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Synthesis and Anti-HIV Activity of Substituted 1,2,4-Triazolo-thiophene Derivatives

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ABSTRACT: *A new series of substituted 1,2,4-triazoles bearing thiophene molecules* **8** *and* **10** *has been synthesized from cycloaddition of thiophene 3- and 2-carbonitriles* **5** *and* **9**, *respectively, with the reactive cumulene intermediates* **4**. *The newly synthesized products have been evaluated for their anti-HIV activity*. © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:443–448, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20319

INTRODUCTION

Several biologically active therapeutics contain five-membered heterocycles in their chemical structures. The 1,2,4-triazole moiety is present, for example, in certain antiasthmatic [1], antiviral (ribavirin) [2], antifungal (fluconazole) [3], antibacterial [4], and hypnotic [5] (triazolam) drugs. Owing to its broad spectrum of biological activity [6–12], the 1,2,4-triazole ring system represents an attractive target for the elaboration of solid-phase synthesis and the production of combinatorial libraries.

RESULTS AND DISCUSSION

Recently, the short-lived reactive intermediates 1-(chloroalkyl)-1-aza-2-azoniaallene salts (**4**) were used by Jochims and coworkers [13] in the synthesis of various 1,2,4-triazole compounds via cycloaddition with various unsaturated precursors in the presence of $SbCl_5$. In our recent work, these cations have been utilized in the synthesis of new types of 1,2,4-triazoles such as *C*-nucleosides [14,15], acyclic *C*-nucleosides [16], pyrimidines [17], *N*-alkylphthalimides [18], D-mannopentitol-1-yl-1,2,4-triazoles [19], 1*H*-indoles [20], quinolones [20], benzotriazoles [21], 3′-triazolo-thymidines [22], acetic acid alkylidene hydrazides [23], and 1,4-disubstituted piperazines [24,25]. The reactive intermediates (**4**) were obtained from the α,α'-dichloroazo compounds **3** [13] by treatment with $SbCl_5$ at $-60^{\circ}C$. At approximately $-30^{\circ}C$, the colour changed from orange to brown, indicating that cumulenes **4a–d** underwent cycloaddition reactions with nitrile **5** to give inseparable 1,2,4-triazolium hexachloroantimonates **6a–d**. After increase in the temperature above $-30^{\circ}C$, compounds **6a–d** rearranged via [1,2]-migration [26,27] of the alkyl group at C-3′ to N-5′ accompanied by the elimination of CR^1R^2Cl group at N-1′ leading to the protonated 1,5-dialkyl-3-((thiophene-3-yl)methyl)-1*H*-1,2,4-triazolium salts **7a–d**. In situ deprotonation of salts **7a–d** with aqueous $NaHCO_3$ and NH_3 solution gave the desired products **8a–d** in 70%–86% yield (Scheme 1). Similarly, compounds **10b–d** were obtained successively from the cycloaddition of **4** with the nitrile **9** in 74%–82% yield (Scheme 2). The structures of the newly prepared compounds were determined by their ^1H and ^{13}C NMR and by mass spectra.

Compounds **8a–d** were identified by the ^1H and ^{13}C NMR spectra, which are in agreement with those of the triazole analogues obtained previously [14–25]. The CH_2 signal appeared as a singlet at the

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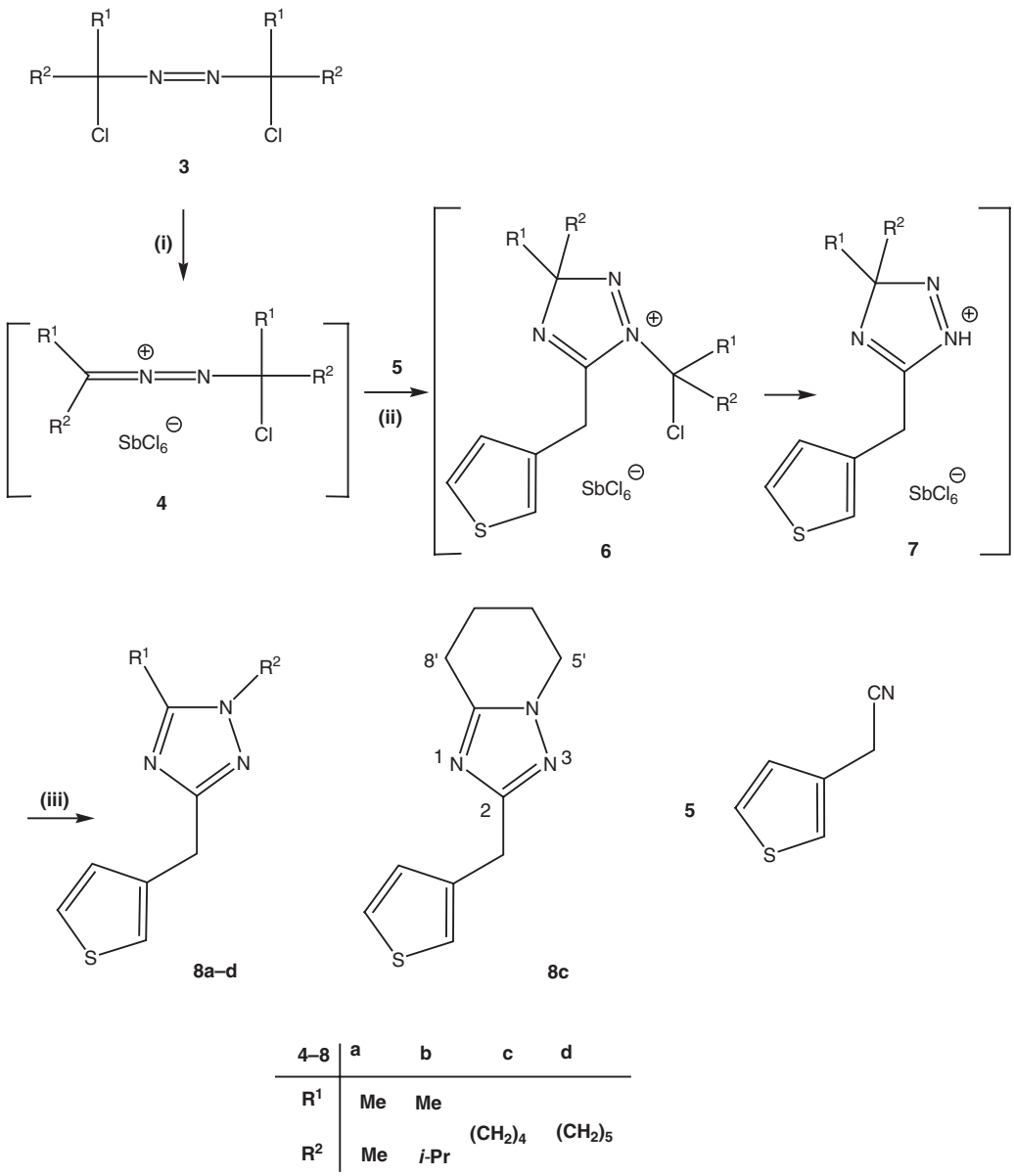
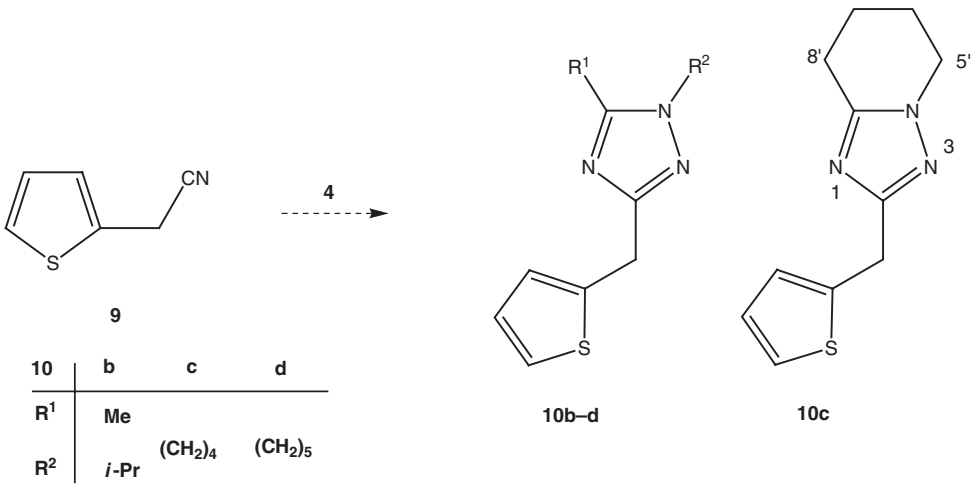


SCHEME 1 Reagents and conditions: (i) $SbCl_5$, CH_2Cl_2, −60°C; (ii) CH_2Cl_2, −60 to 23°C; (iii) $NaHCO_3$, NH_3, MeCN, 0°C, 2 h.

region δ_H 3.93–4.17 ppm. The alkyl groups at N-1′ and C-5′ of the triazole ring were assigned. The ^{13}C NMR spectra of compounds **10a–d** contained similar resonance signals of the triazole ring carbons C-2′ and C-5′. The chemical shifts between δ_C 161.8 and 159.3 ppm were assigned to the (C-2′). The lower field signals at δ_C 150.4–157.7 ppm were attributed to C-5′. The other carbons were fully analyzed (Experimental section).

Similarly, the 1,5-dialkyl-3-((thiophene-2-yl)methyl)-1*H*-1,2,4-triazoles **10b–d** were prepared by cycloaddition of the intermediates **4** with nitrile **9** in the presence of $SbCl_5$ in 77%, 85%, and 70% yields, respectively (Scheme 2).

Next, our work is extended by using substituted thiophene to synthesize new derivatives of triazolo-substituted thiophenes and evaluation of their anti-HIV inhibitory activity in comparison to those of the unsubstituted thiophenes **8a–d** and **10b–d**. Thus, compound **12** was prepared in 78% yield by applying the same method used previously (Scheme 3). The structure of **12** was determined from ^1H NMR, ^{13}C NMR, and mass spectra.



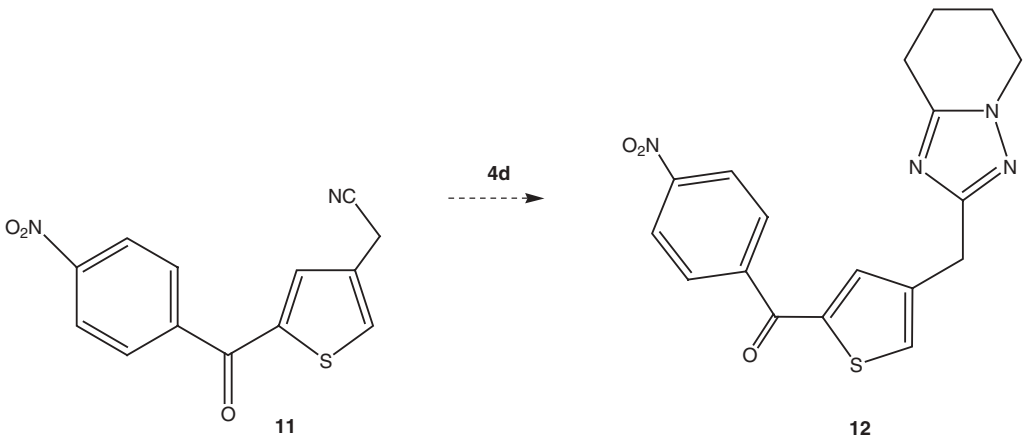
SCHEME 2

In Vitro Anti-HIV Assay

Compounds **8a–d, 10b–d**, and **12** were tested for their in vitro anti-HIV-1 (strain III_B) and HIV-2 (strain ROD) activity in human T-lymphocyte (MT-4) cells. The results are summarized in Table 1, in which the data for efavirenz [28] and capravirine [29] are included for comparison purposes. Compound **10c** was found to be the only compound in the series inhibiting HIV-1 and HIV-2 replication in cell culture. Compound **10c** showed an inhibition against HIV-1 and HIV-2 with EC_{50} of 2.40 and 2.50 μg/mL and CC_{50} of >125.0 μg/mL, respectively, resulting in a selectivity index of >52 and >51, respectively. These data encouraged us to modify the structures of these molecules by substation of the thiophene residue with more potential groups.

EXPERIMENTAL

Melting points are uncorrected and measured on Büchi melting point apparatus B-545 (BÜCHI Labortechnik AG, Switzerland). Microanalytical data were collected using Vario, Elementar apparatus (Shimadzu). NMR spectra were recorded at 250 and 600 MHz (^{1}H) and at 150.91 MHz (^{13}C) spectrometers (Bruker, Germany) in $CDCl_3$ with TMS as an internal standard. The signal assignments for protons were identified by selective proton decoupling. Mass spectra were recorded on 70 eV EI and FAB



SCHEME 3

TABLE 1 In Vitro Anti-HIV-1* and HIV-2† Activity of Some New Triazolo-thiophenes

Compound	*Virus Strain*	*EC_{50} (μg/mL)‡*	*CC_{50} (μg/mL)§*	*SI‖*
8a	III_B	>125.0	125.0	<1
	ROD	125.0	125.0	<1
8b	III_B	>74.0	73.1 ± 2.1	<1
	ROD	>69.9	73.1 ± 2.1	<1
8c	III_B	>119.0	≥ 119.0	≤ 1
	ROD	>125.0	≥ 119.0	≤ 1
8d	III_B	>84.5	94.0 ± 9.9	<1
	III_B	>86.7	94.0 ± 9.9	<1
10b	III_B	>75.4	76.8 ± 4.0	17
	ROD	>72.3	76.8 ± 4.0	<1
10c	III_B	2.4	>125.0	>52
	ROD	2.5	>125.0	>51
10d	III_B	>73.2	73.8 ± 1.4	<1
	ROD	>72.7	73.8 ± 1.4	<1
12	III_B	>98.6	98.8	<1
	ROD	>88.5	98.8	<1
Efavirenz [28]	III_B	0.003	40	13,333
Capravirine [29]	III_B	0.0014	11	7,857

*Anti-HIV-1 activity measured with strain III_B.
†Anti-HIV-2 activity measured with strain ROD.
‡Compound concentration required to achieve 50% protection of MT-4 cells from the HIV-1- and 2-induced cytopathogenic effect.
§Compound concentration that reduces the viability of mock-infected MT-4 cells by 50%.
‖SI: Selectivity index (CC_{50}/EC_{50}).

MAT 8200 spectrometery (Finnigana MAT, USA), using nitrobenzyl alcohol or glycerol as matrices.

*Preparation of 1,3,5-Trisubstituted 1,2,4-Triazoles Bearing a 3-(Thiophene-3-ylmethylene) or 3-(Thiophene-2-ylmethylene) Group (***8, 10***, and* **12***)*

General procedure: To a stirred, cooled (−60°C) solution of the required azo compound **3** (5.0 mmol) [13] and thiophene carbonitrile **5, 9**, or **11** (5.0 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise a solution of $SbCl_5$ (3.0 mmol) in dry CH_2Cl_2 (30 mL). The solution was left with stirring at −60°C for 1 h, then at 0°C for 1 h and finally at 23°C for 10 min., followed by addition of pentane (50 mL). The precipitated solid was dissolved in MeCN (40 mL), cooled to 0°C followed by addition of $NaHCO_3$ aqueous solution (2.52 g, 30 mmol in 30 mL of water) and NH_3 solution (2 mL). The mixture was stirred at 23°C for 2 h, then the organic solvent was evaporated and the residue was extracted with $CHCl_3$ (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to dryness and the residue was recrystallized from EtOH or $CHCl_3$-pentane, and the oily compounds were purified on a SiO_2 column.

*1,5-Dimethyl-3-((thiophene-3-yl)methyl)-1H-1,2,4-triazole (***8a***).* From **3a** (0.92 g) and the nitrile **5**. Yield: 0.81 g (83%); mp 77–80°C. ^{1}H NMR ($CDCl_3$)δ: 7.29–7.04 (m, 3H, H-2, H-4, H-5 of thienyl ring); 4.00 (s, 2H, CH_2); 3,74 (s, 3H, N—CH_3); 2.39 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 161.2 (C-3); 152.4 (C-5); 138.2, 128.3, 125.3, 121.5 (thienyl-*C*); 28.3 (CH_2, N-Me); 11.7 (C_5-Me). Anal. calc. for $C_9H_{11}N_3S$ (193.27): C, 55.93; H, 5.74; N, 21.74. Found: C, 55.73; H, 5.55; N, 21.49. MS *m/z* (%) (EI): 193 (85).

*1-Isopropyl-5-methyl-3-((thiophene-3-yl)methyl)-1H-1,2,4-triazole (***8b***).* From **3b** (1.20 g) and the nitrile **5**. Yield: 0.87 g (78%); brown oil. ^{1}H NMR ($CDCl_3$) δ: 701–6.76 (m, 3H, H-2, H-4, H-5 of thienyl-H); 4.29–4.23 (m, 1H, *CH*Me_2); 4.09 (s, 2H, CH_2); 2.28 (s, 3H, C_5-Me); 1.34 (d, 6H, $J = 8.0$ Hz, CH*Me_2*). ^{13}C NMR ($CDCl_3$) δ: 159.8 (C-2′), 150.4 (C-5′), 140.1, 126.6, 125.1, 123.5 (thienyl-*C*); 49.4 (N—*CH*Me); 29.5 (CH_2); 21.7 (N—CH*Me_2*); 11.2 (C_5—*CH_3*). Anal. calc. for $C_{11}H_{15}N_3S$ (221.32): C, 59.69; H, 6.83; N, 18.99. Found: C, 59.44; H, 6.62; N, 19.17. MS *m/z* (%) (EI): 221 (80).

*5,6,7,8-Tetrahydro-2-((thiophene-3-yl)methyl-[1,2,4]triazolo[1,5-a]pyridine (***8c***).* From **3c** (1.17 g) and the nitrile **5**. Yield: 0.82 g (75%); mp 81–84°C. ^{1}H NMR ($CDCl_3$) δ: 7.28–7.01 (m, 3H, H-2, H-4, H-5 of thienyl-H); 4.08 (t, 2H, $J = 5.0$ Hz, CH_2-5′); 4.03 (s, 2H, CH_2); 2.86 (t, 2H, $J = 5.0$ Hz, CH_2-8′); 2.08–1.91 (m, 4H, CH_2-6′, CH_2-7′). ^{13}C NMR ($CDCl_3$) δ: 161.8 (C-2′), 152.7 (C-9′), 138.2, 128.4, 125.3, 121.6 (thienyl-*C*); 46.6 (C-5′); 29.5 (CH_2); 23.5 (C-8′); 22.8 (C-7′); 20.0 (C-6′). Anal. calc. for $C_{11}H_{13}N_3S$ (219.31): C, 60.24; H, 5.97; N, 19.16. Found: C, 60.01; H, 5.68; N, 19.36. MS *m/z* (%) (EI): 219 (85).

*6,7,8,9-Tetrahydro-2-((thiophene-3-yl)methyl-5H-[1,2,4]triazolo[1,5-a]azepine (***8d***).* From **3d** (1.32 g) and the nitrile **5**. Yield: 1.00 g (86%); brown oil. ^{1}H NMR ($CDCl_3$) δ: 7.08–6.82 (m, 3H, H-2, H-4, H-5 of thienyl-H); 4.13 (t, 2H, $J = 6.0$ Hz, CH_2-5′); 4.00 (s, 2H, CH_2); 2.85 (t, 2H, $J = 6.0$ Hz, CH_2-9′); 1.81–1.18 (m, 6H, CH_2-6′, CH_2-7′, CH_2-8′). ^{13}C NMR ($CDCl_3$) δ: 159.3 (C-2′), 157.4 (C-10′), 140.0, 126.7, 125.6, 124.0 (thienyl-*C*); 50.9 (C-5′); 28.6 (CH_2); 27.3 (C-7′); 27.2 (C-9′); 24.7 (C-8′); 22.5 (C-6′). Anal. calc. for $C_{12}H_{15}N_3S$ (233.33): C, 61.77; H, 6.48; N, 18.01. Found: C, 61.51; H, 6.68; N, 18.28. MS *m/z* (%) (EI): 233 (80).

*1-Isopropyl-5-methyl-3-((thiophene-2-yl)methyl)-1H-1,2,4-triazole (***10b***).* From **3b** (1.20 g) and the nitrile **9**. Yield: 0.85 g (77%); brown oil. ^{1}H NMR

($CDCl_3$) δ: 723–6.97 (m, 3H, H-2, H-4, H-5 of thienyl-H); 4.41–4.33 (m, 1H, *CH*Me_2); 4.02 (s, 2H, CH_2); 2,38 (s, 3H, C_5–Me); 1.46 (d, 6H, $J = 8.0$ Hz, CH*Me*$_2$). ^{13}C NMR ($CDCl_3$) δ: 160.9 (C-3′), 150.8 (C-5′), 138.4, 128.3, 125.4, 123.2 (thienyl-*C*); 49.7 (N–*C*HMe_2); 29.4 (CH_2); 22.2 (N–CH*Me*$_2$);.11.8 (C_5–*Me*). Anal. calc. for $C_{11}H_{15}N_3S$ (221.32): C, 59.69; H, 6.83; N, 18.99. Found: C, 59.51; H, 6.58; N, 19.09. MS *m/z* (%) (EI): 221 (80).

*5,6,7,8-Tetrahydro-2-(thiophene-2-yl)methyl-[1,2,4]triazolo[1,5-a]pyridine (***10c***).* From **3c** (1.17 g) and the nitrile **9**. Yield: 0.93 g (85%); brown oil. ^{1}H NMR ($CDCl_3$) δ: 7.15–6.82 (m, 3H, H-2, H-4, H-5 of thienyl-H); 4.17 (s, 2H, CH_2); 4.02 (t, 2H, $J = 6.0$ Hz, CH_2-5′); 2.84 (t, 2H, $J = 6.0$ Hz, CH_2-8′); 2.02–1.84 (m, 4H, CH_2-6′, CH_2-7′). ^{13}C NMR ($CDCl_3$) δ: 160.1 (C-2′), 152.5 (C-9′), 139.3, 127.1, 126.9, 125.1 (thienyl-*C*); 46.8 (C-5′); 28.5 (CH_2); 23.1 (C-8′); 22.5 (C-7′); 19.9 (C-6′). Anal. calc. for $C_{11}H_{13}N_3S$ (219.31): C, 60.24; H, 5.97; N, 19.16. Found: C, 60.41; H, 5.76; N, 19.31. MS *m/z* (%) (EI): 219 (80).

*6,7,8,9-Tetrahydro-2-(thiophene-2-yl)methyl-5H-[1,2,4]triazolo[1,5-a]azepine (***10d***).* From **3d** (1.32 g) and the nitrile **9**. Yield: 0.82 g (70%); brown oil. ^{1}H NMR ($CDCl_3$) δ: 7.24–6.97 (m, 3H, H-2, H-4, H-5 of thienyl-H); 4.11 (t, 2H, $J = 5.0$ Hz, CH_2-5′); 3.93 (s, 2H, CH_2); 2.84 (t, 2H, $J = 5.0$ Hz, CH_2-9′); 1.85–1.18 (m, 6H, CH_2-6′, CH_2-7′, CH_2-8′). ^{13}C NMR ($CDCl_3$) δ: 159.4 (C-2′), 157.1 (C-10′), 137.7, 128.3, 125.2, 121.6 (thienyl-*C*); 50.8 (C-5′); 29.9 (CH_2); 28.2 (C-7′); 27.2 (C-9′); 26.9 (C-8′); 24.6 (C-6′). MS *m/z* (%) (EI): 233 (90).

*(4-((5,6,7,8-Tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-2-yl)methyl)thiophene-2-yl)(4-nitro-phenyl)methanone (***12***).* From **3c** (1.17 g) and the nitrile **11** (1.36 g) [30]. Yield: 1.43 g (78%); brown oil. ^{1}H NMR ($CDCl_3$) δ: 8.27 (d, 2H, $J = 8.2$ Hz, Ar–H); 7.93 (d, 2H, $J = 8.2$ Hz, Ar–H); 7.63 (s, 1H, thienyl-H); 7.58 (s, 1H, thienyl-H); 4.05 (m, 4H, CH_2-5′, CH_2); 2.87 (t, 2H, $J = 6.0$ Hz, CH_2-8′); 2.03–1.91 (m, 4H, CH_2-6′, CH_2-7′). ^{13}C NMR ($CDCl_3$) δ: 186.0 (C=O), 159.3 (C-2′), 152.6 (C-10′), 149.8, 143.2, 142.5, 136.6, (Ar—*C*); 138.8, 132.4, 129.9, 123.6 (thienyl-*C*); 47.1 (C-5′); 28.8 (CH_2); 23.3 (C-8′); 22.6 (C-7′); 19.8 (C-6′). Anal. calc. for $C_{18}H_{16}N_4O_3S$ (368.41): C, 58.68; H, 4.38; N, 15.21. Found: C, 58.42; H, 4.46; N, 15.41. MS *m/z* (%) (EI): 368 (90).

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