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Graphical abstract

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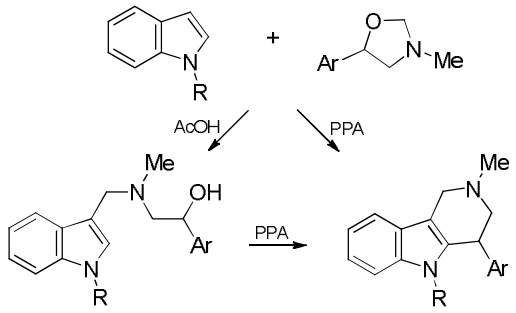

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A one-pot synthesis of 1-aryl-3-methyl-1,2,3,4-tetrahydro-γ-carbolines from 5-aryloxazolidines and indoles via a Mannich/Friedel–Crafts sequence

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A B S T R A C T

Benzaldehydes react smoothly with the nonstabilized azomethine ylide derived from sarcosine and formaldehyde to form 5-aryloxazolidines, which undergo ring-opening to give 2-(indol-3-ylmethylamino)-1-arylethanols in 69–79% yields on reaction with indoles in acetic acid. Their subsequent acid-catalyzed cyclization into 2-methyl-4-aryl-1,2,3,4-tetrahydro-γ-carbolines was performed in polyphosphoric acid in moderate yields. The latter can also be prepared directly from 5-aryloxazolidines and indoles in polyphosphoric acid.

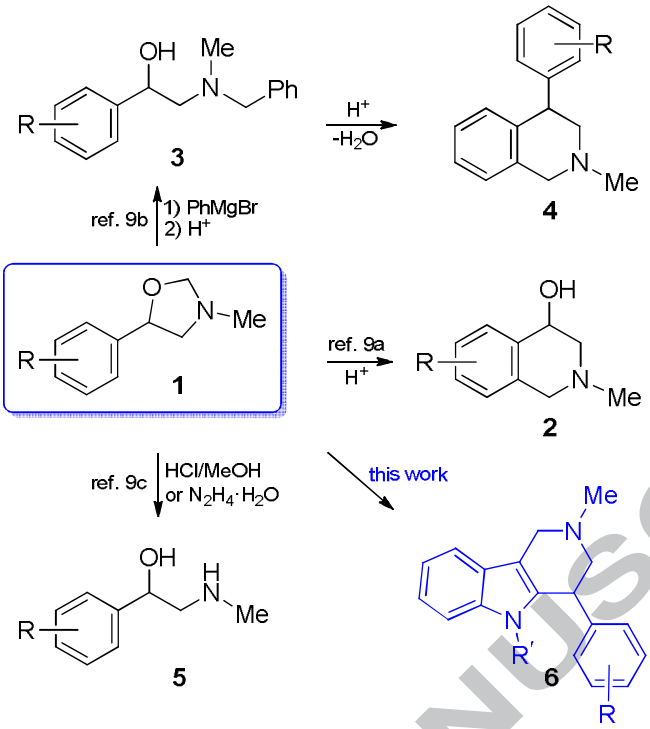
Keywords: 5-Aryloxazolidines; Indoles; 1,2,3,4-Tetrahydro-γ-carbolines; Phenylethanolamines; Benzaldehydes; Nonstabilized azomethine ylides.

Derivatives of 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole, also known as 1,2,3,4-tetrahydro-γ-carboline, constitute the skeleton of a number of physiologically active natural products and such well-known drugs as Diazoline, Dimebon, and their analogues.[1] Tetrahydro-γ-carbolines have attracted strong interest in medicinal chemistry due to their useful biological properties and methods for their synthesis and pharmacological data on these heterocycles have been reviewed.[1,2] Because of the important applications of γ-carboline derivatives, various synthetic methodologies have been developed for the production of these compounds, however, novel methods for annelation of the piperidine fragment to the indole molecule are still required in organic chemistry.

In particular, there are a limited number of syntheses of 1-aryl-1,2,3,4-tetrahydro-γ-carbolines, which afford moderate yields only. Generally, these compounds are synthesized by the Friedel–Crafts reaction starting from 2-(indol-3-ylmethylamino)-1-arylethanols[3] (products of sodium borohydride reduction of imines prepared from indole-3-carboxaldehyde and ethanolamines[4]) and

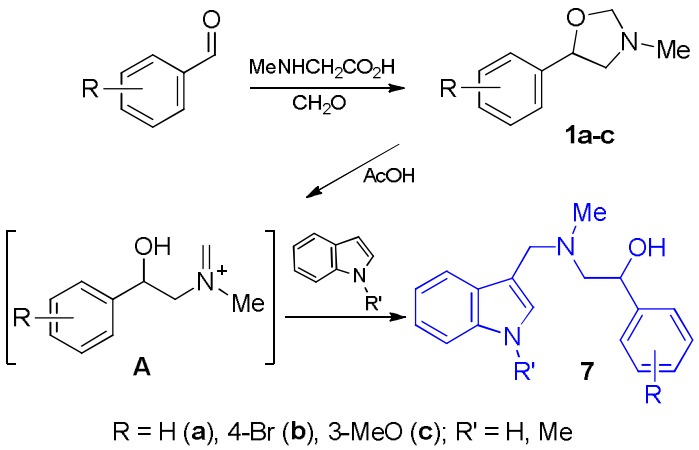
N-(indol-3-ylmethyl)ephedrines[5] (products of the Mannich reaction of ephedrines with formaldehyde and indoles) in concentrated sulfuric acid. The parent 4-phenyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole has been synthesized by the addition of β-nitrostyrene to a lithiated 1-diethoxymethylindole, followed by reduction of the corresponding 1-diethoxymethyl-2-(2-nitro-1-phenylethyl)indole and Pictet–Spengler recyclization.[6] Alternatively, this compound can be obtained by the involvement of the corresponding indol-3-ylmethylaminoethanol in the Friedel–Crafts cyclization.[3] Information on the synthesis of 1,2,3,4-tetrahydro-γ-carbolines from oxazolidines and indoles is absent from the literature. Nevertheless, *N*-alkyl-1,3-oxazolidines react with indole and *N*-methylindole in the presence of $MeSiCl_3$ to form the expected Mannich bases.[7]

In connection with our interest in the chemistry of 5-aryloxazolidines **1**, which are easily obtained from aromatic aldehydes and nonstabilized azomethine ylides,[8] we have developed convenient methods for the preparation of 1,2,3,4-tetrahydroisoquinolin-4-ols **2**, *N*-benzyl-β-hydroxy-β-phenethylamines **3**, 4-aryl-1,2,3,4-tetrahydroisoquinolines **4** and 2-alkylamino-1-arylethanols **5**.[9] Taking into account these results, we envisaged that the ring-opening of 5-aryloxazolidines **1** by slightly nucleophilic indoles would produce the corresponding Mannich bases, which could be converted into the target 1-aryl-1,2,3,4-tetrahydro-γ-carbolines **6** with the assistance of an acidic catalyst to generate a second electrophilic center. To the best of our knowledge, no such approach has been reported previously and we now describe the first use of the oxazolidine system in the one-pot synthesis of 1,2,3,4-tetrahydro-γ-carbolines (Scheme 1).



Scheme 1. One-pot syntheses of phenethylamine derivatives.

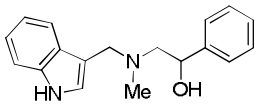
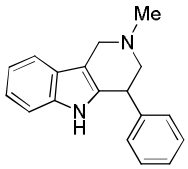
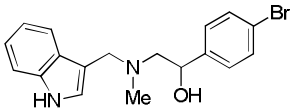
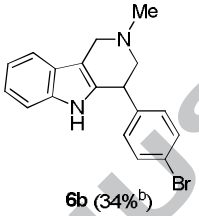
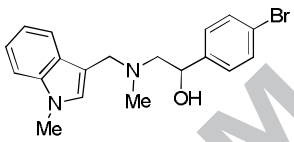
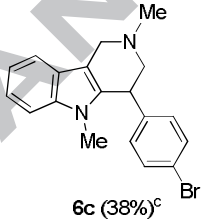
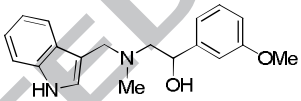
The starting 5-aryloxazolidines **1a–c**, prepared from aromatic aldehydes, sarcosine, and formaldehyde, were used in the subsequent step without any purification. While *p*-bromobenzaldehyde reacted cleanly under the usual conditions (1.5 equiv. of sarcosine, benzene or toluene, azeotropic removal of water), unsubstituted benzaldehyde and *m*-anisaldehyde did not react completely, even using a substantial excess of formaldehyde and sarcosine (up to 2.5 equiv). We have improved the published procedure[8,9] for the preparation of 5-aryloxazolidines **1a,c** via the two-stage addition of a mixture of sarcosine and formaldehyde (first 1.0 equiv of sarcosine and after 2 hours of boiling, a further 0.7 equiv).[10]



Scheme 2. Synthesis of compounds **7**.

Next, it was found that 3-methyl-5-phenyloxazolidine (**1a**) reacted with indole in acetic acid at 70 °C to give liquid Mannich base **7a** after column chromatographic purification (Scheme 2). The first attempt to simplify this process by obtaining the hydrochloride of free base **7a** was not successful due to its low stability. Alternatively, treatment of **7a** with a solution of anhydrous oxalic acid, a weaker acid, in dry Et_2O, allowed us to isolate analytically pure solid hydrogen oxalate **7a** in 76% yield without any chromatography.[10] With optimum conditions for the preparation of Mannich base **7a** in hand, the reactions of oxazolidines **1b,c** as well as *N*-methylindole, were investigated. As can be seen from Table 1, we obtained products **7a**–**d** in high yields (69–79%).[11] An important feature of the present reaction is that oxazolidine **1c**, prepared from *m*-anisaldehyde, reacted smoothly with indole to give amino alcohol **7d**, whereas its intramolecular recyclization into 6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (**2**, R = 6-MeO) via iminium cation **A**, which can act as an internal electrophile, did not occur.[9a] Thus, compounds **2**, **5**, and **7** could be synthesized from the same starting material simply by modifying the reaction conditions. Apparently, the high yield of the Mannich bases **7** might be due to the electron-rich character of the indole ring.

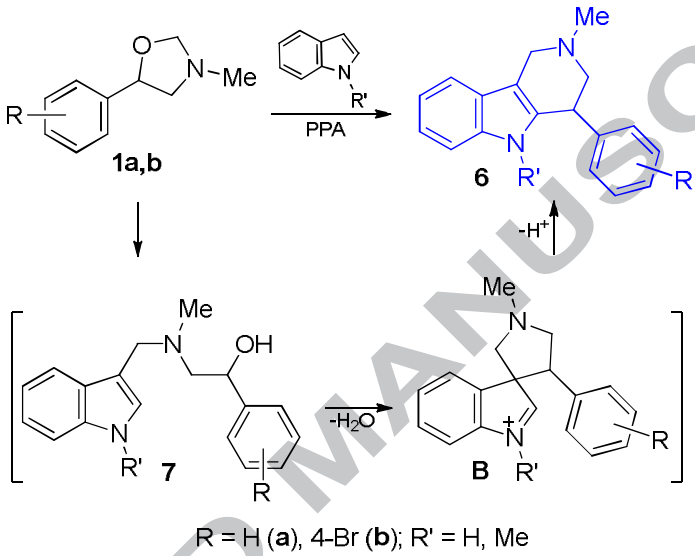
Table 1. The compounds prepared from 5-aryloxazolidines **1** and indoles (yields based on the starting benzaldehyde).

Amino alcohol **7**·$(CO_2H)_2$	Tetrahydro-γ-carboline **6**
 **7a** (76%)	 **6a** (30%, 54%[a])
 **7b** (79%)	 **6b** (34%[b])
 **7c** (73%)	 **6c** (38%)[c]
 **7d** (69%)	–[d]

[a] From **7a**; free base mp 89–93 °C.
[b] As the free base, mp 132–135 °C.
[c] As a hydrogen oxalate salt, mp 179–183 °C.
[d] Inseparable mixture of products.

As mentioned above, the Mannich reaction between indoles and *N*-alkyloxazolidines has been reported,[7] but the preparation of a 1,2,3,4-tetrahydro-γ-carboline via this reaction does not appear to have been described. In connection with this, we attempted to develop optimized conditions for a double electrophilic substitution in a one-pot process from 5-aryloxazolidines **1a–c** and indoles. The development of a one-pot synthesis is attractive since it would obviate the isolation and purification of the intermediate Mannich bases. We found that when 5-aryloxazolidines **1a,b** and indole were heated in polyphosphoric acid (PPA) at 90 °C for 1.5 hours, tetrahydro-γ-carbolines **6a,b** were

obtained in 30% and 34% yields, respectively. Under the same conditions, *N*-methylindole gave the expected product **6c** as a low melting product, which could not be purified by crystallization, and therefore was chromatographed on an SiO_2 column and characterized after conversion into its hydrogen oxalate salt **6c** in 38% yield (Scheme 3). Methods for the cyclization other than by treatment with PPA turned out to be less successful (with catalysts such as trifluoroacetic acid, trifluoroacetic acid in toluene, and *p*-toluenesulfonic acid in toluene or dichloromethane).

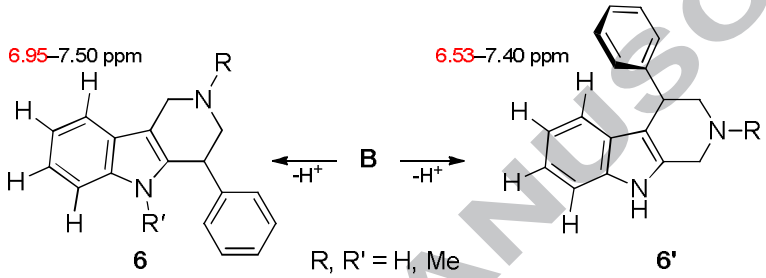


Scheme 3. Synthesis of compounds **6**.

Finally, the cyclization of amino alcohol **7a** to give 2-methyl-4-phenyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (**6a**) was performed in PPA using the above conditions, and the resulting product was isolated after recrystallization from methanol as colorless crystals in 54% yield. All our attempts to cyclize the amino alcohol **7d** or oxazolidine **1c** led to inseparable mixtures of products, probably due to the presence of two nucleophilic aromatic rings, which are able to react with cationic intermediates.

The structures of products **6a–c** and **7a–d** were established by elemental analysis and IR, ^{1}H, and ^{13}C NMR spectroscopy. Despite their simplicity, these compounds were not previously described. It is known that cationic cyclizations such as **7** → **6** occur via spiro intermediate **B**, which can lead to the possibility of the formation of β-carboline **6′** along with γ-carboline **6** (Scheme 4).[5,12,13] The ^{1}H

NMR spectra of known isomers **6′** show significant shielding of the aromatic indole protons (δ 6.53–7.40), being likely due to the mutual influence of two benzene rings.[14] On the other hand, the ^{1}H NMR chemical shifts of the corresponding protons in γ-carbolines **6a–c** are not shielded because of the greater distance between the rings. Indeed, compound **6** (R = R′ = H) had similar proton signals in the δ 6.95–7.50 region as was described earlier.[6] It should be noted that the melting point observed here for **6a** (mp 89–93 °C) differed significantly from that reported for isomeric 3-methyl-1-phenyl-1,2,3,4-tetrahydro-β-carboline (mp 216–218 °C).[15]



Scheme 4. ^{1}H NMR signals of the indole protons.

In conclusion, we have developed a novel and simple method for preparing pharmaceutically valuable 1-aryl-1,2,3,4-tetrahydro-γ-carbolines starting from commercially available benzaldehydes, in a one-pot procedure without purification of the intermediate products. The successful synthesis of these compounds from indoles and oxazolidines suggests that further investigation of other electron-rich heterocycles and arenes might be profitable in this context.

Acknowledgment

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References and notes

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9. (a) Moshkin, V. S.; Sosnovskikh, V. Y. *Tetrahedron Lett.* **2013**, *54*, 2455; (b) Moshkin, V. S.; Sosnovskikh, V. Y. *Tetrahedron Lett.* **2013**, *54*, 2699; (c) Moshkin, V. S.; Sosnovskikh, V. Y. *Tetrahedron Lett.* **2013**, *54*, 5869.
10. *General procedure for the preparation of 5-aryloxazolidines **1***. A mixture of the corresponding aromatic aldehyde (10.0 mmol), finely ground sarcosine (0.89 g, 10 mmol), and paraformaldehyde (0.39 g, 13 mmol of formaldehyde) was refluxed in dry benzene (17 mL), with magnetic stirring and removal of the formed H_2O by means of a Dean-Stark trap. After 2 h, a second portion of sarcosine (0.62 g, 7 mmol), and paraformaldehyde (0.30 g, 10 mmol of formaldehyde) was added. Refluxing was continued for an additional 3–5 h. The resulting solution was evaporated in vacuo to give oily 5-aryl-3-methyloxazolidines **1**, which were used without additional purification.

    *General procedure for the preparation of amino alcohols **7a–d***. To a solution of indole or *N*-methylindole (1.0 mmol) in oxazolidine **1** (1.0 mmol) was added AcOH (1.5 mL). The resulting solution was concentrated in vacuo on a rotary evaporator at 70 °C for 30 min, then H_2O (5 mL) and conc. NH_3 (0.5 mL) were added. The product was extracted with Et_2O (2×7 mL), dried over Na_2SO_4, and the Et_2O removed in vacuo to give crude compound **7**, which was dissolved in dry Et_2O (5 mL) and converted into the hydrogen oxalate salt by treatment with a solution of anhydrous oxalic acid (0.09 g, 1.0 mmol) in dry Et_2O (5 mL). The filtered and washed salt was dried in vacuo on a rotary evaporator at 50 °C for 90 min (stored without moisture).

    *General procedure for the preparation of tetrahydro-γ-carbolines **6a–c***. To a solution of indole or *N*-methylindole (1.0 mmol) in oxazolidine **1** (1.0 mmol) was added warm PPA (1.3 mL) and the resulting mixture was heated to 90 °C for 90 min with stirring (interval 10–15 min) using a spatula. H_2O was added to the residue at room temperature, followed by addition of excess concentrated aqueous NaOH solution with cooling. The mixture was extracted with CH_2Cl_2 (2×7 mL) using a magnetic stirrer, dried over Na_2SO_4, and evaporated to give the crude γ-carboline **6**.

11. *2-{[(1H-Indol-3-yl)methyl](methyl)amino}-1-(3-methoxyphenyl)ethanol hydrogen oxalate (**7d**)*. Light pink powder, yield 69%, mp 68–72 °C (with slow decomposition). IR (ATR): 3304, 3114, 3052, 2963, 2838, 1715, 1600, 1487, 1456, 1432, 1339, 1239, 1191, 1155, 1068, 1035, 919, 870, 743, 694 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.82 (s, 3H, MeN), 3.10–3.20 (m, 2H, CH_2), 3.73 (s, 3H, MeO), 4.51 (d, J = 13.6 Hz, 1H, C*H*H), 4.58 (d, J = 13.6 Hz, 1H, CH*H*), 5.03–5.09 (m, 1H, CH), 6.81 (ddd, J = 8.1, 2.3, 0.8 Hz, 1H, H-4′), 6.89–6.93 (m, 2H, H-2′, H-6′), 7.05 (td, J = 7.4, 0.9 Hz, 1H, H-5/6), 7.12 (td, J = 7.5, 1.0 Hz, 1H, H-6/5), 7.23 (t, J = 8.1 Hz, 1H, H-5′), 7.42 (d, J = 8.0 Hz, 1H, H-4/7), 7.60 (d, J = 2.4 Hz, 1H, H-2), 7.74 (d, J = 7.9 Hz, 1H, H-7/4), 11.51 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 50.7, 55.1, 60.0, 65.0, 67.1, 102.5, 111.5, 112.0, 113.2, 118.0, 118.5, 119.7, 121.7, 127.6, 129.2, 129.5, 136.1, 143.6, 159.3, 164.4. Anal. Calcd for $C_{19}H_{22}N_2O_2 \cdot (CO_2H)_2 \cdot H_2O$: C, 60.28; H, 6.26; N, 6.69. Found: C, 60.42; H, 6.13; N, 6.55.

*2-Methyl-4-phenyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (**6a**)*. The crude product **6a** was dissolved in warm toluene (3.5 mL) and diluted with hexane (13 mL). The mixture was cooled to 0 °C and filtered. The mother liquid was evaporated in vacuo and the residue was recrystallized from MeOH (by cooling in a fridge). Colourless crystals, yield 54% (from **7a**), 30% (from **1a**) mp 89–93 °C (MeOH). IR (ATR): 3392, 3145, 3055, 3027, 2965, 2937, 2870, 2845, 2784, 2743, 1622, 1598, 1492, 1451, 1349, 1326, 1307, 1237, 1225, 1159, 1148, 1121, 1098, 1075, 1052, 1031, 1008, 974, 736, 697 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.40 (s, 3H, MeN), 2.62 (dd, J = 11.3, 6.2 Hz, 1H, 3-C*H*H), 2.98 (dd, J = 11.3, 5.2 Hz, 1H, 3-CH*H*), 3.58 (d, J = 13.6 Hz, 1H, 1-C*H*H), 3.67 (d, J = 13.6 Hz, 1H, 1-CH*H*), 4.25 (t, J = 5.5 Hz, 1H, H-4), 6.94 (t, J = 7.4 Hz, 1H, H-7/8), 7.00 (t, J = 7.5 Hz, 1H, H-8/7), 7.19–7.25 (m, 4H, H-6/9, Ph), 7.27–7.32 (m, 2H Ph), 7.38 (d, J = 7.7 Hz, 1H, H-9/6), 10.56 (s, 1H, NH); ^{13}C NMR (101 MHz, DMSO-d_6) δ 40.9, 45.6, 51.7, 61.7, 108.8, 111.3, 117.6, 118.6, 120.8, 125.4, 126.8, 128.47, 128.54, 134.2, 136.5, 143.1. Anal. Calcd for $C_{18}H_{18}N_2$: C, 82.41; H, 6.92; N, 10.68. Found: C, 82.23; H, 6.76; N, 10.69.

*4-(4-Bromophenyl)-2,5-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole hydrogen oxalate (**6c**)*. The crude product was chromatographed on an SiO_2 column (CH_2Cl_2/MeOH, 100:3). The low melting free base obtained was dissolved in dry acetone and converted into the hydrogen oxalate salt by treatment with a solution of oxalic acid (0.09 g, 1.0 mmol) in dry acetone, then diluted with dry Et_2O. After filtration and washing with Et_2O, the salt was dried in vacuo on a rotary evaporator at 50 °C for 90 min. Light yellow powder, yield 38%, mp 179–183 °C. IR (ATR): 2960, 2879, 2697, 2590, 1717, 1605, 1487, 1472, 1425, 1404, 1354, 1324, 1252, 1184, 1137, 1087, 1014, 956, 818, 752, 700 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.84 (s, 3H, MeN), 3.23 (s, 3H, MeN), 3.33 (dd, J = 11.3, 8.5 Hz, 1H, 3-C*H*H), 3.72 (dd, J = 11.3, 5.4 Hz, 1H, 3-CH*H*), 4.36 (d, J = 14.0 Hz, 1H, 1-C*H*H), 4.44 (d, J = 14.0 Hz, 1H, 1-CH*H*), 4.75 (br t, J = 6.0 Hz, 1H, H-4), 7.09 (t, J = 7.3 Hz, 1H, H-7/8), 7.15–7.24 (m, 3H, H-2′, H-6′, H-8/7), 7.39 (d, J = 8.1 Hz, 1H, H-6/9), 7.53 (d, J = 7.8 Hz, 1H, H-9/6), 7.57 (d, J = 7.8 Hz, 2H, H-3′, H-5′); ^{13}C NMR (101 MHz, DMSO-d_6) δ 30.2, 37.1, 42.5, 50.2, 57.9, 104.9, 109.6, 117.9, 119.4, 120.7, 121.8, 124.1, 130.5, 131.8, 132.6, 137.3, 139.3, 163.8. Anal. Calcd for $C_{19}H_{19}BrN_2 \cdot (CO_2H)_2 \cdot 0.5H_2O$: C,

55.52; H, 4.88; N, 6.17. Found: C, 55.35; H, 4.84; N, 6.12.

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