 3040, 2913, 1664, 1634, 1612, 1588, 1569, 1489, 1443, 1376, 1342, 1317, 1277, 1243, 1192, 1170, 1098 cm^{-1}; ^{1}H-NMR (500 MHz, CD_3OD): δ 1.65 (s, 3H, CH_3), 1.79 (s, 3H, CH_3), 3.91-3.96 (s, 5H, OCH_3, Ar*CH*$_2$-), 5.22 (m, 1H, $ArCH_2$*CH*=$C(CH_3)_2$), 7.14 (td, *J* = 2.4, 8.8 Hz, 1H, Ar-H), 7.43 (dd, *J* = 4.3, 8.8 Hz, 1H, Ar-H), 7.70 (dd, *J* = 2.4, 8.8 Hz, 1H, Ar-H), 8.45 (s, 1H, Ar-H); ^{13}C-NMR (125.7 MHz, CD_3OD): δ 18.19 (CH_3), 25.92 (CH_3), 26.66 (CH_2), 61.35 (OCH_3), 106.53 (d, *J* = 23.86), 113.05 (d, *J* = 9.34), 114.64 (d, *J* = 25.93), 121.28, 123.29, 125.34, 125.42, 125.79, 131.63, 134.35, 138.10, 138.41, 144.79, 158.96 (d, *J* = 234.47, C-6), 171.92 (C=O). Anal. Calcd for $C_{19}H_{18}FNO_3$: C, 69.71; H, 5.54; N, 4.28%. Found: C, 69.67; H, 5.58; N, 4.22.

*Synthesis of 3-(2-Hydroxypropan-2-yl)-5-methoxy-3,4-dihydropyrano[4,3-b]carbazol-1(6H)-one (**1**)*

To an ice-cold solution of **23** (0.025 g, 0.081 mmol) in anhydrous CH_2Cl_2 (5 mL) was added *m*-CPBA (0.021 g, 0.122 mmol) and the reaction was stirred for 2 h at room temperature. After the completion of reaction (TLC analysis) the solvent was evaporated under vacuum and

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residue was diluted with H_2O (5 mL) and extracted with ethyl acetate (2 x 10 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (2 x 6 mL) followed by water (6 mL) and brine (6 mL). The organic phase was dried over Na_2SO_4 and evaporated under vacuum. The residue was purified by silica column, eluting with hexanes:ethyl acetate (50:50) to get the title compound **1** as a light brown solid. Yield: 0.02 g, 78%. All the spectral data of **1** matched with those of natural mafaicheenamine A [12]. ^{1}H-NMR (500 MHz, acetone-d_6): δ 1.37 (s, 3H, H-4'/ H-5'), 1.38 (s, 3H, H-4'/H-5'), 3.01 (dd, *J* = 12.5, 16.4 Hz, 1H, H-1'b), 3.47 (dd, *J* = 2.5, 16.4 Hz, 1H, H-1'a), 3.98 (s, 3H, OCH_3), 4.30 (dd, *J* = 2.5, 12.6 Hz, 1H, H-2'), 7.25 (ddd, *J* = 1.3, 7.4, 8.1 Hz, 1H, H-6), 7.47 (ddd, *J* = 1.2, 7.3, 8.1 Hz, 1H, H-7), 7.56 (d, *J* = 8.1 Hz, 1H, H-8), 8.24 (d, *J* = 8.1 Hz, 1H, H-5), 8.60 (s, 1H, H-4), 10.95 (br. s, 1H, NH); ^{13}C-NMR (125.7 MHz, acetone-d_6): δ 23.30 (C-1'), 25.29 (C-5'), 26.86 (C-4'), 61.39 (OCH_3), 71.28 (C-3'), 85.21 (C-2'), 112.62 (C-8), 118.04 (C-3), 119.92 (C-4), 121.09 (C-6), 121.52 (C-5), 124.46 (C-4a), 124.93 (C-4b), 127.59 (C-7), 129.69 (C-2), 137.50 (C-9a), 141.68 (C-8a), 142.17 (C-1), 166.49 (C-10).

Natural mafaicheenamine A [12]

^{1}H-NMR (400 MHz, acetone-d_6): δ 1.37 (s, 6H, H-4', H-5'), 3.02 (dd, *J* = 12.4, 16.4 Hz, 1H, H-1'b), 3.47 (dd, *J* = 2.4, 16.4 Hz, 1H, H-1'a), 3.99 (s, 3H, OCH_3), 4.29 (dd, *J* = 2.4, 12.4 Hz, 1H, H-2'), 7.26 (ddd, *J* = 1.2, 7.2, 8.0 Hz, 1H, H-6), 7.46 (ddd, *J* = 1.2, 7.2, 8.0 Hz, 1H, H-7), 7.56 (d, *J* = 8.0 Hz, 1H, H-8), 8.23 (d, *J* = 8.0 Hz, 1H, H-5), 8.59 (s, 1H, H-4), 10.96 (br. s, 1H, NH); ^{13}C-NMR (100 MHz, acetone-d_6): δ 23.2 (C-1'), 25.3 (C-5'), 26.8 (C-4'), 61.3 (OCH_3), 71.2 (C-3'), 85.1 (C-2'), 112.5 (C-8), 118.0 (C-3), 119.8 (C-4), 121.0 (C-6), 121.5 (C-5), 124.4 (C-4a), 124.9 (C-4b), 127.5 (C-7), 129.6 (C-2), 137.4 (C-9a), 141.6 (C-8a), 142.1 (C-1), 166.4 (C-10).

*Synthesis of 9-Fluoro-3-(2-hydroxypropan-2-yl)-5-methoxy-3,4-dihydropyrano[4,3-b]carbazol-1(6H)-one (**2**)*

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Following the same procedure adopted for the synthesis of **1**, the oxidative cyclization of **24** gave the title compound **2** as a white crystalline solid from. Yield: 0.036 g, 80%; m.p. 276-277 ºC; IR (neat): 3506, 3218, 2989, 2971, 2933, 1691, 1634, 1612, 1584, 1506, 1482, 1385, 1362, 1323, 1293, 1265, 1240, 1216, 1166, 1121, 1080, 1045 cm^{-1}; ^{1}H-NMR (500 MHz, CD_3OD): δ 1.38 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 3.00 (dd, *J* = 12.8, 16.4 Hz, 1H, H-1'b), 3.45 (dd, *J* = 16.4, 2.7 Hz, 1H, H-1'a), 3.98 (s, 3H, OCH_3), 4.29 (dd, *J* = 2.7, 12.8 Hz, 1H, H-2'), 7.20 (dd, *J* = 6.4, 8.8 Hz, 1H, Ar-H), 7.48 (dd, *J* = 4.3, 8.8 Hz, 1H, Ar-H), 7.80 (dd, *J* = 2.4, 8.8 Hz, 1H, Ar-H), 8.55 (s, 1H, Ar-H); ^{13}C-NMR (125.7 MHz, CD_3OD): δ 21.96 (C-1'), 23.69 (CH_3), 24.94 (CH_3), 59.99 (OCH_3), 70.41 (C-3'), 84.53 (C-2'), 105.55 (d, *J* = 24.90), 111.94 (d, *J* = 9.34), 113.98 (d, *J* = 25.98), 115.65, 119.32, 123.66, 123.86 (d, *J* = 9.33), 123.89, 128.53, 137.06, 137.84, 141.09, 157.79 (d, *J* = 235.50, C-6), 167.49 (C=O). Anal. Calcd for $C_{19}H_{18}FNO_4$: C, 66.46; H, 5.28; N, 4.08%. Found: C, 66.40; H, 5.33; N, 4.03.

Conclusions

In conclusion, the first total synthesis of mafaicheenamine A, an antitumoral carbazole alkaloid having potent activity against breast cancer cell lines and moderate activities against oral cavity cancer and small lung cancer have been described. In addition, owing to high importance and utility of fluorine substituents in drug discovery, the synthesis of unnatural 6-fluoromafaicheenamine A has also been achieved. Moreover, our synthetic approach furnishes an expedient synthesis of clausine E, a key intermediate in the course of synthesis of mafaicheenamine A and 6-fluoromafaicheenamine A**.**

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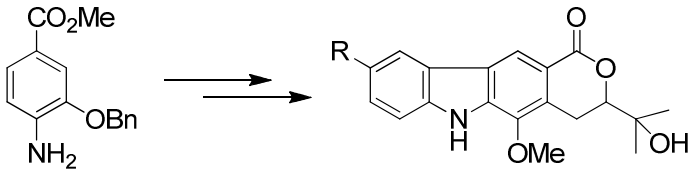
Graphical Abstract



(**1**) R = H
($1C_{50}$ = 2.96 µg/mL)
breast cancer (MCF7)
(**2**) R = F

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