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SYNTHESIS OF 4-AZACHROMENO[2,3-*b*]INDOL-11(6*H*)-ONE AND ITS DERIVATIVES AS ANALOGUES OF ELLIPTICINE

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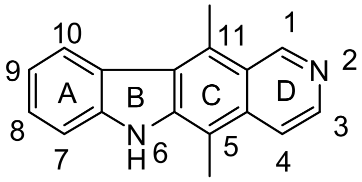
Abstract – 4-Azachromeno[2,3-*b*]indol-11(6*H*)-ones **(4)** and their derivatives **(5)** as analogues of ellipticine were synthesized through a straightforward, two or three-step process. Tetracyclic heterocycles **(4)** were obtained by facile cyclization of indolin-2-ones **(2)** or **(3)** and 2-chloronicotinoyl chloride under the condition of the 'Jensen'-reaction. Alkylation of the compounds **(4)** afforded 6-substituted 4-azachromeno[2,3-*b*]indol-11(6*H*)-ones.

INTRODUCTION

Ellipticine **(1)**, isolated from the leaves of *Ochrosia elliptica Labill* (family Apocynaceae), was discovered to have antitumor activities in 1967.[1-3] Its mechanism of action was considered to be based mainly on DNA intercalation or the inhibition of topoisomerase II.[4, 5] Nevertheless, its early clinical development was limited by poor drug solubility and in vivo host toxicities such as hemolytic activity, decreased heart rate and hepatotoxicity.[6, 7] In view of that, many interests have been focused on modification of the structure of ellipticine to improve its solubility and reduce the side effects. Many analogues of ellipticine had been reported; the compounds, however, are simply a replacment of functional groups at the 1-, 2-, 5-, 6-, 9- and 11-positions, or an addition of a nitrogen atom on the tetracyclic skeleton.[8, 9] The change of core structure of ellipticine was reported only by few literatures.[9, 10]



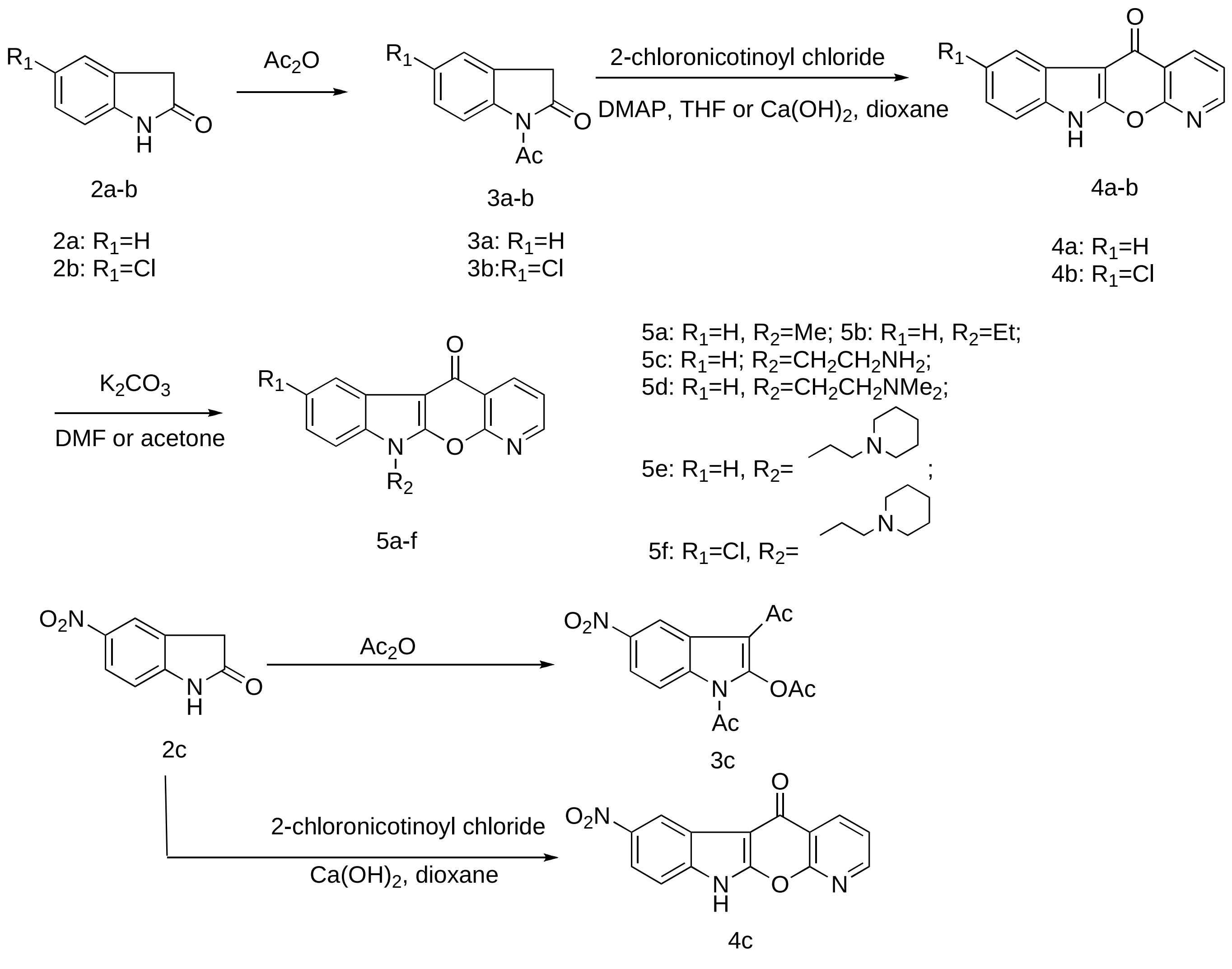
1. ellipticine

Therefore, we synthesized 4-azachromeno[2,3-*b*]indol-11(6*H*)-ones which replaced C nucleus of ellipticine with 4*H*-pyran-4-one via the reaction of indolin-2-ones with 2-chloronicotinoyl chloride under the condition of the 'Jensen'-reaction (calcium hydroxide, refluxing, 1,4-dioxane).[11] The compounds with novel structure could be regarded as the analogues of ellipticine merging the heterocyclic frameworks of both ellipticine and isoflavone. As it had been demonstrated that addition of a basic side chain to the ellipticine structure could improve DNA binding property,[12] it prompted us to introduce a basic side chain to 4-azachromeno[2,3-*b*]indol-11(6*H*)-ones. Herein, we describe the convenient synthesis of 4-azachromeno[2,3-*b*] indol-11(6*H*)-one derivatives as novel antitumor agents.

RESULTS AND DISCUSSION

A facile two or three-step process for the preparation of 4-azachromeno[2,3-*b*]indol-11(6*H*)-ones and their derivatives were reported in Scheme 1. Compounds **(2a)** and **(2b)** were acetylated with acetic anhydride under reflux. The acetylated products **(3a)** and **(3b)** were then annulated with 2-chloronicotinoyl chloride which was prepared according to the known procedure[13] under the conditions of DMAP in refluxing THF or $Ca(OH)_2$ in refluxing 1,4-dioxane (the 'Jensen'-reaction condition) to gain 4-azachromeno[2,3-*b*]indol-11(6*H*)-one **(4a)** and 9-chloro-4-azachromeno[2,3-*b*]indol-11(6*H*)-one **(4b)** respectively. The protecting group was removed simultaneously during the annulation. However, the reaction under the former conditions completed after 24 h and the product needed to be purified by column chromatography on silica gel. The latter could be completed in shorter time and the pure products were obtained easily by dilution of the reaction mixture with water, filtration, washing and drying. Finally, the desired derivatives **(5a-5f)** of **(4a)** or **(4b)** were obtained by alkylation with corresponding alkyl halide using K_2CO_3 as base and DMF or acetone as solvent.

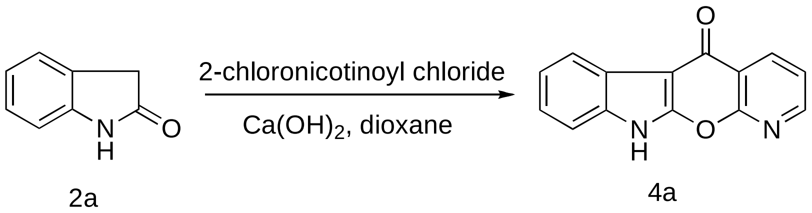
For the synthesis of 9-nitro-4-azachromeno[2,3-*b*]indol-11(6*H*)-one **(4c)**, 5-nitroindolin-2-one was prepared by nitration of indolin-2-one according to the literature.[14] The product of acetylation of 5-nitroindolin-2-one was not 1-acetyl-5-nitroindolin-2-one but triacetyl compound **(3c)**. Considering the potent electron-withdrawing nitro group, 2-chloronicotinoyl chloride might attack C-3 easier than N-1. Experiments proved our prediction and **(4c)** was obtained without any protecting groups. In order to get reduced product of compound **(4c),** various procedures were examined including Pd/C, H_2 in DMF, 15% $TiCl_3$ in $AcOH/H_2O$, Fe/NH_4Cl in $MeOH/H_2O$ and so on, but all cases did not succeed.



Scheme 1

To verify whether it was necessary to protect nitrogen atom when indolin-2-one **(2a)** or 5-chloroindolin-2-one **(2b)** reacted as starting material, indolin-2-one was reacted with 2-chloronicotinoyl chloride directly under the same condition which was illustrated in Scheme 2. 4-Azachromeno[2,3-*b*]indol-11(6*H*)-one was also obtained with unprotected indolin-2-one in a much lower yield (yield: 4.2%).

Unfortunately, 4-chloronicotinoyl chloride failed to give the corresponding product with compound **(3a)** under those conditions described above.



Scheme 2

In conclusion, we established a convenient procedure for the synthesis of 4-azachromeno[2,3-*b*]indol-11(6*H*)-one and its derivatives. Some of them display potent antitumor activities and will be reported elsewhere.

EXPERIMENTAL

Chemical reagents were commercial products and used without purification in all cases. Solvents were dried by standard methods. The ^{1}H NMR spectra were recorded by GEMINI spectrometer at 300 MHz. MS and HRMS spectra were recorded on a MAT-95 spectrometer. Melting points were measured by Büchi 510 melting point apparatus and were uncorrected.

1-Acetylindolin-2-one (3a)

The suspension of indolin-2-one (1 g, 7.5 mmol) in 5 mL of acetic anhydride was heated under reflux for 4 h. After cooling, the resulted pink precipitate was filtered, washed with cold water and dried. Yield: 775 mg (58.9%); mp 120-122°C (lit.,[15] mp 125-126°C); ^{1}H NMR (300MHz, DMSO-d_6): δ 8.07 (1H, d, J=8.3 Hz, Ar-H), 7.32 (2H, m, Ar-H), 7.19 (1H, td, J=7.5, 1.1 Hz, Ar-H), 3.82 (2H, s, CH_2), 2.56 (3H, s, CH_3).

1-Acetyl-5-chloroindolin-2-one (3b)

Compound **(3b)** was prepared in the same way as **(3a)** from 5-chloroindolin-2-one (1 g, 6.0 mmol) and 5 mL of acetic anhydride to give brown precipitate. Yield: 653 mg (51.9%); mp 125-127°C; ^{1}H NMR (300MHz, $CDCl_3$): δ 8.17 (1H, d, J=8.4 Hz, Ar-H), 7.27 (1H, d, J=8.4 Hz, Ar-H), 7.26 (1H, s, Ar-H), 3.71 (2H, s, CH_2), 2.67 (3H, s, CH_3); MS (EI) *m/z* (%): 211 (M+2, 6), 209 (M^+, 20), 167 (100), 169 (33). HRMS (EI) calcd. for $C_{10}H_8ClNO_2$, 209.0244; found 209.0244.

1,3-Diacetyl-5-nitro-1*H*-indol-2-yl acetate (3c)

Compound **(3c)** was prepared in the same way as **(3a)** from 5-nitroindolin-2-one (400 mg, 2.2 mmol) and 5 mL of acetic anhydride. After cooling and adding 20 mL of water, the resulting yellow precipitate was filtered, washed with EtOAc and dried. Yield: 154 mg (22.5%); mp 144-146°C; ^{1}H NMR (300MHz, $CDCl_3$): δ 8.51 (1H, d, J=2.5 Hz, Ar-H), 8.45 (1H, d, J=9.1 Hz, Ar-H), 8.24 (1H, dd, J=9.1, 2.5 Hz, Ar-H), 2.77 (3H, s, CH_3), 2.76 (3H, s, CH_3), 2.51 (3H, s, CH_3); MS (EI) *m/z* (%): 304 (M^+, 5), 262 (50), 220 (100), 205 (25). HRMS (EI) calcd. for $C_{14}H_{12}N_2O_6$, 304.0695; found 304.0694.

4-Azachromeno[2,3-*b*]indol-11(6*H*)-one (4a)

Method A: A mixture of 1-acetylindolin-2-one (205 mg, 1.17 mmol), 2-chloronicotinoyl chloride (207 mg, 1.17 mmol) and DMAP (276 mg, 2.26 mmol) in 5 mL of dry THF was heated under reflux for 24 h. The crude product was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc, 7/1, v/v). Yield: 99 mg (35.8%).

Method B: Under anhydrous conditions, to a suspension of 1-acetylindolin-2-one (4.976 g, 28.4 mmol) and $Ca(OH)_2$ (4.208 g, 56.8 mmol) in 40 mL of dry 1,4-dioxane, a solution of 2-chloronicotinoyl chloride (5.2 g, 29.7 mmol) in 15 mL of dry 1,4-dioxane was added. The reaction mixture was heated at reflux for 15 h under stirring. After cooling to rt, the mixture was treated with 114 mL of 2 N HCl, stirred for 15 min, and poured into 100 mL of H_2O. After 30 min, the pink solid was filtered off, washed with H_2O and dried. Yield: 3.036 g (45.2%); mp＞300°C; ^{1}H NMR (300MHz, DMSO-*d*$_6$): δ 13.24 (1H, s, NH), 8.74 (1H, dd, J=4.8, 2.2 Hz, Ar-H), 8.69 (1H, dd, J=7.5, 2.2 Hz, Ar-H), 8.10 (1H, dd, J=7.1, 1.9 Hz, Ar-H), 7.69 (1H, m, Ar-H), 7.55 (1H, dd, J=6.9, 1.2 Hz, Ar-H), 7.34 (2H, m, Ar-H); MS (EI) *m/z* (%): 236 (M$^+$, 100), 208 (18), 179 (33). HRMS (EI) calcd. for $C_{14}H_8N_2O_2$, 236.0585; found 236.0590.

Method C: Compound **(4a)** was also prepared in the same way as method B from indolin-2-one (133 mg, 1 mmol), $Ca(OH)_2$ (148 mg, 2 mmol), and 2-chloronicotinoyl chloride (175 mg, 1 mmol). The crude product was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 50/1, v/v). Yield: 10 mg (4.2%)

9-Chloro-4-azachromeno[2,3-*b*]indol-11(6*H*)-one (4b)

Compound **(4b)** was prepared in the same way as method B from 1-acetyl-5-chloroindolin-2-one (209 mg, 1 mmol), $Ca(OH)_2$ (148 mg, 2 mmol), and 2-chloronicotinoyl chloride (175 mg, 1 mmol) to give gray solid. Yield: 167 mg (61.8%); mp＞300°C; ^{1}H NMR (300MHz, DMSO-*d*$_6$): δ 13.28 (1H, s, NH), 8.75 (1H, dd, J=4.7, 2.1 Hz, Ar-H), 8.69 (1H, dd, J=7.7, 2.1 Hz, Ar-H), 8.03 (1H, d, J=1.8 Hz, Ar-H), 7.70 (1H, m, Ar-H), 7.56 (1H, d, J=8.6 Hz, Ar-H), 7.39 (1H, dd, J=8.6, 1.8 Hz, Ar-H); MS (EI) *m/z* (%): 272 (M+2, 33), 270 (M$^+$, 100), 235 (13). HRMS (EI) calcd. for $C_{14}H_7ClN_2O_2$, 270.0196; found 270.0188.

9-Nitro-4-azachromeno[2,3-*b*]indol-11(6*H*)-one (4c)

Compound **(4c)** was prepared in the same way as method B from 5-nitroindolin-2-one (178 mg, 1 mmol) , $Ca(OH)_2$ (148 mg, 2 mmol), and 2-chloronicotinoyl chloride (175 mg, 1 mmol) to give red solid. Yield: 108 mg (38.4%); mp＞300°C; ^{1}H NMR (300MHz, DMSO-*d*$_6$): δ 13.80 (1H, s, NH), 8.85 (1H, d, J=2.1 Hz, Ar-H), 8.78 (1H, dd, J=4.9, 1.7 Hz, Ar-H), 8.71 (1H, dd, J=7.5, 1.7 Hz, Ar-H), 8.24 (1H, dd, J=8.8, 2.1 Hz, Ar-H), 7.72 (2H, m, Ar-H); MS (EI) *m/z* (%): 281 (M$^+$, 15), 235 (7). HRMS (EI) calcd. for $C_{14}H_7N_3O_4$, 281.0436; found 281.0432.

6-Methyl-4-azachromeno[2,3-*b*]indol-11(6*H*)-one (5a)

To a solution of 4-azachromeno[2,3-*b*]indol-11(6*H*)-one(118 mg, 0.5 mmol) in 10 mL of DMF was added K_2CO_3 (276 mg, 2 mmol). After 30 min, CH_3I (71 mg, 31 μL, 0.5 mmol) was added. The reaction mixture was stirred at rt for 6 h and poured into 100 mL of water . The resulting white solid was filtered, and dried. Yield: 56 mg (44.8%); mp 244-247°C; ^1H NMR (300MHz, DMSO-d_6): δ 8.75 (1H, dd, J=4.3, 1.2 Hz, Ar-H), 8.68 (1H, dd, J=7.7, 1.2 Hz, Ar-H), 8.11 (1H, d, J=7.0 Hz, Ar-H), 7.69 (2H, m, Ar-H), 7.38 (2H, m, Ar-H), 3.92 (3H, s, NCH_3); MS (EI) *m/z* (%): 250 (M^+, 100), 221 (12). HRMS (EI) calcd. for $C_{15}H_{10}N_2O_2$, 250.0742; found 250.0750.

6-Ethyl-4-azachromeno[2,3-*b*]indol-11(6*H*)-one (5b)

The compound was synthesized from 4-azachromeno[2,3-*b*]indol-11(6*H*)-one (118 mg, 0.5 mmol) and EtI (78 mg, 41 μL, 0.5 mmol) according to the procedure for compound **(5a)**. Yield: 47 mg (35.6%); mp 180-182°C; ^1H NMR (300MHz, DMSO-d_6): δ 8.75 (1H, dd, J=4.4, 2.0 Hz, Ar-H), 8.68 (1H, dd, J=7.7, 2.0 Hz, Ar-H), 8.13 (1H, d, J=7.1 Hz, Ar-H), 7.71 (2H, m, Ar-H), 7.38 (2H, m, Ar-H), 4.47 (2H, q, J=7.0 Hz, CH_2), 1.46 (3H, t, J=7.0 Hz, CH_3); MS (EI) *m/z* (%): 264 (M^+, 100), 249 (80). HRMS (EI) calcd. for $C_{16}H_{12}N_2O_2$, 264.0899; found 264.0894.

6-(2-Aminoethyl)- 4-azachromeno[2,3-*b*]indol-11(6*H*)-one (5c)

To a suspension of 4-azachromeno[2,3-*b*]indol-11(6*H*)-one (118 mg, 0.5 mmol) in 10 mL of acetone was added K_2CO_3 (207 mg, 1.5 mmol). After 30 min, 2-bromoethanamine hydrobromide (103 mg, 0.5 mmol) was added. The reaction mixture was heated under reflux for 3 days and filtered. The filtrate was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 10/1, v/v) to give compound **(5c)**. Yield: 16 mg (11.5%); mp 179-183°C; ^1H NMR (300MHz, DMSO-d_6): δ 8.75 (1H, dd, J=4.8, 2.0 Hz, Ar-H), 8.71 (1H, dd, J=7.6, 2.0 Hz, Ar-H), 8.14 (1H, dd, J=7.2, 1.8 Hz, Ar-H), 7.77 (1H, dd, J=7.1, 1.1 Hz, Ar-H), 7.70 (1H, m, Ar-H), 7.39 (2H, m, Ar-H), 4.40 (2H, t, J=6.1 Hz, CH_2), 3.04 (2H, t, J=6.1 Hz, CH_2); MS (EI) *m/z* (%): 279 (M^+, 36), 250 (100), 249 (85). HRMS (EI) calcd. for $C_{16}H_{13}N_3O_2$, 279.1008; found 279.1002.

6-[2-(Dimethylamino)ethyl]- 4-azachromeno[2,3-*b*]indol-11(6*H*)-one (5d)

2-Chloro-*N*, *N*-dimethylethanamine hydrochloride was prepared according to known procedures.[16] Yield: 650 mg (40.0%); mp 228-229°C (lit., mp 201-203°C); ^1H NMR (300MHz, CD_3OD): δ 3.99 (2H, t, J=5.7 Hz, CH_2Cl), 3.58 (2H, t, J=5.7 Hz, NCH_2), 2.97 (6H, s, $N(CH_3)_2$).

Compound **(5d)** was synthesized from 4-azachromeno[2,3-*b*]indol-11(6*H*)-one (236 mg, 1mmol) and 2-chloro-*N*, *N*-dimethylethanamine hydrochloride (143 mg, 1 mmol) according to the procedure for compound **(5a)**. The reaction was not completed after 24 h. After workup, the precipitated solid was 55 mg of the mixture of the starting material and the product. The mixture was not soluble , so it was difficult to separate. The filtrate stayed overnight to gain 18 mg of pure product. Yield: 18 mg (5.8%); mp 130-133°C; ^1H NMR (300MHz, DMSO-d_6): δ 8.76 (1H, dd, J=4.4, 2.0 Hz, Ar-H), 8.70 (1H, dd, J=7.8, 2.0 Hz, Ar-H), 8.13 (1H, dd, J=7.4, 1.8 Hz, Ar-H), 7.71 (2H, m, Ar-H), 7.39 (2H, m, Ar-H), 4.51 (2H, t, J=6.3 Hz, CH_2), 2.74 (2H, t, J=6.3 Hz, CH_2), 2.22 (6H, s, NMe_2); MS (EI) *m/z* (%): 307 (M^+, 100), 249 (40). HRMS (EI) calcd. for $C_{18}H_{17}N_3O_2$, 307.1321; found 307.1321.

6-[2-(Piperidin-1-yl)ethyl]- 4-azachromeno[2,3-*b*]indol-11(6*H*)-one (5e)

To a solution of 4-azachromeno[2,3-*b*]indol-11(6*H*)-one(118 mg, 0.5 mmol) in 10 mL of DMF was added K_2CO_3 (207 mg, 1.5 mmol). After 30 min, 1-(2-chloroethyl)piperidine hydrochloride (92 mg, 0.5 mmol) and NaI (7.5 mg, 0.05 mmol) was added. The reaction mixture was stirred at rt for 7 h and poured into 100 mL of water . The resulting yellow solid was filtered, and dried. The crude product was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 25/1, v/v) to give compound **(5e)**. Yield: 14 mg (8%); mp 167-169°C; ^1H NMR (300MHz, DMSO-d_6): δ 8.75 (1H, dd, J=4.5, 2.0 Hz, Ar-H), 8.70 (1H, dd, J=7.7, 2.0 Hz, Ar-H), 8.13 (1H, d, J=6.6 Hz, Ar-H), 7.73 (1H, d, J=7.9 Hz, Ar-H), 7.70 (1H, m, Ar-H), 7.38 (2H, m, Ar-H), 4.52 (2H, t, J=6.2 Hz, CH_2), 2.70 (2H, t, J=6.2 Hz, CH_2), 2.41 (4H, s, CH_2), 1.29 (6H, m, CH_2); MS (EI) *m/z* (%): 347 (M^+, 4), 249 (5), 98 (100). HRMS (EI) calcd. for $C_{21}H_{21}N_3O_2$, 347.1634; found 347.1633.

9-Chloro-6-[2-(piperidin-1-yl)ethyl]- 4-azachromeno[2,3-*b*]indol-11(6*H*)-one (5f)

Compound **(5f)** was synthesized from 9-chloro-4-azachromeno[2,3-*b*]indol-11(6*H*)-one (135 mg, 0.5 mmol) and 1-(2-chloroethyl)piperidine hydrochloride (102 mg, 0.55 mmol) according to the procedure for compound **(5e)**. The reaction mixture was stirred for 48 h at rt, filtered to remove K_2CO_3 and poured into 50 mL of water to gain gray solid. Yield: 60 mg (31.5%); mp 176-179°C; ^1H NMR (300MHz, $CDCl_3$): δ 8.84 (1H, dd, J=7.7, 2.0 Hz, Ar-H), 8.67 (1H, dd, J=4.4, 2.0 Hz, Ar-H), 8.33 (1H, t, J=1.2 Hz, Ar-H), 7.55 (1H, m, Ar-H), 7.35 (2H, m, Ar-H), 4.47 (2H, t, J=6.2 Hz, CH_2), 2.78 (2H, t, J=6.2 Hz, CH_2), 2.49 (4H, s, CH_2), 1.47 (4H, s, CH_2), 1.38 (2H, s, CH_2); MS (EI) *m/z* (%): 381 (M^+, 8), 283 (22), 98 (100). HRMS (EI) calcd. for $C_{21}H_{20}ClN_3O_2$, 381.1244; found 381.1229.

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