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NOVEL AND EFFICIENT SYNTHESIS OF 5,8-DIMETHYL-9*H*-CARBAZOL-3-OL *VIA* A HYDROXYDEBORONATION REACTION

Anna Caruso,[a,b] Anne Sophie Voisin-Chiret,[a] Jean-Charles Lancelot,[a] Maria Stefania Sinicropi,[b] Antonio Garofalo,[b] and Sylvain Rault[a,*]

[a]*Université de Caen Basse-Normandie, U.F.R. des Sciences Pharmaceutiques, Centre d'Etudes et de Recherche sur le Médicament de Normandie, 14032 Caen, France,* [b]*Dipartimento di Scienze Farmaceutiche, Università della Calabria, 87036 Arcavacata di Rende, (Cs), Italy*

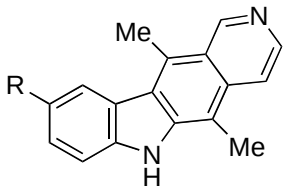
[*]Corresponding author:
tel. +33 2 31 93 4169; fax +33 2 31 93 1188; e-mail sylvain.rault@unicaen.fr

Abstract – *N*-Protected carbazol-3-yl-boronic acid derivatives have been efficiently hydroxydeboronated under mild conditions by employing hydrogen peroxide. The method allows to easily obtain 3-hydroxycarbazoles as precursors of new analogs of the anticancer agent 9-hydroxyellipticine.

INTRODUCTION

Since thirty years, Ellipticine (5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole) (**I)** (Chart 1) is a well known alkaloid with antitumor properties, acting as a DNA intercalating agent and inhibiting the activity of topoisomerase II. Currently, recent works demonstrated that Ellipticine induces apoptotic cell death by the generation of cytotoxic free radicals and interestingly, a recent study by Hagg et al.[1g] reported that Ellipticine mediated apoptosis induced by endoplasmic reticulum stress.[1] However, some limitations, such as low water solubility and cardiovascular side effects, preclude its therapeutic use. Many structural modifications on the original molecule have been designed in order to obtain several derivatives with a better pharmacological profile.[2,3]

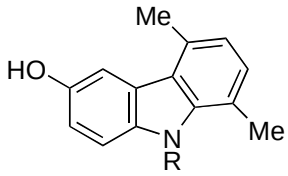
Chart 1



(I) R = H
(II) R = OH

In particular, 9-hydroxyellipticine, Celiptium®, (**II)** (Chart 1) showed to possess a higher DNA affinity than ellipticine itself, high activity on L1210 mice leukaemia, and lack of toxicity at therapeutic doses.[4] The introduction of the hydroxy group in position 9 would strenghten the interaction with the DNA through the formation of a hydrogen bond with the negatively charged oxygen of a phosphate group. The preparation of 9-hydroxy derivatives of ellipticine is tightly related with 5,8-dimethyl-9*H*-carbazol-3-ol **(III)** (Chart 2), which were previously obtained by a quite demanding synthetic route using 5-methoxyindole, a very expensive starting material.[5] Herein, we describe a convenient alternative method for the synthesis of compounds **III** as precursors of new analogs of **II**.

Chart 2



(III)

The key step of the process consists in the conversion of *N*-protected 5,8-dimethyl-9*H*-carbazol-3-yl-boronic acids into the corresponding 3-hydroxy derivatives using hydrogen peroxide in mild reaction conditions.[6] The suitable boronic acids were in turn prepared starting from 5-bromoindole by a smooth multi-step process, going through the formation of corresponding boronic dimethyl esters. This procedure allows also the preparation of the boronic pinacolyl ester but all attempts to apply a similar hydroxydeboronation with this boronic pinacolyl ester failed. The method allows the preparation of 9-unsubstituted 5,8-dimethyl-9*H*-carbazol-3-ols when the easily removable *N*-protecting Boc group was used.

RESULTS AND DISCUSSION

The new synthetic pathway to 5,8-dimethyl-9*H*-carbazol-3-ols is described in the Scheme. The starting 6-bromo-1,4-dimethyl-9*H*-carbazole (**1)** was prepared by reaction of 5-bromoindole with hexane-2,4-dione

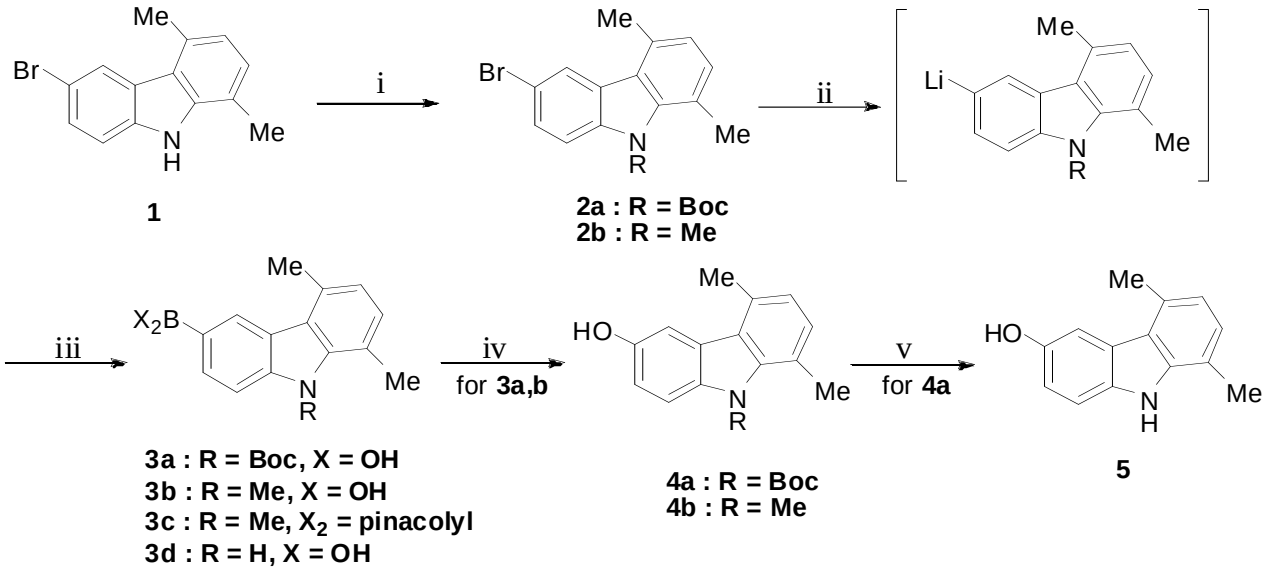
in the presence of *p*-toluenesulphonic acid.[7-9] This starting compound was *N*-protected by $(Boc)_2O$ to give compound **2a**[10] or, alternatively, *N*-methylated by iodomethane and sodium hydride under standard conditions to give compound **2b**.[11] Compounds **2a** and **2b** were subjected to lithiation-boronation at very low temperature, using *n*-BuLi and trimethyl borate after an usual hydrolytic work-up to give the corresponding 3-boronic acid derivatives **3a** and **3b**, respectively.[6, 12-15]

N-Boc-5,8-dimethyl-9*H*-carbazol-3-boronic acid (**3a)** was first treated with an aqueous mixture of bases (NaOH and $NaHCO_3$) at 50°C, then hydrogen peroxide was added to the reaction mixture at room temperature.

The expected 3-hydroxy derivative **4a** was obtained in 82% yield by a final moderate acidification (1N HCl, pH 4). In the same way, compound **3b** was converted into 3-hydroxy derivative **4b** in 70% yield. The corresponding pinacolyl ester **3c**, obtained after a similar fashion to that described for compounds **3a**, but using tri-*i*-propyl borate and pinacol instead of trimethyl borate, proved to be unreactive under similar reaction conditions.

Finally, Boc protecting group of compound **4a** was removed by hydrolytic treatment (6N HCl, pH 1), after the hydroxydeboronation step, to give 5,8-dimethyl-9*H*-carbazol-3-ol (**5)** in 75% yield. The attempt to directly perform the hydroxydeboronation reaction on the previously *N*-deprotected boronic acid **3d** also led to compound **5**, but in a considerably lower yield.

Scheme[a]



[a]*Reagents:* (i) $(Boc)_2O$, DMAP, TEA, MeCN, 0-25°C to **2a**, NaH, MeI, DMF, 25 °C, to **2b**; (ii) *n*-BuLi, THF, -90 °C; (iii) $B(OMe)_3$, then 1N HCl, pH 4 to **3a,b**, $B(OiPr)_3$, pinacol then $MeCO_2H$, pH 4 to **3c**, $B(OMe)_3$, then 6N HCl, pH 1 to **3d**; (iv) NaOH, $NaHCO_3$, H_2O_2, rt, 24 h then 1N HCl, pH 4; (v) 6N HCl, pH 1.

EXPERIMENTAL

Melting points were determined on a Kofler melting point apparatus and are uncorrected. IR spectra were taken with a Perkin Elmer BX FT-IR. HRMS (EI) determinations were made using a spectrometer JEOL JMS GCMate. ESI-MS was performed using a spectrometer LC-MS Waters alliance 2695 (ESI+). ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) were recorded on a JEOL Lambda 400 Spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. Thin layer chromatography (TLC) was performed on silica gel 60F-264 (Merck). Elemental analyses were performed at the 'Institut de Recherche en Chimie Organique Fine' (Rouen).

6-Bromo-1,4-dimethyl-9*H*-carbazole (1)

A suspension of 5-bromoindole (5.0 g, 25.0 mmol), hexane-2,4-dione (3.5 g, 31.0 mmol) and *p*-toluenesulphonic acid (3.86 g, 20.0 mmol) in absolute EtOH (200 mL) was refluxed for 4 h and then left overnight at rt. The resulting solution was diluted with water (400 mL) and Et_2O (800 mL). The organic layer was separated and shaken with saturated aqueous $NaHCO_3$ until neutrality then dried and evaporated to give pure compound **1** as a purple solid (4.9 g, 70% yield), mp 134 °C (EtOAc/hexanes). IR (KBr): 3407, 1447, 1297, 811, 797, 537 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 11.36 (s, 1H, NH); 8.17 (s, 1H, H5); 7.51-7.48 (m, 2H, H7-H8); 7.11 (d, J_{H2-3} = 7.32 Hz, 1H, H2); 6.87 (d, J_{H3-2} = 7.32 Hz, 1H, H3); 2.77 (s, 3H, CH_3); 2.54 (s, 3H, CH_3).

6-Bromo-9-*tert*-butoxycarbonyl-1,4-dimethyl-9*H*-carbazole (2a)

To a solution of 6-bromo-1,4-dimethyl-9*H*-carbazole (**1) (**5.0 g, 18.2 mmol) in MeCN (70 mL) cooled to 0 °C were added Et_3N (5.07 mL, 36.5 mmol), DMAP (4.46 g, 36.5 mmol) and di-*tert*-butyl dicarbonate (7.96 g, 36.5 mmol). The mixture was stirred for 1 h at 0 °C, then left at rt for 3 h. The residue obtained after removal of the solvent was diluted with EtOAc (100 mL) and shaken with water (2 x 100 mL). The residue obtained after an usual work-up was purified by silica gel column chromatography using cyclohexane/Et_2O (7:3) as eluent to give compound **2a** as a yellow solid (4.3 g, 63% yield), mp 112 °C. IR (KBr): 3446, 2971, 1738, 1448, 1368, 1296, 1248, 1153, 794, 535 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 8.24 (d, J_{H5-7} = 1.96 Hz, 1H, H5); 7.99 (dd, J_{H7-8} = 8.80 Hz, 1H, H7); 7.74 (dd, J_{H8-7} = 8.80 Hz, 1H, H8); 7.29 (d, J_{H2-3} = 7.80 Hz, 1H, H2); 7.20 (d, J_{H3-2} = 7.80 Hz, 1H, H3); 2.81(s, 3H, CH_3); 2.55 (s, 3H, CH_3); 1.73 (s, 9H, CH_3). ^{13}C NMR (DMSO-d_6) δ 149.8, 138.1, 138.0, 130.3, 130.1, 129.0, 127.8, 125.5, 124.4, 123.2, 122.7, 115.7, 115.2, 84.6, 27.5, 26.3, 20.0, 19.9. MS *m/z* (%): 373-375 (19) [$M^{+\cdot}$]; 317-319 (48) [M^+ - (-*t*Bu)]; 273-275 (100) [M^+ - (-CO_2*t*Bu)]; 193 (52) [M^+ - (Br, -CO_2*t*Bu)]; 81 (39). Anal. Calcd for $C_{19}H_{20}BrNO_2$: C, 60.97; H, 5.39; N, 3.74. Found: C, 60.75; H, 5.08; N, 3.51.

6-Bromo-1,4,9-trimethyl-9*H*-carbazole (2b)

A mixture of 6-bromo-1,4-dimethyl-9*H*-carbazole (**1)** (2.0 g, 7.3 mmol) and dry DMF (60 mL) was stirred at rt until clear. NaH 60% oil dispersion (0.44 g, 10.9 mmol) and was added at 0 °C. After 15 min stirring, iodomethane (1.46 mL, 21.9 mmol) was added and the mixture was stirred for 1 h at rt. Water (200 mL) was then added and the resulting mixture was extracted with EtOAc (2 x 200 mL). Removal of the solvent gave pure compound **2b** as a white solid (2.0 g, 95% yield), mp 138 °C (EtOAc/hexanes). IR (KBr): 3435, 2921, 1469, 1296, 1092, 791, 533 cm^{-1}. ^1H NMR (DMSO-d_6) δ 8.18 (d, J_{H5-7} = 1.48 Hz, 1H, H5); 7.61-7.55 (m, 2H, H7-H8); 7.10 (d, J_{H2-3} = 7.32 Hz, 1H, H2); 6.88 (d, J_{H3-2} = 7.32 Hz, 1H, H3); 4.10 (s, 3H, NCH_3); 2.79 (s, 3H, CH_3); 2.72 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 140.0, 139.7, 130.8, 129.3, 127.4, 124.4, 124.1, 121.1, 120.2, 118.5, 111.2, 110.9, 32.4, 20.5, 19.8. MS *m/z* (%): 287 (100) [$M^{+\cdot}$]; 272 (25) [M^+- (-CH_3)]; 193 (24) [M^+- (Br, -CH_3)]. Anal. Calcd for $C_{15}H_{14}BrN$: C, 62.52; H, 4.90; N, 4.86. Found: C, 62.67; H, 5.13; N, 4.63.

9-*tert*-Butoxycarbonyl-5,8-dimethyl-9*H*-carbazole-3-boronic acid (3a)

To a solution of the bromoderivative **2a** (3.7 g, 10.0 mmol) in anhydrous THF (250 mL) cooled to -90 °C was added dropwise a solution of 2.5 M *n*-BuLi in hexanes (4.8 mL, 12.0 mmol). The mixture was allowed to react at -85 °C for 1 h. Trimethyl borate (1.2 mL, 11.0 mmol) was added dropwise at the same temperature. The resulting solution was stirred for an additional 1 h then it was acidified to pH 4 by dropwise addition of 0.5N HCl at -30 °C. The mixture was allowed to warm to rt then poured into H_2O (300 mL). Et_2O (2 x 250 mL) extraction gave pure compound **3a** as a white solid (2.0 g, 60% yield), mp 250 °C (EtOH). IR (KBr): 3435, 2975, 1738, 1607, 1434, 1334, 1246, 1152, 1080, 801, 716 cm^{-1}. ^1H NMR (CD_3OD) δ 8.40 (s, 1H, H5); 8.03 (d, J_{H7-8} = 8.56 Hz, 1H, H7); 7.73 (d, J_{H8-7} = 8.56 Hz, 1H, H8); 7.15 (d, J_{H2-3} = 7.56 Hz, 1H, H2); 7.07 (d, J_{H3-2} = 7.56 Hz, 1H, H3); 2.77 (s, 3H, CH_3); 2.44 (s, 3H, CH_3); 1.74 (s, 9H, CH_3). ^{13}C NMR (CD_3OD) δ 150.9, 139.8, 132.5, 131.1, 130.5, 128.7, 127.5, 126.2, 126.1, 124.1, 123.1, 114.8, 85.0, 28.3, 20.7. MS *m/z* (%): 295 (12) [M^+- (-$B(OH)_2$)]; 239 (21) [M^+ - (-*t*Bu)]; 195 (100) [M^+ - (-$B(OH)_2$, -CO_2*t*Bu)]. Anal. Calcd for $C_{19}H_{22}BNO_4$: C, 67.28; H, 6.54; N, 4.13. Found: C, 67.49; H, 6.32; N, 4.29.

5,8,9-Trimethyl-9*H*-carbazole-3-boronic acid (3b)

Following a procedure identical to that described for compound **3a**, but using compound **2b** (2.9 g, 10.0 mmol) as starting material, compound **3b** was obtained as a white solid (1.3 g, 50% yield), mp > 270 °C (EtOH). IR (KBr): 3426, 2923, 1611, 1348, 1251, 1094, 796, 711 cm^{-1}. ^1H NMR (DMSO-d_6) δ 8.61 (s, 1H, H5); 7.89 (d, J_{H7-8} = 8.32 Hz, 1H, H7); 7.84 (s, 2H, OH); 7.51 (d, J_{H8-7} = 8.32 Hz, 1H, H8); 7.04 (d, J_{H2-3} = 7.56 Hz, 1H, H2); 6.85 (d, J_{H3-2} = 7.56 Hz, 1H, H3); 4.10 (s, 3H, NCH_3); 2.80 (s, 3H, CH_3), 2.79 (s, 3H, CH_3). MS *m/z* (%): 209 (100) [M^+- (-$B(OH)_2$)]; 194 (46)[M^+-(CH_3, -$B(OH)_2$)]. Anal. Calcd for $C_{15}H_{16}BNO_2$: C, 71.18; H, 6.37; N, 5.53. Found: C, 70.90; H, 6.28; N, 5.43.

5,8-Dimethyl-9*H*-carbazole-3-boronic acid (3d)

Following a procedure identical to that described for compound **3a**, but reaching pH 1 by the use of 6N HCl for the hydrolytic work-up, compound **3d** was obtained as a white solid (2.1 g, 90% yield), mp > 260 °C (EtOH). IR (KBr): 3214, 1567, 1418, 1257, 867, 719, 546 cm^{-1}. ^1H NMR (DMSO-d_6) δ 8.57 (s, 1H, H5); 8.16 (s, 3H, OH, NH); 7.94-7.93 (m, 2H, H7-8); 7.18 (d, J_{H2-3} = 7.56 Hz, 1H, H2); 7.12 (d, J_{H3-2} = 7.56 Hz ,1H, H3); 2.78 (s, 3H, CH_3); 2.40 (s, 3H, CH_3). Anal. Calcd for $C_{14}H_{14}BNO_2$: C, 70.33; H, 5.90; N, 5.86. Found: C, 70.00; H, 5.70; N, 5.80.

1,4,9-Trimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-9*H*-carbazole (3c)

To a solution of the bromoderivative **2b** (1.0 g, 3.5 mmol) in anhydrous THF (100 mL) cooled to -90 °C was added dropwise a solution of 2.5 M *n*-BuLi in hexanes (1.8 mL, 4.5 mmol). The mixture was allowed to react at -85 °C for 1 h. Triisopropyl borate (0.9 mL, 3.9 mmol) was added dropwise at the same temperature. The resulting solution was stirred for an additional 1 h, then warmed to 0°C and a solution of pinacol (0.41 g, 3.5 mmol) in anhydrous THF (7 mL) was added slowly. The mixture was allowed to warm at rt then it was acidified to pH 4 by dropwise addition of acetic acid. Et_2O (2 x 150 mL) extraction gave pure compound **3c** as a white solid (0.9 g, 77% yield), mp > 270 °C. IR (KBr): 3434, 2924, 1611, 1353, 1253, 1149, 1098, 878, 801, 785, 679 cm^{-1}. ^1H NMR (DMSO-d_6) δ 8.43 (s, 1H, H5); 7.75 (d, J_{H7-8} = 8.32 Hz, 1H, H7); 7.58 (d, J_{H8-7} = 8.32 Hz, 1H, H8); 7.07 (d, J_{H2-3} = 7.32 Hz, 1H, H2); 6.88 (d, J_{H3-2} = 7.32 Hz, 1H, H3); 4.12 (s, 3H, NCH_3); 2.80 (s, 3H, CH_3); 2.74 (s, 3H, CH_3); 1.32 (s, 12H, CH_3). ^{13}C NMR (DMSO-d_6) δ 143.2, 139.2, 131.1, 130.1, 128.6, 128.5, 121.2, 120.9, 118.1, 118.0, 108.4, 108.3, 83.2, 81.1, 32.1, 24.7, 24.5, 20.4, 19.6. MS *m/z* (%): 335 (100) [$M^{+\cdot}$]; 209 (51). Anal. Calcd for $C_{21}H_{26}BNO_2$: C, 75.24; H, 7.82; N, 4.18. Found: C, 75.08; H, 7.69; N, 4.02.

***tert*-Butyl 6-hydroxy-1,4-dimethyl-9*H*-carbazole-9-carboxylate (4a)**

A mixture of boronic acid **3a** (1.6 g, 4.8 mmol), H_2O (40 mL), acetone (5 mL), solid NaOH (0.19 g, 4.8 mmol) and $NaHCO_3$ (0.4 g, 4.8 mmol) was warmed to 50 °C for 1 h. After cooling to rt, 35% hydrogen peroxide solution (1.9 mL, 19.2 mmol) was added dropwise. The reaction was stirred at rt for 24 h, then it was shaken with EtOAc (50 mL) and the aqueous layer was separated and acidified to pH 4 by dropwise addition of 2 N HCl, keeping the temperature below 5 °C. Extraction with EtOAc (2 x 50 mL) gave pure compound **4a** as a white solid (1.2 g, 82% yield), mp 205 °C (Et_2O). IR (KBr): 3410, 1701, 1449, 1329, 1157, 807 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.85 (s, 1H, H5); 7.63 (d, J_{H8-7} = 8.56 Hz, 1H, H8); 7.46 (s, 1H, OH); 7.09 (d, J_{H2-3} = 7.32 Hz, 1H, H2); 6.98 (d, J_{H3-2} = 7.32 Hz, 1H, H3); 6.91 (d, J_{H7-8} = 8.56 Hz, 1H, H7); 2.74 (s, 3H, CH_3); 2.43 (s, 3H, CH_3); 1.64 (s, 9H, CH_3). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.31; H, 6.75; N, 4.50.

5,8,9-Trimethyl-9*H*-carbazol-3-ol (4b)

Following a procedure identical to that described for compound **4a**, but using compound **3b** (1.2 g, 4.8 mmol) as starting material, compound **4b** was obtained as a white solid (0.94 g, 70% yield), mp 202 °C (Et_2O). IR (KBr): 3415, 1587, 1460, 1165, 809, 543 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.23 (d, J_{H5-7} = 1.96 Hz, 1H, H5); 7.52 (dd, J_{H7-8} = 8.80 Hz, 1H, H7); 7.23 (dd, J_{H8-7} = 8.80 Hz, 1H, H8); 7.07 (d, J_{H2-3} = 7.32 Hz, 1H, H2); 6.88 (d, J_{H3-2} = 7.32 Hz, 1H, H3); 4.07 (s, 3H, NCH_3); 2.80 (s, 3H, CH_3); 2.78 (s, 3H, CH_3). Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 80.00; H, 6.70; N, 6.00.

5,8-Dimethyl-9*H*-carbazol-3-ol (5)

Following a procedure identical to that described for compound **4a** (1.6 g, 4.8 mmol), but reaching pH 1 by the use of 6N HCl for the hydrolytic work-up, compound **5** was obtained as a white solid (0.75 g, 75% yield), mp 174 °C (EtOH). IR (KBr): 3517, 3415, 1461, 1165, 847, 809, 543 cm^{-1}. ^1H NMR (DMSO-d_6) 10.88 (s, 1H, NH); 9.12 (bs, 1H, OH); 7.53 (s, 1H, H5); 7.40 (d, J_{H8-7} = 8.56 Hz, 1H, H8); 7.08 (d, J_{H2-3} = 7.36 Hz, 1H, H2); 6.95 (d, J_{H7-8} = 8.56 Hz, 1H, H7); 6.83 (d, J_{H3-2} = 7.36 Hz, 1H, H3); 2.61 (s, 3H, CH_3); 2.50 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ 150.2, 139.7, 133.8, 129.4, 125.4, 123.9, 120.3, 119.2, 117.2, 114.0, 111.1, 107.0, 20.1, 16.7. MS (ESI): [M+1] 212.

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REFERENCES

1. (a) M. Romero, P. Renard, D. H. Caignard, G. Atassi, X. Solans, P. Constans, C. Bailly, and M. D. Pujol, *J. Med. Chem.,* 2007, **50**, 294. (b) T. L. Ho and S. Y. Hsieh, *Helv. Chim. Acta*, 2006, **89**, 111. (c) Y. C. Kuo, P. L. Kuo, Y. L. Hsu, C. Y. Cho, and C. C. Lin, *Life Sci.*, 2006, **78**, 2550. (d) N. C. Garbett and D. E. Graves, *Curr. Med. Chem.,* 2004, **4**, 149. (e) P. L. Kuo, Y. L. Hsu, Y. C. Kuo, C. H. Chang, and C. C. Lin, *Anti-Cancer Drug.*, 2005, **16**, 789. (f) P. L. Kuo, Y. L. Hsu, C. H. Chang, and C. C. Lin, *Cancer Lett.,* 2005, **223**, 293. (g) M. Hagg, M. Berdtsson, A. Mandic, R. Zhou, M. C. Shoshan, and S. Linder, *Mol. Cancer Ther.,* 2004, **3**, 489.

2. H. Chabane, C. Lamazzi, V. Thiéry, G. Guillaumet, and T. Besson, *Tetrahedron Lett.,* 2002, **43**, 2483.

3. N. Harada, T. Kawaguchi, I. Inoue, M. Ohashi, and K. Oda, *Chem. Pharm. Bull.*, 1997, **45**, 134.

4. (a) J. B. Le Pecq, N. D. Xuong, C. Gosse, and C. Paoletti, *P. Natl. Acad. Sci. USA*, 1974, **71**, 5078. (b) A. J. F. Searle, C. Gee, and R. L. Willson, *Oxygen Radicals Chem. Biol.,* 1984, 377.

5. (a) J. B. Le Pecq, C. Paoletti, and N. D. Xuong, *Eur. Pat. Appl.,* 1980, EP 9445. (b) J. C. Lancelot, B. Letois, S. Rault, and M. Robba, *Heterocycles,* 1990, **31**, 241. (c) A. Langendoen, J. P. M. Plug, G. J.

Koomen, and U. K. Pandit, *Tetrahedron,* 1989, **45**, 1759. (d) A. Langendoen, G. J. Koomen, and U. K. Pandit, *Heterocycles,* 1987, **26**, 91.

6. A. S. Voisin, A. Bouillon, J. C. Lancelot, and S. Rault, *Tetrahedron,* 2005, **61**, 1417.

7. (a) A. Cranwell and J. E. Saxton, *J. Chem. Soc.*, **1967**, 3482. (b) J. C. Lancelot, S. Rault, M. Robba, and H. D. Nguyen, *Chem. Pharm. Bull.,* 1987, **35**, 425.

8. (a) T. Tabka, B. Letois, J. C. Lancelot, P. Gauduchon, J. F. Heron, J. Y. Le Talaer, S. Rault, and M. Robba, *Eur. J. Med. Chem.*, 1989, **24**, 605. (b) A. Testard, L. Picot, I. Fruitier-Arnaudin, J. M. Piot, H. Chabane, L. Domon, V. Thiery, and T. Besson, *J. Enzym. Inhib. Med. Chem.,* 2004, **19**, 467.

9. V. Moinet-Hedin, T. Tabka, F. Sichel, P. Gauduchon, J. Y. Le Talaer, C. Saturnino, B. Letois, J. C. Lancelot, and M. Robba, *Eur. J. Med. Chem.,* 1997, **32**, 113.

10. (a) B. R. Henke, C. J. Aquino, L. S. Birkemo, D. K. Croom, R. W. Dougherty, G. N. Ervin, M. K. Grizzle, G. C. Hirst, M. K. James, M. F. Johnson, K. L. Queen, R. G. Sherrill, E. E. Sugg, E. M. Suh, J. W. Szewczyk, R. J. Unwalla, J. Yingling, and T. M. Willson, *J. Med. Chem.*, 1997, **40**, 2706. (b) V. Diep, J. J. Dannenberg, and R. W. Franck, *J. Org. Chem.*, 2003, **68**, 7907. (c) A. Kuwahara, K. Nakano, and K. Nozaki, *J. Org. Chem.*, 2005, **70**, 413. (d) M. Chakrabarty, T. Kundu, and Y. Harigaya, *Synth. Commun.*, 2006, **36**, 2069. (e) S. Routier, L. Sauge, and N. Ayerbe, *Tetrahedron Lett.,* 2002, **43**, 589.

11. R. Cao, Q. Chen, X. Hou, H. Chen, H. Guan, Y. Ma, W. Peng, and A. Xu, *Bioorg. Med. Chem.,* 2004, **12**, 4613.

12. (a) A. Bouillon, J. C. Lancelot, V. Callot, P. R. Bovy, and S. Rault, *Tetrahedron,* 2002, **58**, 2885. (b) J. Sopkovà-de Oliveira Santos, J. C. Lancelot, A. Bouillon, and S. Rault, *Acta Crystallogr. C,* 2003, **59**, o111.

13. A. Bouillon, J. C. Lancelot, V. Callot, P. R. Bovy, and S. Rault, *Tetrahedron,* 2002, **58**, 3323.

14. A. Bouillon, J. C. Lancelot, V. Callot, P. R. Bovy, and S. Rault, *Tetrahedron,* 2002, **58**, 4369.

15. (a) A. Bouillon, J. C. Lancelot, J. Sopkovà-de Oliveira Santos, V. Callot, P. R. Bovy, and S. Rault, *Tetrahedron,* 2003, **59**, 10043. (b) J. Sopkovà-de Oliveira Santos, A. Bouillon, J. C. Lancelot, and S. Rault, *Acta Crystallogr. C,* 2003, **59**, o596.