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SYNTHESIS OF NEW THIAZOLO[5,4-*a*]ACRIDINE DERIVATIVES

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Abstract- Three 2-substituted thiazolo[5,4-*a*]acridin-11(6*H*)-ones and seven 11-thioxo-, 11-alkylimino-, and 11-phenoxythiazolo[5,4-*a*]acridines have been prepared. All these new acridines obtained in good yields have an angularly fused ring system, which has been determined by ^{1}H- and ^{13}C-NMR spectral data.

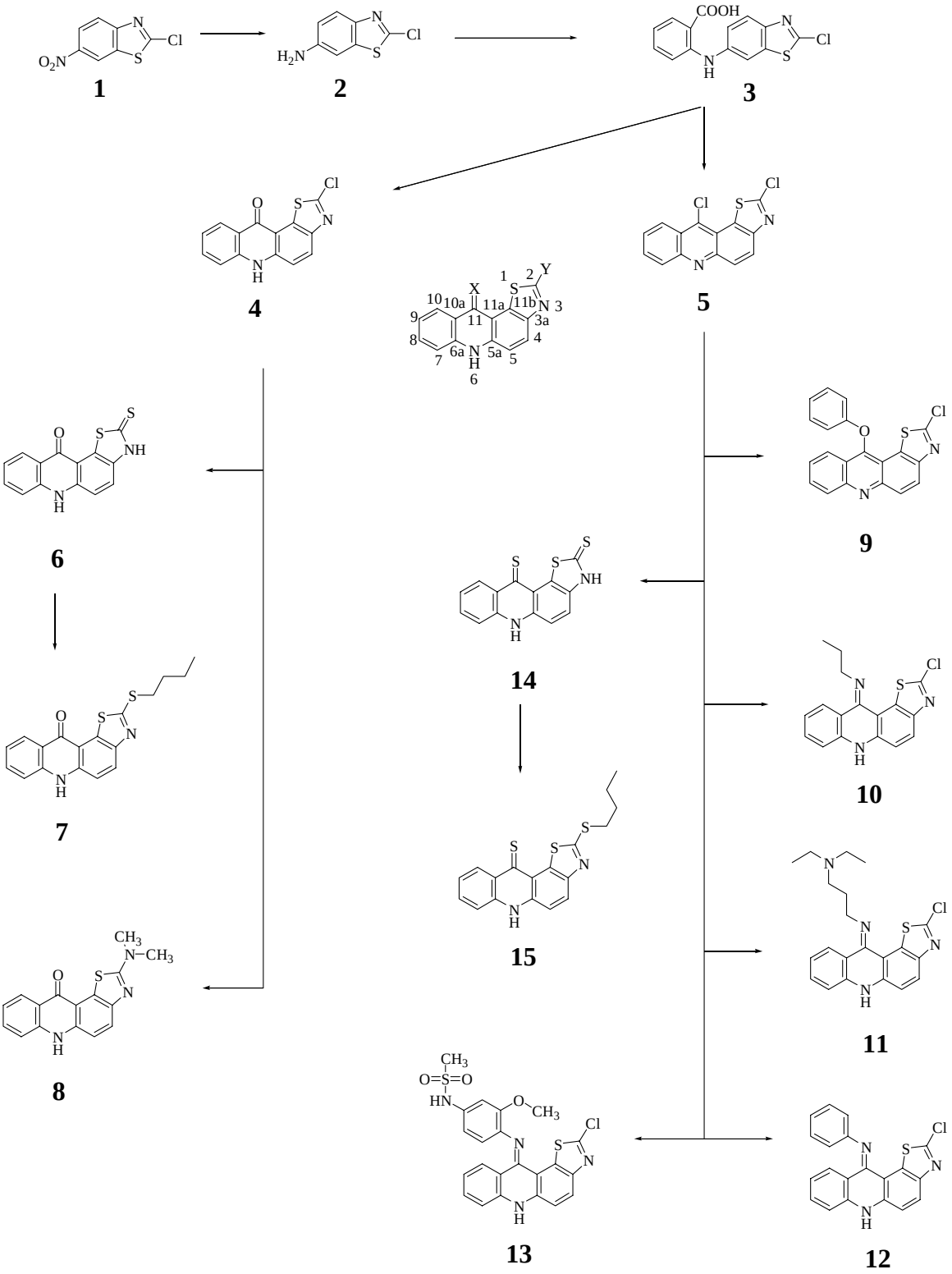
INTRODUCTION

There is considerable interest in polycyclic acridine derivatives, in particular when they contain additional side chains on the acridine moiety. One of their main features is their ability to interact with DNA,[1] making them potential chemotherapeutic drugs such as the antileukemic compound *m*-amsacrine.[2-7] Some acridine derivatives can also inhibit the activity of DNA enzyme topoisomerase II.[8] Moreover acridines bearing polyamine side chain bulk like the *N*-[2-(dimethylamino)ethyl]acridine-4-carboxamide[9] (DACA, NSC 601316) are intercalating agents with inhibitory activity against the DNA regulatory enzymes topoisomerase I[10] and II.[11] The inhibitory effect against these enzymes seems to be unaffected by P-glycoprotein-mediated Multi Drug Resistance[12] (P-gp m. MDR). Recent work has shown that thioacridine derivatives affect the function of P-gp mediated MDR,[13] and enhance other antimicrobial activities.[14-16] Moreover, these acridine derivatives might be a new class of HIV-1 Tat antagonist[17] due to their competitive inhibition with the Tat-Tar complex, which blocks HIV expression in a cellular Tat transactivation system. These compounds could therefore behave as a new type of inhibitory agent: «In-PRINTs», that is inhibitor of protein-ribonucleotide sequences. Based on the works aforementioned, we have synthesized new thiazolo[5,4-*a*]acridines combining the intercalating effects of acridine, thiazole ring,[18] and the high affinity of polyamine to bind DNA.

RESULTS AND DISCUSSION

The preparation of these new thiazolo[5,4-*a*]acridines (**5-15**) is summarized in scheme 1.

Scheme 1



Compound (**1**) was synthesized by the nitration of commercial 2-chlorobenzothiazole according to a procedure already described.[19] Reduction of **1** to **2** was done with iron powder in hydrochloric acid.[19] The Ullmann condensation of **2** with *o*-bromobenzoic acid gave **3** in 87% yield using ultrasound irradiation.[20]

Cyclization of **3** with sulfuric acid[21,22] or with phosphorus oxychloride[23] afforded **4** or **5**, respectively. The ^{1}H- and ^{13}C- NMR spectral data for **4** and **5** confirmed the "bent" structure thiazolo[5,4-*a*]acridine reported so far[24,25] [AB system for protons H4 and H5 (J_{AB}= 9 Hz) and ^{13}C chemical shifts for C_4 and C_5 in 120-130 ppm range]. The O, S, and N substitutions were performed using **4** and **5** as starting compounds. The choice of various substituents was based on the potential pharmacological properties of *m*-amsacrine, thio derivatives and *N*-arylamines. Synthesis of **9-15** was performed under an inert atmosphere because of the instability of **5**, which tended to be rapidly hydrolyzed into **4**, decreasing yields of **9-14**. In spite of this possible side reaction, we could still obtain some pure products in sufficient yields (45-70%). Their structure was unambiguously determined by ^{1}H- and ^{13}C-NMR. Thio derivatives (**6**) and (**14**) were synthesized by the reaction of **4** and **5** with phosphorus pentasulfide, respectively. The ^{13}C-NMR spectra showed the thioxo function at 190.2 ppm for **6**, and 189.3 and 192.0 ppm for **14**. Alkylation of **14** gave **15**, whose structure was determined by the HMBC spectrum between α–methylene protons and C_2 carbon.

For **10** to **13**, substitution occurred in the C_{11} position (HMBC results) of the acridine skeleton. These compounds possess an imino structure shown by the N_6-H proton at δ 11.1 ppm and the ^{13}C chemical shifts of acridine.[25]

In conclusion, we report the synthesis of ten new "bent" thiazolo[5,4-*a*]acridines. Some of these products are currently being tested for pharmacological use.

EXPERIMENTAL

Melting points were determined with an Electrothermal 9300 apparatus and are uncorrected. Reagents and solvents were purchased from common commercial suppliers. The NMR spectra were recorded on a Bruker AC 200 spectrometer operating at 200 MHz for ^{1}H and ^{13}C. Two-D NMR spectra, both of homonuclear (COSY) and heteronuclear (HMBC, HMQC) correlations, were obtained with a Bruker AMX 400. In all cases TMS was used as an internal standard. Compounds (**1**) to (**4**) were previously described: 2-chloro-6-nitrobenzothiazole (**1**), [19] 6-amino-2-chlorobenzothiazole (**2**),[19] anthranilic acid (**3**)[20] and 2-chlorothiazolo[5,4-*a*]acridin-11(6*H*)-one (**4**);[21,22] 2-chlorobenzothiazole is a commercial compound.

2,11-Dichlorothiazolo[5,4-*a*]acridine (5)

Compound (**3**) (2.13 g, 7 mmol) and 20 mL (220 mmol) of phosphorus oxychloride were introduced into a 100 mL round bottom flask and heated at 80°C for 15 min, and then the solution was heated up to 120°C for 30 min. The solution was cooled at rt and the excess of $POCl_3$ was eliminated with 200 mL of petroleum spirit (60-80°C). The resulting orange slurry was poured onto ice (100 g) and neutralized with

10% ammonia. The precipitate was collected by filtration, dried, and recrystallized from 20 mL of CH_2Cl_2 [yield, 2.04 g (92 %), mp: 221°C]. **^{1}H**-NMR ($CDCl_3$, δ): 7.70 (1H, t, *J*=8.8 Hz, H-9), 7.85 (1H, t, *J*=8.8 Hz, H-8), 8.15-8.26 (3H, m, H-4, H-5, H-7), 8.39 (1H, dd, *J*= 1.1, 8.8 Hz, H-10). **^{13}C**-NMR ($CDCl_3$, δ): 155.4 (C-2), 150.0 (C-3a), 126.9 (C-4), 129.6 (C-5), 147.3 (C-5a or C-6a), 147.5 (C-5a or C-6a), 129.6 (C-7), 130.8 (C-8), 128.2 (C-9), 124.3 (C-10), 124.3 (C-10a), 138.7 (C-11), 120.0 (C-11a), 129.4 (C-11b). *Anal.* Calcd for $C_{14}H_6N_2Cl_2S$: C, 55.05; H, 1.97; N, 9.17. Found: C, 55.18; H, 2.19; N, 9.33.

2,3,6,11-Tetrahydro-11-oxo-2-thioxothiazolo[5,4-*a*]acridine (6)

Compound (**4**) (0.3 g, 1 mmol), 0.22 g (0.5 mmol) of phosphorus pentasulfide, and 15 mL of hexamethylphosphoramide (HMPA) were introduced into a 50 mL round bottom flask. The solution was stirred for 2 h at 140°C, and then poured into hot water (300 mL). The yellow precipitate was filtered, washed with water, dried, and then recrystallized from 20 mL of ethanol [yield, 0.27 g (95 %), mp: > 400°C]. **^{1}H**-NMR (DMSO-d_6, δ): 7.32 (1H, t, *J*= 8.0 Hz, H-9), 7.64 (3H, m, H-4, H-5, H-7), 7.78 (1H, t, *J*=8.4 Hz, H-8), 8.22 (1H, d, *J*=8.0 Hz, H-10), 12.21 (1H, s, H-6), 13.91 (1H, s, H-3). **^{13}C**-NMR (DMSO-d_6, δ): 190.2 (C-2), 135.7 (C-3a), 118.4 (C-4), 116.9 (C-5), 138.1 (C-5a), 140.4 (C-6a), 117.8 (C-7), 133.7 (C-8), 121.7 (C-9), 125.5 (C-10), 119.9 (C-10a), 175.4 (C-11), 114.0 (C-11a), 127.0 (C-11b). *Anal*. Calcd for $C_{14}H_8N_2OS_2$: C, 59.09; H, 2.81; N, 9.85. Found : C, 59.21; H, 3.11; N, 10.07.

2-Butylthiothiazolo[5,4-*a*]acridin-11(6*H*)-one (7)

Compound (**4**) (0.3 g, 1 mmol), 25 mL (277 mmol) of 2-butanone (99%), 12 mL (53 mmol) of potassium hydroxide 30%, and 0.15 g (1 mmol) of 1-bromobutane were introduced into a 50 mL two-necked round bottom flask under nitrogen atmosphere and heated at 80°C for 4 h. The resulting orange solution was poured into 200 mL of hot water, and the yellow precipitate was filtered, washed with water, and dried. Pure product was obtained without further purification [yield, 0.28 g (82 %), mp: 310°C]. **^{1}H**-NMR (DMSO-d_6, δ): 0.93 (3H, t, *J*=7.4 Hz, H-δ), 1.47 (2H, sex, *J*=7.4 Hz, H-γ), 1.77 (2H, quint, *J*=7.2 Hz, H-β), 3.38 (2H, t, *J*=7.2 Hz, H-α),7.36 (1H, t, *J*=8.2 Hz, H-9), 7.67 (2H, m, H-5, H-7), 7.92 (1H, t, *J*=8.4 Hz, H-8), 8.23 (1H, d, *J*=8.9 Hz, H-4), 8.29 (1H, d, *J*=8.1 Hz, H-10), 12.28 (1H, s, H-6). **^{13}C**-NMR (DMSO-d_6, δ): 166.8 (C-2), 148.0 (C-3a), 127.0 (C-4), 116.6 (C-5), 138.5 (C-5a), 140.3 (C-6a), 118.0 (C-7), 133.6 (C-8), 121.9 (C-9), 125.7 (C-10), 120.0 (C-10a), 174.1 (C-11), 114.5 (C-11a), 130.7 (C-11b), 32.7 (C-α), 31.1 (C-β), 21.4 (C-γ), 13.5 (C-δ). *Anal.* Calcd for $C_{18}H_{16}N_2OS_2$: C, 63.44; H, 4.70; N, 8.22. Found: C, 63.65; H, 4.85; N, 8.40.

2-Dimethylaminothiazolo[5,4-*a*]acridin-11(6*H*)-one (8)

Compound (**4**) (0.44 g, 1.5 mmol) and 20 mL of HMPA were introduced into a 100 mL round bottom flask, and the mixture was heated under reflux with vigorous stirring for 24 h. The solution was then allowed to cool at rt and poured into water (100 mL). The yellow precipitate obtained was filtered, dried, and then recrystallized from 50 mL of ethanol [yield, 0.24 g (54 %), mp: 355°C]. **^{1}H**-NMR (DMSO-d_6, δ): 3.18 (6H, s, H-α), 7.26 (1H, m, H-9), 7.66 (1H, d, *J*=8.8 Hz, H-5), 7.71 (2H, m, H-7, H-8), 7.90 (1H, d, *J*=8.8 Hz, H-4), 8.25 (1H, d, *J*=8.1 Hz, H-10), 12.37 (1H, s, H-6). **^{13}C**-NMR (DMSO-d_6, δ): 170.4 (C-2), 147.8 (C-3a), 124.9 (C-4), 115.5 (C-5), 136.4 (C-5a), 140.5 (C-6a), 117.7 (C-7), 133.0 (C-8), 120.9 (C-9), 125.7 (C-10), 119.5 (C-10a), 175.0 (C-11), 115.2 (C-11a), 125.5 (C-11b), 39.9 (C-α). *Anal.* Calcd for $C_{16}H_{13}N_3OS$: C, 65.00; H, 4.40; N, 14.22. Found : C, 64.64; H, 4.25; N, 14.60.

2-Chloro-11-phenoxythiazolo[5,4-*a*]acridine (9)

Compound (**5**) (0.6 g, 2 mmol) and 2 g (21 mmol) of phenol were introduced into a 100 mL two-necked flask and stirred at 80°C under nitrogen for 4 h. The solution was cooled to rt and poured into 30 mL of ethyl acetate. The resulting orange powder was filtered and dried. Pure product was obtained without further purification [yield, 0.64 g (90 %), mp: 230°C]. **^{1}H**-NMR ($CDCl_3$, δ): 6.83 (2H, dd, *J*=1.5, 9.2 Hz, H-2'), 7.09 (1H, dt, *J*=1.1, 8.4 Hz, H-4'), 7.28 (2H, d, *J*=8.4 Hz, H-3'), 7.45 (1H, ddd, *J*=1.0, 6.6, 8.7 Hz, H-9), 7.79 (1H, ddd, *J*=1.0, 6.7, 8.8 Hz, H-8), 7.88 (1H, dd, *J*=0.7, 8.8 Hz, H-10), 8.21 (1H, d, *J*=9.2 Hz, H-5), 8.24 (1H, d, *J*=9.2 Hz, H-4), 8.29 (1H, dd, *J*=0.7, 8.8 Hz, H-7). **^{13}C**-NMR ($CDCl_3$, δ): 155.3 (C-2), 148.8 (C-3a), 126.7 (C-4), 129.2 (C-5), 148.8 (C-5a), 150.0 (C-6a), 130.1 (C-7), 130.7 (C-8), 126.7 (C-9), 122.6 (C-10), 119.6 (C-10a), 152.9 (C-11), 116.1 (C-11a), 127.2 (C-11b), 157.1 (C-1'), 115.7 (C-2'), 130.3 (C-3'), 123.6 (C-4'). *Anal.* Calcd for $C_{20}H_{11}N_2OClS$: C, 66.21; H, 3.11; N, 7.74. Found : C, 64.62; H, 3.01; N, 8.21.

2-Chloro-6,11-dihydro-11-propyliminothiazolo[5,4-*a*]acridine (10)

Compound (**5**) (0.3 g, 1 mmol) and 2 g (21 mmol) of phenol were introduced into a 100 mL two-necked flask, and the mixture was heated at 100°C under nitrogen. After compound (**5**) was dissolved in phenol, the temperature was decreased to 50-60°C. Propylamine (0.1 mL, 1 mmol) was then introduced into the reaction mixture. The whole mixture was stirred at 80°C for 4 h, cooled to rt, and poured into 100 mL of ethyl acetate. The precipitate was then filtered, washed, and recrystallized from 30 mL of ethanol [yield, 0.18 g (53 %), mp: 315°C]. **^{1}H** -NMR (DMSO-d_6, δ): 1.13 (3H, t, *J*=7.3 Hz, H-γ), 2.00 (2H, sex, *J*=7.2 Hz, H-β), 4.07 (2H, t, *J*=6.7 Hz, H-α), 7.15 (1H, dt, *J*=1.1, 8.2 Hz, H-9), 7.41 (1H, d, *J*=8.1 Hz, H-7), 7.43 (1H, d, *J*=8.7 Hz, H-5), 7.57 (1H, dt, *J*=1.1, 8.2 Hz, H-8), 8.02 (1H, d, *J*=8.7 Hz, H-4), 8.33 (1H, d, *J*=7.9 Hz, H-10), 11.17 (1H, s, H-6). **^{13}C**-NMR (DMSO-d_6, δ): 154.8 (C-2), 144.6 (C-3a), 125.1 (C-4),

115.4 (C-5), 136.5 (C-5a), 140.3 (C-6a), 117.4 (C-7), 131.4 (C-8), 120.1 (C-9), 129.1 (C-10), 116.8 (C-10a), 148.6 (C-11), 115.9 (C-11a), 130.9 (C-11b), 55.1 (C-α), 25.8 (C-β), 12.5 (C-γ). *Anal.* Calcd for $C_{17}H_{14}N_3ClS$: C, 62.23; H, 4.27; N, 12.81. Found : C, 62.58; H, 4.39; N, 12.50.

2-Chloro-11-(3-diethylaminopropyl)imino-6,11-dihydrothiazolo[5,4-*a*]acridine (11)

Following the procedure described in **10**, compound (**5**) (0.3 g, 1 mmol), 2 g (21 mmol) of phenol and 0.2 mL (1 mmol) of diethylaminopropylamine gave a pale brown powder [yield, 0.18 g (45 %), mp: 241°C]. **^{1}H**-NMR (DMSO-d_6, δ): 1.08 (6H, t, *J*=7.1 Hz, H-ε), 2.27 (2H, m, H-β), 2.98 (4H, m, H-δ), 3.04 (2H, m, H-γ), 3.98 (2H, t, *J*=6.2 Hz, H-α), 7.13 (1H, t, *J*=7.4 Hz, H-9),7.42 (2H, m, H-5, H-7), 7.56 (1H, t, *J*=7.4 Hz, H-8), 8.11 (1H, d, *J*=8.7 Hz, H-4), 8.35 (1H, d, *J*=8.3 Hz, H-10), 11.47 (1H, s, H-6). **^{13}C**-NMR (DMSO-d_6 + TFA, δ): 154.4 (C-2), 150.8 (C-3a), 133.0 (C-4), 121.2 (C-5), 141.9 (C-5a or C-6a), 142.0 (C-5a or C-6a), 121.7 (C-7), 138.3 (C-8), 127.8 (C-9), 128.1 (C-10), 117.0 (C-10a), 160.7 (C-11), 112.6 (C-11a), 133.2 (C-11b), 50.2 (C-α), 27.5 (C-β), 51.6 (C-γ), 49.8 (C-δ), 10.2 (C-ε). *Anal.* Calcd for $C_{21}H_{23}N_4ClS$: C, 62.22; H, 5.81; N, 14.04. Found: C, 62.11; H, 5.96; N, 13.96.

2-Chloro-6,11-dihydro-11-phenyliminothiazolo[5,4-*a*]acridine (12)

Following the procedure described in **10**, compound (**5**) (0.3 g, 1 mmol), 2 g (21 mmol) of phenol, and 0.2 mL (2 mmol) of aniline afforded a red powder [yield, 0.27 g (75 %), mp: 294°C]. **^{1}H**-NMR (DMSO-d_6, δ): 6.80 (1H, t, *J*=8.0 Hz, H-9), 6.91 (2H, d, *J*=7.6 Hz, H-2'), 7.08 (1H, t, *J*=7.2 Hz, H-4'), 7.39 (4H, m, H-5, H-8, H-3'), 7.50 (1H, d, *J*=7.9 Hz, H-7), 7.56 (1H, d, *J*=8.9 Hz, H-4), 8.15 (1H, d, *J*=8.2 Hz, H-10), 11.65 (1H, s, H-6). **^{13}C**-NMR (DMSO-d_6, δ): 154.1 (C-2), 144.6 (C-3a), 126.1 (C-4), 115.8 (C-5), 137.2 (C-5a), 140.2 (C-6a), 118.2 (C-7), 131.9 (C-8), 120.1 (C-9), 127.4 (C-10), 114.6 (C-10a), 151.1 (C-11), 114.4 (C-11a), 131.3 (C-11b), 148.0 (C-1'), 118.9 (C-2'), 129.6 (C-3'), 122.3 (C-4'). *Anal*. Calcd for $C_{20}H_{12}N_3ClS$: C, 66.39; H, 3.34; N, 11.61. Found : C, 67.12; H, 3.32; N, 11.58.

2-Chloro-6,11-dihydro-11-(4-methanesulfonylamino-2-methoxyphenyl)iminothiazolo[5,4-*a*]acridine (13)

Following the procedure described in **10**, compound (**5**) (0.3 g, 1 mmol), 2 g (21 mmol) of phenol, and *N*-(4-amino-3-methoxyphenyl)methanesulfonamide[26] (0.22 g, 1 mmol), provided a red powder [yield, 0.3 g (62 %), mp: 144°C]. **^{1}H**-NMR (DMSO-d_6, δ): 3.03 (3H, s, SO_2CH_3), 3.53 (3H, s, OCH_3), 6.90 (3H, m, H-8, H-9, H-5'), 6.94 (1H, s, H-3'), 7.50 (3H, m, H-5, H-7, H-6'), 7.59 (1H, d, *J*=8.7 Hz, H-4), 8.15 (1H, d, *J*=8.4 Hz, H-10), 9.58 (1H, s, H-8'), 11.76 (1H, s, H-6). **^{13}C**-NMR (DMSO-d_6, δ): 154.4 (C-2), 144.7 (C-3a), 126.4 (C-4), 115.9 (C-5), 136.7 (C-5a), 139.6 (C-6a), 118.0 (C-7), 132.0 (C-8), 120.5 (C-9), 126.1

(C-10), 116.0 (C-10a), 149.0 (C-11), 114.7 (C-11a), 131.5 (C-11b), 137.1 (C-1'), 149.1 (C-2'), .105.9 (C-3'), 133.8 (C-5'), 120.4 (C-6'), 55.5 (C-7'), 39.9 (C-9'). *Anal.* Calcd for $C_{22}H_{16}N_3O_3ClS_2$: C, 56.22; H, 3.43; N, 8.94. Found: C, 56.35; H, 3.15; N, 9.01.

Thiazolo[5,4-*a*]acridine-2(3*H*),11(6*H*)-dithione (14)

Compound (**5**) (0.3 g, 1 mmol), 0.2 g (0.5 mmol) of phosphorus pentasulfide, and 5 mL of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) were introduced into a 50 mL round bottom flask. The solution was stirred for 5 h at 140°C and then poured into hot water (300 mL). The yellow precipitate was filtered, washed with water, dried, and then recrystallized from 20 mL of hot ethanol [yield, 0.28 g (93 %), mp: 368°C]. ^{1}**H**-NMR (DMSO-d_6, δ): 7.39 (1H, t, *J*=8.2 Hz, H-9), 7.67 (3H, m, H-4, H-5, H-7), 7.79 (1H, t, *J*=8.1 Hz, H-8), 8.67 (1H, d, *J*=8.4 Hz, H-10), 13.16 (1H, s, H-6), 13.91 (1H, s, H-3). ^{13}**C**-NMR (DMSO-d_6, δ): 189.3 (C-2), 137.6 (C-3a), 119.3 (C-4), 118.1 (C-5), 134.2 (C-5a), 135.1 (C-6a), 117.8 (C-7), 133.8 (C-8), 124.0 (C-9), 129.3 (C-10), 128.8 (C-10a), 192.0 (C-11), 123.6 (C-11a), 129.3 (C-11b). *Anal.* Calcd for $C_{14}H_8N_2S_3$: C, 55.93; H, 2.66; N, 9.32. Found: C, 55.77; H, 2.67; N, 9.56.

2-Butylthiothiazolo[5,4-*a*]acridine-11(6*H*)-thione (15)

Compound (**14**) (0.3 g, 1 mmol), 25 mL (277 mmol) of 2-butanone (99%), 12 mL (53 mmol) of potassium hydroxide (30%), and 0.1 g (1 mmol) of 1-bromobutane were introduced into a 50 mL round bottom flask under nitrogen atmosphere, and the mixture was heated at 80°C for 20 h. The resulting red solution was poured into 300 mL of hot water. The yellow precipitate was filtered, washed, and dried. Pure product was obtained without further purification [yield, 0.15 g (42 %), mp: 255°C]. ^{1}**H**-NMR (DMSO-d_6, δ): 0.80 (3H, t, *J*=7.2 Hz, H-δ), 1.38 (2H, sex, *J*=7.4 Hz, H-γ), 1.76 (2H, quint, *J*=7.2 Hz, H-β), 3.46 (2H, t, *J*=7.2 Hz, H-α), 7.40 (1H, m, H-8), 7.64 (2H, m, H-9, H-5), 7.76 (1H, d, *J*=8.4 Hz, H-7), 8.38 (1H, d, *J*=8.8 Hz, H-4), 9.38 (1H, d, *J*=8.4 Hz, H-10), 13.16 (1H, s, H-6). ^{13}**C**-NMR (pyridine-d_6, δ): 168.0 (C-2), 150.8 (C-3a), 128.5 (C-4), 118.7 (C-5), 135.8 (C-5a), 136.1 (C-6a), 117.1 (C-7), 133.3 (C-8), 123.8 (C-9), 131.0 (C-10), 130.1 (C-10a), 193.2 (C-11), 124.0 (C-11a), 125.8 (C-11b), 33.2 (C-α), 31.8 (C-β), 22.1 (C-γ), 13.7 (C-δ). *Anal.* Calcd for $C_{18}H_{16}N_2S_3$: C, 60.59; H, 4.49; N, 7.85. Found: C, 60.75; H, 4.71; N, 7.97.

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