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SYNTHESIS OF 8-SUBSTITUTED 12-METHYL-12H- IMIDAZO[4',5': 2, 3][1,4]DIAZEPINO[6,7,1-*jk*]CARBAZOLES

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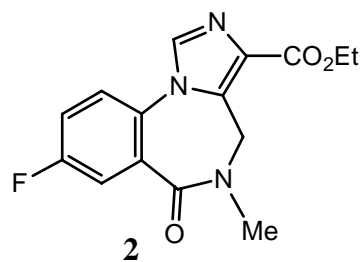
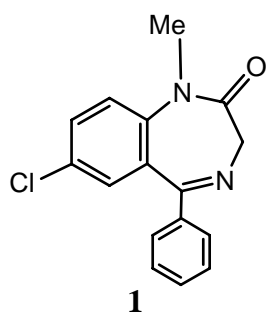
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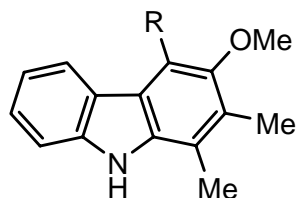
Abstract– A synthesis of model 8-substituted-12-methyl-12*H*-imidazo[4', 5': 2, 3][1,4]-diazepino[6,7,1-*jk*]carbazoles (**10a-c**), based on the classical Bischler-Napieralski method, is described. Thus interaction of carbazole with 5-chloro-1-methyl-4-nitro-1*H*-imidazole (in the presence of sodium hydride) produced the corresponding 9-(1-methyl-4-nitro-1*H*-imidazole-5-yl)-9*H*-carbazole (**7**). Chemical reduction of the nitro group of **7** into the respective amino derivative **8**, and subsequent acylation of the resulting amino group furnished the respective amides **9a-c**. Cyclocondensation of the latter amides, using polyphosphoric acid under Bischler-Napieralski reaction conditions, delivered the target compounds **10a-c**. The structures of these new pentacyclic heterocycles were supported by IR, MS, and NMR spectral data.

INTRODUCTION

The synthetic interest in 1,4-benzodiazepines (*e.g.* valium **1**) arises from their well-established role as potential psychotherapeutics.¹ Several studies have reported² the preparation of related members of the 1,4-benzodiazepine family exemplified by clozapine **2**. Currently, compound **2** is a typical antipsychotic drug, used clinically to treat schizophrenia.

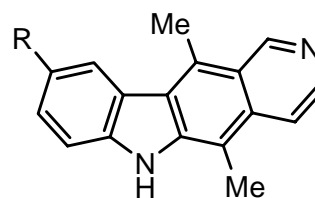


On the other hand, the carbazole system is found in a number of naturally occurring alkaloids, such as carbazomycins A and B (**3a** and **3b**, respectively),³ and ellipticine **4a** (and the related derivative **4b**) having a pyrido[4,3-*b*]carbazole system.⁴ The former carbazoles **3a**, **3b** prevent the growth of pyropathogenic fungi, and possess antibacterial and anti-yeast activities,³ while the latter derivatives (ellipticines **4**) are of interest as anticancer agents.



carbazomycin A (**3a**: R = OMe)

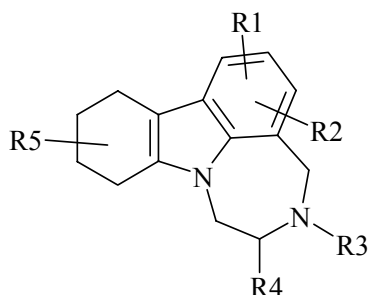
carbazomycin B (**3b**: R = OH)



ellipticines (**4a**: R = H)

(**4b**: R = OMe)

A large number of octahydro[1,4]diazepino[6,7,1-*jk*]carbazole derivatives (**5**) and (**6**) have recently been prepared and found to act as serotonin 5-HT_{2C} receptor agonists.^{5,6} Compound **5** was reported to be selective for the 5-HT_{2C} receptor versus several other serotonin receptor subtypes, the serotonin transporter, and other non-serotonin receptors and ion channels.⁶ These derivatives have been patented as useful agents for the treatment of diseases involving the central nervous system such as obsessive – compulsive disorder, depression, anxiety, schizophrenia, panic disorder, migraine, sleep disorders, obesity, epilepsy and spinal cord injury.⁵



5 (R1 → R5 = H)

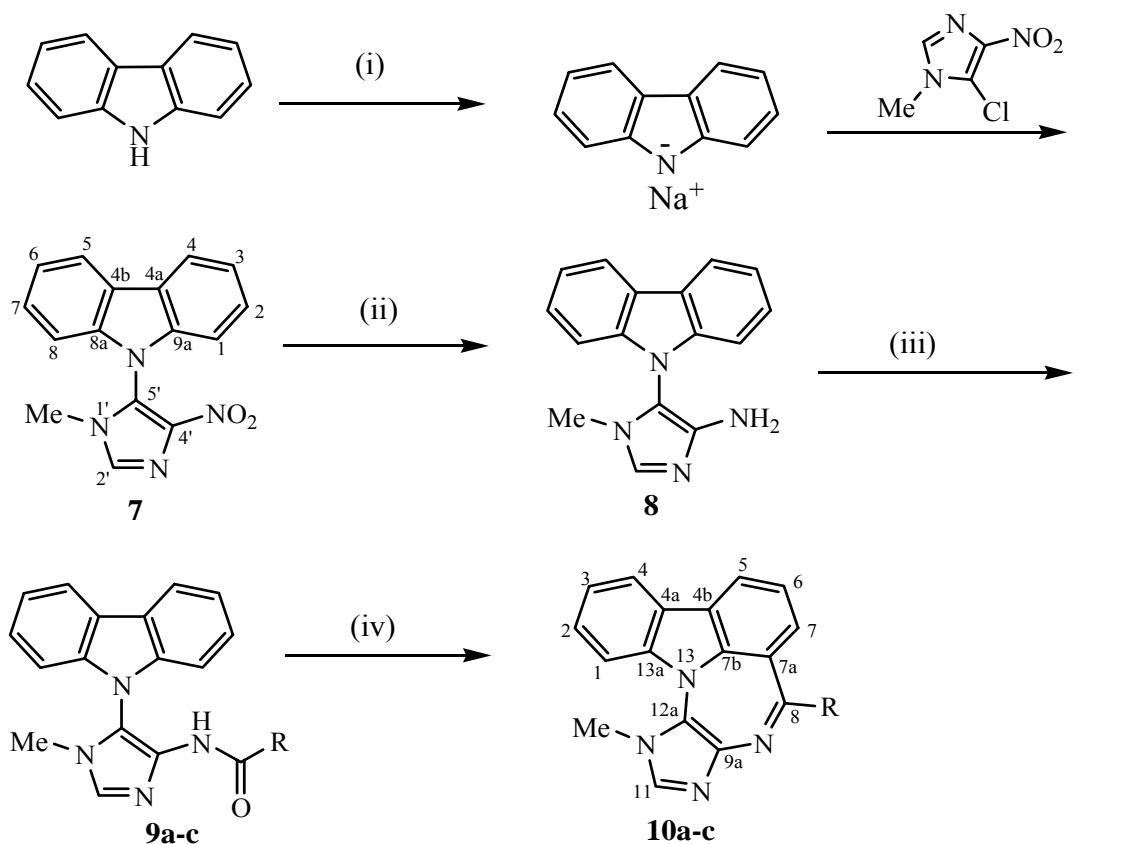
6 (R1, R2 = H / alkyl, *c*-alkyl, alkoxy, halo)

(R3, R4 and R5 = H / alkyl)

We sought to prepare model derivatives of the hitherto undescribed pentacyclic heteroring system incorporating an imidazodiazepine moiety condensed with carbazole (compounds **10a-c** / Scheme 1). Herein we report on the spectral characterization of **10a-c** for which the synthetic steps are summarized in Scheme 1.

RESULTS AND DISCUSSION

The first step towards a synthesis of the target compounds **10a-c** involved direct interaction between a solution of carbazole (in the form of its nitrogen anion) and 5-chloro-4-nitro-1-methylimidazole in dry THF at room temperature. This nucleophilic aromatic substitution ($S_N\text{-Ar}$) reaction is facilitated by the presence of the nitro group and delivered the respective 9-(1-methyl-4-nitro-1*H*-imidazol-5-yl)-9*H*-carbazole **7** which, in turn, is reduced to the corresponding amino derivative **8** using Tin(II) chloride (Scheme 1).



Scheme 1. (i) NaH / THF; (ii) SnCl₂/EtOH
 (iii) RCOCl, THF / 0 – 20 °C
 (iv) PPA / 120 – 140 °C

entry	a	b	c
R	Me		

Acylation of the amino group in **8** with the appropriate acyl chlorides produced the respective carboxamido derivatives **9a-c**. The latter compounds readily underwent cyclization in polyphosphoric acid (PPA) at 120-140 °C to furnish the desired products **10a-c**. The later acylation-cyclocondensation steps are applications of the Bischler-Napieralski type reaction⁷ (Scheme 1). The IR, MS and NMR spectral data of compounds **7**, **8**, **9a-c** and **10a-c** are in accordance with the suggested structures, and are given in the experimental part. Thus, their MS spectra display the correct M^+ data which are in agreement with the calculated values as suggested by their molecular formulae. Assignment of the ¹H- and ¹³C

signals to the different respective protons and carbons are based on DEPT and 2D (COSY, HMQC, and HMBC) experiments, which showed correlations that helped in these assignments.

EXPERIMENTAL

5-Chloro-1-methyl-4-nitro-1*H*-imidazole and carbazole were purchased from Acros. Melting points (uncorrected) were measured on a SMP2 Stuart apparatus. Infrared (IR) spectra were recorded as KBr discs on a Nicolet-MAGNA-IR-560 spectrometer. ¹H- and ¹³C-NMR spectra were measured on Bruker DPX-300 spectrometers with CDCl₃ or DMSO-*d*₆ as solvents and tetramethylsilane as an internal standard. Electron impact mass spectra were measured using a Varian MAT-112S spectrometer at 70 eV. Microanalyses were performed at the Microanalytical Laboratory, Chemistry Department, The Hashemite University, Jordan.

9-(1-Methyl-4-nitro-1*H*-imidazol-5-yl)-9*H*-carbazole (7)

Sodium hydride (0.13 g, 5.4 mmol) was added to a stirred solution of carbazole (0.84 g, 5 mmol) in dry THF (10 mL). To this carbazole anion was added dropwise a solution of 5-chloro-4-nitro-1-methylimidazole (0.81 g, 5 mmol) in dry THF (3 mL). The reaction mixture was stirred at rt for 3-4 days, then concentrated under reduced pressure and the residual solid product was collected, washed several times with water, air-dried, and recrystallization from CHCl₃ / petroleum ether (40-60 °C) to afford yellow crystals. Yield of **7** = 1.2 g (82%), mp 217-219 °C. *Anal.* Calcd for C₁₆H₁₂N₄O₂ (292.29): C, 65.75; H, 4.14; N, 19.17. Found: C, 65.67; H, 4.2; N, 19.13; IR(KBr): ν 1598 cm⁻¹ (C=N), and (1516, 1375) cm⁻¹ (NO₂); EI MS *m/z* (%): 291 (100, M⁺); ¹H NMR (300 MHz, CDCl₃): δ 3.32 (s, 3H, N-CH₃), 7.04 (d, 2H, *J* = 7.8 Hz, H-1 / H-8), 7.40 (m, 4H, H-2 / H-7 and H-3 / H-6), 7.80 (s, 1H, H-2'), 8.14 (d, 2H, *J* = 7.6 Hz, H-4 / H-5); ¹³C NMR (75 MHz, CDCl₃): δ 33.1(N-CH₃), 108.2 (C-1 / C-8), 121.7 (C-4a / C-4b), 122.3 (C-2 / C-7), 124.3 (C-4 / C-5), 124.4 (C-8a / C-9a), 124.6 (C-5'), 128.3 (C-3 / C-6), 135.1 (C-2'), 140.0 (C-4').

9-(4-Amino-1-methyl-1*H*-imidazol-5-yl)-9*H*-carbazole (8)

Anhydrous tin(II) chloride (3.1 g, 16.3 mmol) was added to a stirred solution of 9-(1-methyl-4-nitro-1*H*-imidazol-5-yl)-9*H*-carbazole (**7**) (1.17 g, 4 mmol) in absolute EtOH (20 mL). The reaction mixture was refluxed at 95 °C for 3-4 h. The resulting solution was cooled, basified with a saturated aqueous NaHCO₃ to pH~12 and extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried (anhydrous MgSO₄), the solvent was concentrated under reduced pressure and the residual product was purified by washing several times with petroleum ether (40-60 °C) to give the desired compound as a pale yellow solid. Yield of **8** = 0.7 g (67%), mp 158-160 °C. *Anal.* Calcd for

$C_{16}H_{14}N_4$ (262.32): C, 73.26; H, 5.38; N, 21.36. Found: C, 73.11; H, 5.26; N, 21.47; IR(KBr): ν 1628 cm^{-1} (C=N), and (3283, 3420) cm^{-1} (NH₂); EI MS m/z (%): 261 (100, M⁺); ¹H NMR (300 MHz, CDCl₃): δ 3.32 (s, 3H, N-CH₃), 3.51 (bs, 2H, NH₂), 7.10 (d, 2H, $J = 7.7$ Hz, H-1 / H-8), 7.34 (m, 4H, H-2 / H-7 and H-3 / H-6), 7.43 (s, 1H, H-2'), 8.10 (d, 2H, $J = 7.7$ Hz, H-4 / H-5); ¹³C NMR (75 MHz, CDCl₃): δ 31.1 (N-CH₃), 109.9 (C-1 / C-8), 120.3 (C-4'), 120.5 (C-2 / C-7), 120.7 (C-4 / C-5), 123.7 (C-8a / C-9a), 124.6 (C-9), 126.5 (C-3 / C-6), 132.7 (C-2'), 141.5 (C-5'), 141.8 (C-4a / C-4b)

***N*-[5-(Carbazol-9-yl)-1-methyl-1*H*-imidazol-4-yl]carboxamides (9a-c)**

General procedure:

The appropriate acid chloride (1.5 mmol) was added dropwise to a solution of 9-(1-methyl-4-amino-1*H*-imidazol-5-yl)-9*H*-carbazole (**8**) (0.26 g, 1 mmol) in 30 mL of dry THF at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h, and stirring was then maintained at ambient temperature overnight. The solvent was removed under vacuum and the residual solid product was filtered, washed with petroleum ether (40-60 °C), dried and recrystallized from EtOH to give the desired product. The compounds **9a-c** were prepared following the above procedure:

***N*-[5-(Carbazol-9-yl)-1-methyl-1*H*-imidazol-4-yl]acetamide (9a)**

This compound was prepared from **8** (0.26 g, 1 mmol) and acetyl chloride (0.1 g, 1.26 mmol). Yield of **9a** = 0.21 g, (70 %), mp 259-260 °C. *Anal.* Calcd for C₁₈H₁₆N₄O (304.35): C, 71.04; H, 5.30; N, 18.41. Found: C, 70.93; H, 5.17; N, 18.36; IR(KBr): ν 1678 cm^{-1} (C=O), 1613 cm^{-1} (C=N), and 3415 cm^{-1} (NH); EI MS m/z (%): 304 (64, M⁺), 261 (18), 43(100); ¹H NMR (300 MHz, DMSO-*d*₆): δ 1.82 (s, 3H, CO-CH₃), 3.30 (s, 3H, N-CH₃), 7.22 (d, 2H, $J = 7.8$ Hz, H-1 / H-8), 7.31 (dd, 2H, $J = 7.8, 7.4$ Hz, H-3 / H-6), 7.42 (dd, 2H, $J = 7.8, 7.4$ Hz, H-2 / H-7), 8.23 (d, 2H, $J = 7.7$ Hz, H-4 / H-5), 9.14 (s, 1H, H-2'), 10.63 (s, 1H, NH); ¹³C NMR (75 MHz, CDCl₃): δ 22.9 (CO-CH₃), 33.1 (N-CH₃), 110.8 (C-1 / C-8), 115.0 (C-5'), 121.2 (C-4 / C-5), 121.9 (C-3 / C-6), 123.9 (C-4a / C-4b), 126.9 (C-4'), 127.3 (C-2 / C-7), 133.5 (C-2'), 140.9 (C-8a / C-9a), 170.1 (C=O).

***N*-[5-(Carbazol-9-yl)-1-methyl-1*H*-imidazol-4-yl]-4-methylbenzamide (9b)**

This compound was prepared from **8** (0.26 g, 1 mmol) and 4-methylbenzoyl chloride (0.16 g, 1.1 mmol). Yield of **9b** = 0.3 g, (79 %), mp 238-240 °C. *Anal.* Calcd for C₂₄H₂₀N₄O (380.45): C, 75.77; H, 5.30; N, 14.73. Found: C, 75.64; H, 5.41; N, 14.76; IR(KBr): ν 1692 cm^{-1} (C=O), 1619 cm^{-1} (C=N), and 3414 cm^{-1} (NH); EI MS m/z (%): 380 (58, M⁺), 261 (14), 119 (100); ¹H NMR (300 MHz, DMSO-*d*₆): δ 2.23 (s, 3H, C(4'')-CH₃), 3.32 (s, 3H, N-CH₃), 7.11 (d, 2H, $J = 7.9$ Hz, H-3'' / H-5''), 7.20 (d, 2H, $J = 7.7$ Hz, H-1 / H-8), 7.34 (dd, 2H, $J = 7.7, 7.0$ Hz, H-3 / H-6), 7.42 (dd, 2H, $J = 7.7, 7.0$ Hz, H-2 / H-7), 7.60 (d, 2H, $J = 7.9$ Hz, H-2'' / H-6''), 8.23 (d, 2H, $J = 7.6$ Hz, H-4 / H-5), 8.91 (s, 1H, H-2'), 10.62 (s, 1H,

NH), ^{13}C NMR (75 MHz, CDCl_3): δ 21.4 (C-4''-CH₃), 33.1 (N-CH₃), 110.8 (C-1 / C-8), 121.2 (C-4 / C-5), 121.7 (C-3 / C-6), 123.8 (C-4a / C-4b), 127.1 (C-2 / C-7), 128.2 (C-2'' / C-6''), 129.3 (C-3'' / C-5''), 129.4 (C-2'), 130.3 (C-5'), 134.4 (C-4'), 138.7 (C-4''), 140.7 (C-8a / C9a), 143.0 (C-1''), 166.8 (C=O).

***N*-[5-(Carbazol-9-yl)-1-methyl-1*H*-imidazol-4-yl]thiophene-2-carboxamide (9c)**

This compound was prepared from **8** (0.26 g, 1 mmol) and thiophene 2-carbonyl chloride (0.16 g, 1.1 mmol). Yield of **9c** 0.27 g, (73 %), mp 255-256 °C. *Anal.* Calcd for C₂₁H₁₆N₄OS (372.45): C, 67.72; H, 4.33; N, 15.04; S, 8.61. Found: C, 67.46; H, 4.51; N, 15.01; S, 8.51 ; IR(KBr): ν 1686 cm⁻¹ (C=O), 1610 cm⁻¹ (C=N), and 3414 cm⁻¹ (NH); EI MS *m/z* (%): 372 (75, M⁺), 261 (55), 111 (100); ^1H NMR (300 MHz, DMSO-*d*₆): δ 3.31 (s, 3H, N-CH₃), 7.05 (dd, 1H, *J* = 3.7, 3.9 Hz, H-4''), 7.24 (dd, 2H, *J* = 7.7, 7.1 Hz, H-3 / H-6), 7.30 (d, 2H, *J* = 7.6 Hz, H-1 / H-8), 7.41 (dd, 2H, *J* = 7.6, 7.1 Hz, H-2 / H-7), 7.75 (d, 1H, *J* = 3.9 Hz, H-3''), 7.82 (d, 1H, *J* = 3.7 Hz, H-5''), 8.10 (d, 2H, *J* = 7.7 Hz, H-4 / H-5), 8.93 (s, 1H, H-2'), 10.92 (s, 1H, NH); ^{13}C NMR (75 MHz, CDCl_3): δ 33.1 (N-CH₃), 110.8 (C-1 / C-8), 118.5 (C-5'), 121.2 (C-4 / C-5), 121.7 (C-3 / C-6), 123.8 (C-4a / C-4b), 127.2 (C-2 / C-7), 128.6 (C-4''), 131.0 (C-3''), 133.3 (C-5''), 134.7 (C-2'), 138.0 (C-4'), 140.7 (C-8a / 9a), 147.2 (C-2''), 161.2 (C=O).

12-Methyl-12*H*-imidazo[4',5': 2,3][1,4]diazepino[6,7,1-*jk*]carbazoles (10a-c)

General procedure:

A stirred suspension of *N*-(5-carbazol-9-yl-1-methyl-1*H*-imidazol-4-yl)carboxamides (**9a-c**) in 15 mL of polyphosphoric acid was heated at 140 °C for 4 h. The reaction mixture was then slowly poured, with stirring, onto crushed ice (20 g). To this solution, was added NH₄OH (25%) until the solution was basic (pH~12). The reaction mixture was extracted with Et₂O (3 x 75 mL), the combined organic extracts were dried (anhydrous Na₂CO₃) and the solvent was concentrated under reduced pressure to give a crude product which was purified on preparative TLC plates precoated with silica gel, using MeOH:CHCl₃ (2:98 v/v) as eluent, to afford the respective compounds **10a-c**.

8,12-Dimethyl-12*H*-imidazo[4',5': 2,3][1,4]diazepino[6,7,1-*jk*]carbazole (10a)

This compound was obtained by the cyclization reaction of **9a** (0.3 g, 1 mmol) with polyphosphoric acid (15 mL). Yield of **10a** = 0.04 g (14 %), mp 118-120 °C. *Anal.* Calcd for C₁₈H₁₄N₄ (286.34): C, 75.51; H, 4.93; N, 19.57. Found: C, 75.41; H, 5.01; N, 19.48; IR(KBr): ν 1633 cm⁻¹ (C=N); EI MS *m/z* (%): 286 (36, M⁺), 231(8), 191(31), 166 (100); ^1H NMR (300 MHz, CDCl_3): δ 2.42 (s, 3H, C(8)-CH₃), 3.32 (s, 3H, N-CH₃), 7.10 (d, 1H, *J* = 7.7 Hz, H-1), 7.27 (s, 1H, H-11), 7.31 (d, 1H, *J* = 8.1 Hz, H-7), 7.34 (dd, 1H, *J* = 7.1, 7.7 Hz, H-2), 7.42 (dd, 1H, *J* = 8.1, 8.2 Hz, H-6), 7.51 (dd, 1H, *J* = 7.1, 7.5 Hz, H-3), 8.10 (d, 1H, *J* = 7.5 Hz, H-4), 8.22 (d, 1H, *J* = 8.2 Hz, H-5); ^{13}C NMR (75 MHz, CDCl_3): δ 30.0 (C(8)-CH₃), 31.2 (N-CH₃), 107.9 (C-7a), 110.2 (C-1), 120.3 (C-4), 121.4 (C-5), 121.6 (C-7), 122.8 (C-2), 123.2 (C-4a),

125.0 (C-3), 125.6 (C-7b), 126.6 (C-4b), 127.2 (C-6), 132.5 (C-11), 138.0 (C-9a), 140.6 (C-12a), 142.7 (C-13a), 166.2 (C-8).

12-Methyl-8-(*p*-tolyl)-12*H*-imidazo[4',5':2,3][1,4]diazepino[6,7,1-*jk*]carbazole (10b)

This compound was obtained by the cyclization reaction of **9b** (0.3 g, 0.8 mmol) with polyphosphoric acid (15 mL). Yield of **10b** = 0.06 g (21 %), mp 146-148 °C. *Anal.* Calcd for C₂₄H₁₈N₄ (362.44): C, 79.54; H, 5.01; N, 15.46. Found: C, 79.44; H, 4.79; N, 15.41; IR(KBr): ν 1628 cm⁻¹ (C=N); EI MS *m/z* (%): 262 (38, M⁺), 307 (22), 191 (18), 117 (70), 166 (100); ¹H NMR (300 MHz, CDCl₃): δ 2.35 (s, 3H, C(4'')-CH₃), 3.04 (s, 3H, N-CH₃), 7.05 (d, 1H, *J* = 6.6 Hz, H-7), 7.14 (dd, 1H, *J* = 6.6, 6.3 Hz, H-6), 7.22 (d, 2H, *J* = 8.2 Hz, H-3'' / H-5''), 7.33 (dd, 1H, *J* = 7.0, 7.1 Hz, H-2), 7.33 (d, 1H, *J* = 7.0 Hz, H-1), 7.36 (s, 1H, H-11), 7.43 (dd, 1H, *J* = 7.1, 6.3 Hz, H-3), 7.52 (d, 2H, *J* = 8.2 Hz, H-2'' / H-6''), 8.12 (d, 1H, *J* = 6.3 Hz, H-5), 8.21 (d, 1H, *J* = 6.3 Hz, H-4); ¹³C NMR (75 MHz, CDCl₃): δ 21.7 (C(4'')-CH₃), 30.8 (N-CH₃), 107.4 (C-1''), 110.2 (C-1), 120.3 (C-6), 120.4 (C-5), 121.2 (C-4), 121.7 (C-3), 123.3 (C-4b), 124.3 (C-4a), 125.4 (C-7), 126.5 (C-4''), 127.1 (C-2), 129.0 (C-2'' / C-6''), 129.4 (C-3'' / C-5''), 132.6 (C-11), 134.7 (C-7a), 139.1 (C-7b), 141.6 (C-13a), 142.2 (C-12a), 144.2 (C-9a), 166.1 (C-8),

12-Methyl-8-(2-thienyl)-12*H*-imidazo[4',5':2,3][1,4]diazepino[6,7,1-*jk*]carbazole (10c)

This compound was obtained by the cyclization reaction of **9c** (0.3 g, 0.8 mmol) with polyphosphoric acid (15 mL). Yield of **10c** = 0.02 g (14 %), mp 138-140 °C. *Anal.* Calcd for C₂₁H₁₄N₄S (354.44): C, 71.16; H, 3.98; N, 15.81; S, 9.05. Found: C, 71.21; H, 4.11; N, 15.68; S, 9.04; IR(KBr): ν 1633 cm⁻¹ (C=N); EI MS *m/z* (%): 354 (36, M⁺), 299 (10), 191 (42), 166 (100), 109 (70); ¹H NMR (300 MHz, CDCl₃): δ 3.23 (s, 3H, N-CH₃), 5.50 (d, 1H, *J* = 7.3 Hz, H-7), 6.08 (dd, 1H, *J* = 7.3, 6.1 Hz, H-6), 6.60 (d, 1H, *J* = 3.9 Hz, H-3''), 6.82 (dd, 1H, *J* = 3.9, 4.8 Hz, H-4''), 7.11 (d, 1H, *J* = 7.0 Hz, H-1), 7.25 (dd, 1H, *J* = 6.7, 6.3 Hz, H-3), 7.35 (dd, 1H, *J* = 6.7, 7.0 Hz, H-2), 7.42 (d, 1H, *J* = 4.8 Hz, H-5''), 7.71 (s, 1H, H-11), 7.75 (d, 1H, *J* = 6.1 Hz, H-5), 7.85 (d, 1H, *J* = 6.3 Hz, H-4); ¹³C NMR (75 MHz, CDCl₃): δ 29.7 (N-CH₃), 110.2 (C-1), 110.3 (C-6), 117.0 (C-5), 120.3 (C-4), 121.0 (C-3), 123.1 (C-4b), 123.7 (C-4a), 124.9 (C-7), 126.9 (C-2), 127.0 (C-4''), 128.6 (C-7a), 130.9 (C-5''), 131.7 (C-3''), 135.7 (C-11), 139.5 (C-7b), 140.1 (C-13a), 141.0 (C-9a), 141.1 (C-12a), 148.0 (C-2''), 161.9 (C-8).

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