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Synthesis and biological evaluation of *N*-(aryl)-2-thiophen-2-ylacetamides series as a new class of antitubercular agents

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Abstract—The present article describes a series of 21 *N*-(aryl)-2-thiophen-2-ylacetamides, which were synthesized and evaluated for their in vitro antibacterial activity against *Mycobacterium tuberculosis*, and the activity expressed as the minimum inhibitory concentration (MIC) in μg/mL. The compounds **2**, **3**, **7**, **8**, **11**, **12**, **15**, **16**, and **20** exhibited activity between 25 and 100 μg/mL and could be a good start point to find new lead compounds in the fight against multidrug resistant tuberculosis.

Nowadays, microorganisms resistant to multiple antimicrobial agents are a serious problem worldwide in the fight against infectious diseases, increasing morbidity and mortality with an overall increase in healthcare costs. In this context, Tuberculosis (TB) has become again an important public health problem worldwide since the mid-1980s, due to two major factors, the AIDS epidemic and the advent of multidrug resistant strains (MDR). TB is responsible for 20% of all deaths in adults, and each year there are about 8.9–9 millions of new cases, of which 15% are children, and 1.7–2 millions of deaths, of which 450,000 are children. Globally, the number of TB cases is currently rising at 2% per year with the estimative of 32% of the world population, about 2 billion people, being infected by latent TB. In the case of patients with AIDS, TB is the most common opportunistic infection and cause of death killing 1 of every 3 patients.[1] Due to the increase of MDR-TB and AIDS cases worldwide and the lack of new drugs nowadays, there is an urgent need for new drugs to fight against this disease. In this context, thiophene nucleus represents a very important field in drug discovery, which is present in many natural and synthetic products with a wide range of pharmacological activities.[2] Considering that, the aim of this article is to present a series of 21 *N*-(aryl)-2-thiophen-2-ylacetamide derivatives, which have been synthesized, see Scheme 1, and evaluated for their in vitro antibacterial activity against *Mycobacterium tuberculosis*.

The synthesis of *N*-(aryl)-2-thiophen-2-ylacetamide derivatives (**2**–**22**) involved the reaction between appropriate anilines and thiopheneacetyl chloride, as described in the general procedure, leading to the desired compounds (**2**–**22**) in 68–100% yields (Scheme 1).[3] All the compounds were identified by spectral data. In general, IR spectra showed the C=O peak at 1652–1695 cm^{-1}. The ^1H NMR spectrum showed the hydrazide (N*H*) proton as a large singlet at 9.25–10.78 ppm and CH_2CO proton as a singlet at 3.99–3.82 ppm. The ^{13}C NMR spectrum showed the C=O signals at 175.2–167.5, CH_2CO signals at 40.4–36.1, and aromatic carbons at the region of 140–104 ppm[3].

The antimycobacterial activities of compounds (**2**–**22**) were assessed against *M. tuberculosis* ATTC 27294,[4]

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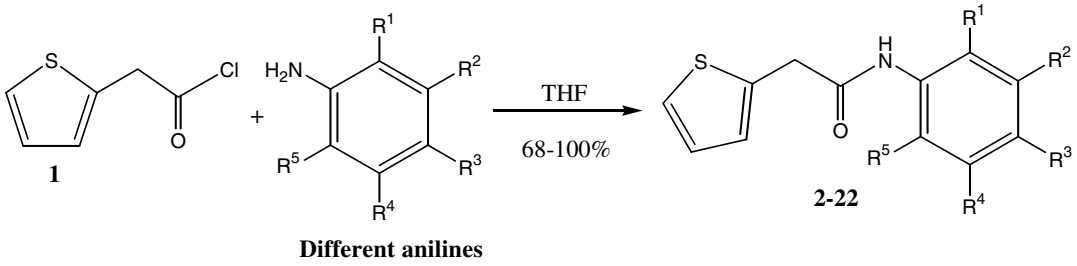

Scheme 1.

using the microplate Alamar blue assay (MABA)[5] (Table 1). This methodology is nontoxic, uses thermally stable reagent, and shows good correlation with proportional and BACTEC radiometric methods.[6,7] Briefly, two hundred microliters of sterile deionized water was added to all outer-perimeter wells of sterile 96-well plates (falcon, 3072: Becton Dickinson, Lincoln Park, NJ) to minimize evaporation of the medium in the test wells during incubation. The 96-well plates received 100 μL of the Middlebrook 7H9 broth (Difco laboratories, Detroit, MI, USA) and a serial dilution of the compounds **9**–**16** was made directly on the plate. The final drug concentrations tested were 0.01–10.0 μL/mL. Plates were covered and sealed with parafilm and incubated at 37 °C for 5 days. After this time, 25 mL of a freshly prepared 1:1 mixture of Alamar blue (Accumed International, Westlake, Ohio) reagent and 10% Tween 80 was added to the plate and incubated for 24 h. A blue color in the well was interpreted as no bacterial growth, and a pink color was scored as growth. The MIC (Minimal Inhibition Concentration) was defined as the lowest drug concentration, which prevented a color change from blue to pink.

Cellular viability in the presence and absence of test compounds was determined by Mosmans's MTT (3-(4,5-dimethylthiazol-2yl)-2,5-dimethyl tetrazolium bromide; Merck) microcultured tetrazolium assay as described.[8,9] The cells (macrophage cell line, J774) were plated in flat-bottomed 96-well plates (2.5×10^6 cells/mL), cultured for 1 h in controlled atmosphere (CO_2 5% at 37 °C), and non-adherent cells were washed by gentle flushing with RPMI 1640. Adherent cells were cultured in the presence of medium alone, Tween 20 (3%) (live and dead controls, respectively) or different concentrations of compounds (0.1, 1.0, 10.0, and 100 μg/mL) in a triplicate assay. After 18 h, stock MTT solution (5 mg/mL of saline; 20 μL/well) was added to the culture and 4 h later, supernatant was discharged and DMSO (100 μL/well) was added for formazan crystal solubilization and the absorbance was read at 540 nm in a plate reader (Bio-Rad—450). The results were represented as percentage cell viability (Table 2).

Table 1. Antimycobacterial activities, Log *P* measurements, and yields of *N*-(arryl)-2-thiophen-2-ylacetamides (**2**–**22**)

Compound	R^1	R^2	R^3	R^4	R^5	MIC[a]	Log P[b]	Yield
2	—	—	—	—	—	25	2.55	96
3	CH_3	—	—	—	—	100	2.74	90
4	OCH_3	—	—	—	—	Resistant	2.66	100
5	NO_2	—	—	—	—	Resistant	2.81	100
6	CF_3	—	—	—	—	Resistant	3.86	100
7	—	Cl	—	—	—	50	3.55	70
8	—	OCH_3	—	—	—	50	2.71	70
9	—	CF_3	—	—	—	Resistant	3.94	68
10	—	NO_2	—	—	—	Resistant	2.86	100
11	—	—	CH_3	—	—	100	2.96	88
12	—	—	F	—	—	100	3.01	98
13	—	—	Br	—	—	Resistant	3.31	96
14	—	—	OCH_3	—	—	Resistant	2.75	86
15	—	—	Cl	—	—	100	3.44	76
16	—	—	NO_2	—	—	50	2.77	92
17	CH_3	—	—	—	CH_3	Resistant	2.92	90
18	Cl	—	—	—	Cl	Resistant	3.96	76
19	Cl	—	F	—	—	Resistant	3.56	97
20	F	—	Cl	—	—	100	3.41	98
21	OCH_3	—	—	OCH_3	—	Resistant	2.67	70
22	—	–OCH_2O–	—	—	—	Resistant	2.66	72
INH						0.2	−0.58	—
RIP						1.0	−2.38	—

[a] Minimal inhibition concentration is expressed in μg/mL.
[b] Calculated by www.logp.com.

Table 2. Cytotoxic effects of test compounds on murine macrophage cells 18 h after the treatment

Compound	100 μg/mL	10 μg/mL	1 μg/mL	0.1 μg/mL
2	100%	100%	100%	100%
7	100%	100%	100%	100%
8	100%	100%	100%	100%
16	85,35%	100%	100%	100%

The percentage cell viability of compounds **2**, **7**, **8**, and **16** in all concentrations tested.

In conclusion, the antimycobacterial activities of the *N*-(aryl)-2-thiophen-2-ylacetamide derivatives described here suggest that they may be selectively targeted to *M. tuberculosis* growth. These compounds are not cytotoxic to host cells at the concentrations effective in inhibiting *M. tuberculosis* infection. The compounds **2**, **3**, **7**, **8**, **11**, **12**, **15**, **16**, and **20** exhibited activity between 25 and 100 μg/mL when compared with first line drugs such as isoniazid (INH) and rifampin (RIP), which could be a good start point to further studies, as well as find new lead compounds.

References and notes

1. http://www.who.int/tdr/diseases/tb/default.htm.
2. Kleemann, A.; Engel, J.; Kutscher; Reichert *Pharmaceutical Substances*; *Syntheses, Patents, Applications*; Thieme, 4th, ed.; 2001; vols. 1 and 2.
3. *General procedures.* Melting points were determined on a Buchi apparatus and are uncorrected. Infrared spectra were recorded on a Thermo Nicolet Nexus 670 spectrometer as potassium bromide pellets and frequencies are expressed in cm^{-1}. Mass spectra (CG/MS) were recorded on a Agilent Technologies 6890/5972A mass spectrometer. NMR spectra were recorded on a Bruker Avance 500 spectrometer operating at 500.00 MHz (^1H) and 125.0 MHz (^{13}C), in deuterated dimethylsulfoxide. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane. Proton and carbon spectra were typically obtained at room temperature. For TLC plates coated with silica gel were run in ethyl acetate and spots were developed in Ultraviolet.
*General procedures for the synthesis of N-(aryl)-2-thiophen-2-ylacetamide derivatives (**2**–**22**):* The *N*-(aryl)-2-thiophen-2-ylacetamides derivatives (**2**–**22**) were prepared by reaction between the appropriate anilines and thiophenylacetylchloride in tetrahydrofuran, under nitrogen atmosphere (Scheme 1). After stirring for 2–3 h at room temperature the reaction mixture was quenched with 30 mL of water and extracted with ethylacetate (20 mL × 2). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to produce the desired amides without further purification.
*Compound **2**:* *N*-(Phenyl)-2-thiophen-2-ylacetamide; yield: 96%; mp: 101–106 °C; CG/MS: *m/z* $[M]^{+\cdot}$ 217; ^1H NMR [500.00 MHz (FIDRES ± 0.15 Hz), DMSO-d_6] δ: 10.15 (1H; s; N*H*); 7.58 (d; 2H; *J* = 8.0 Hz; H2′6′); 7.37 (dd; 1H; *J* = 5.0 and 2.0 Hz; H1); 7.30 (t; 2H; *J* = 8.0 Hz; H3′,5); 7.05 (t; 1H; *J* = 8.0 Hz; H4′); 6.98–6.96 (m; 2H; H2,3); 3.87 (s, 2H, C*H*$_2$CO) ppm. ^{13}C NMR (125.0 MHz, DMSO-d_6) δ: 168.0; 139.0; 137.1; 128.8; 126.7; 126.3; 125.1; 123.4; 119.1; 37.6 ppm; IV ν_{max} (cm^{-1}; KBr pellets): 1657 (CO); *compound **3**:* *N*-(2-methylphenyl)-2-thiophen-2-ylacetamide; yield: 90%; mp: 126–127 °C; CG/MS: *m/z* $[M]^{+\cdot}$: 231; ^1H NMR [500.00 MHz (FIDRES ± 0.15 Hz), DMSO-d_6] δ: 9.49 (1H; s; N*H*); 7.39–7.37 (m; 2H; H1,6′); 7.19 (d; 2H; *J* = 7.5 Hz; H3′); 7.15 (t; 1H; *J* = 7.0 Hz; H4′); 7.07; (t; 1H; *J* = 7.5 Hz; H5′); 7.0–6.97 (m; 2H; H2,3); 3.90 (s, 2H, C*H*$_2$CO); 2.18 (s; 3H; C*H*$_3$) ppm. ^{13}C NMR (125.0 MHz, DMSO-d_6) δ: 168.0; 137.4; 136.0; 131.7; 130.3; 126.6; 126.2; 125.9; 125.3; 125.0; 36.9; 17.7 ppm; IVν_{max}(cm^{-1}; KBr pellets): 1652 (CO); *compound **4**:* *N*-(2-methoxyphenyl)-2-thiophen-2-ylacetamide; yield: 100%;mp: 58–60 °C; CG/MS: *m/z* $[M]^{+\cdot}$: 247; ^1H NMR [500.00 MHz (FIDRES ± 0.15 Hz), DMSO-d_6] δ: 9.27 (s; 1H; NH); 7.94 (d, 1H, H3′; *J* = 8.0 Hz) 7.38 (dd; 1H; *J* = 5.0 and 1.5 Hz; H1); 7.08–7.02 (m; 2H; H6′,4′); 6.99–6.95 (m; 2H; H2,3); 6.88 (t; 1H; *J* = 8.0 Hz); 3.98 (s; 2H; CH_2CO); 3.82 (s; 3H; OCH_3) ppm. ^{13}C NMR (125.0 MHz, DMSO- d_6) δ: ppm 175.2; 144.4; 136.8; 135.0; 132.6; 131.1; 128.1; 124.0; 122.8; 118.9; 113.5; 56.4; 40.4 ppm; IV ν_{max} (cm^{-1}; KBr pellets): 1670 (CO); *compound **5**:* *N*-(2-nitrophenyl)-2-thiophen-2-ylacetamide; yield: 100%; mp: 40–42 °C; CG/MS: *m/z* $[M]^{+\cdot}$: 262; ^1H NMR [500.00 MHz (FIDRES ± 0.15 Hz), DMSO-d_6] δ: 10.45 (1H; s; N*H*); 7.96 (t; 1H; *J* = 8.0 Hz; H3′); 7.69–7.75 (m, 2H, H4′,6′); 7.41 (dd; 1H; *J* = 4.5 Hz and 1.0 Hz; H1); 7.37 (t, 1H, *J* = 8.0 Hz; H5′); 7.10–6.99 (m; 2H; H2,3); 3.95 (s, 2H, C*H*$_2$CO) ppm. ^{13}C NMR (125.0 MHz, DMSO-d_6) δ: 168.2; 147.2; 141.9; 135.6; 134.0; 131.1; 126.7; 125.3; 125.2; 119.1; 115.4; 36.9 ppm; IV ν_{max} (cm^{-1}; KBr pellets): 1695 (CO); *compound **6**:* *N*-(2-trifluorophenyl)-2-thiophen-2-ylacetamide; yield: 100%; mp: 85–87 °C; CG/MS: *m/z* $[M]^{+\cdot}$: 285; ^1H NMR [500.00 MHz (FIDRES ± 0.15 Hz), DMSO-d_6] δ: 9.73 (1H; s; N*H*); 7.72 (d; 1H; *J* = 10.0 Hz; H3′); 7.67 (t; 1H; *J* = 10.0 Hz; H4′); 7.50 (d; 1H; *J* = 10.0 Hz; H6′); 7.45 (t; 1H; *J* = 10.0 Hz; H5′); 7.39 (t; 1H; *J* = 4.5 Hz; H1); 6.99–6.97 (m; 2H; H2,3); 3.93 (s, 2H, C*H*$_2$CO) ppm. ^{13}C NMR (125.0 MHz, DMSO-d_6) δ: 168.9; 136.7; 135.1; 132.9; 129.7; 126.6–123.1 (m); 125.0; 124.3; 122.1; 36.4 ppm; IV ν_{max} (cm^{-1}; KBr pellets): 1666 (CO); *compound **7**:* *N*-(3-chlorophenyl)-2-thiophen-2-ylacetamide; yield: 70%; mp: 75–77 °C; CG/MS: *m/z* $[M]^{+\cdot}$: 251; ^1H NMR [500.00 MHz (FIDRES ± 0.15 Hz), DMSO-d_6] δ: 10.38 (1H; s; NH); 7.80 (s; 1H; H2′); 7.44 (dd;1H; *J* = 8.0 and 0.5 Hz; H4′); 7.38 (dd; 1 H; *J* = 5.0 and 1.5 Hz; H1); 7.33 (t; 1H; *J* = 8.0 Hz; H5′); 7.10 (d; 1H; *J* = 8.0 Hz; H6′); 6.99–6.97 (m; 2H; H2,3); 3.88 (s, 2H, C*H*$_2$CO) ppm. ^{13}C NMR (125.0 MHz, DMSO-d_6) δ: 168.3; 140.4; 136.6; 133.0; 130.4; 126.6; 126.4; 125.0; 123.0; 118.6; 117.5; 37.4 ppm; IVν_{max} (cm^{-1}; KBr pellets): 1684 (CO); *compound **8**:* *N*-(3-methoxyphenyl)-2-thiophen-2-ylacetamide; yield: 70%; mp: 68–70 °C; CG/MS: *m/z* $[M]^{+\cdot}$: 247; ^1H NMR [500.00 MHz (FIDRES ± 0.15 Hz), DMSO-d_6] δ: 10.15 (s; 1H; NH); 7.38 (dd; *J* = 4.0 and 2.0 Hz; H1); 7.29 (s; 1H; H2′); 7.20 (t; 1H; *J* = 8.0 Hz; H5′); 7.11 (d; 1H; *J* = 8.0 Hz; H4′); 6.98–6.96 (m; 2H; H2,3); 6.62 (dd; 1H; *J* = 8.0 and 2.0 Hz; H6′); 3.86 (s; 2H; CH_2CO); 3.70 (s; 3H; OCH_3) ppm. ^{13}C NMR (125.0 MHz, DMSO-d_6) δ: 167.9; 159.5; 140.1; 137.0; 129.5; 126.6; 126.3; 125.0; 111.4; 108.8; 104.9; 54.9; 37.5 ppm; IV ν_{max} (cm^{-1}; KBr pellets): 1682 (CO); *compound **9**:* *N*-(3-trifluoromethylphenyl)-2-thiophen-2-ylacetamide; yield: 68%; mp: 66–68 °C; CG/MS: *m/z* $[M]^{+\cdot}$: 285; ^1H NMR [500.00 MHz (FIDRES ± 0.15 Hz), DMSO-d_6] δ: 10.53 (1H; s; NH); 8.07 (s; 1H; H2′); 7.76 (d; 1H; *J* = 10.0 Hz; H4′); 7.53 (t; 1H; *J* = 10 Hz; H5′); 7.41–7.38 (m; 2H; H6′,1); 6.99–6.97 (m; 2H; H2,3); 3.90 (s, 2H, C*H*$_2$CO) ppm. ^{13}C NMR (125.0 MHz, DMSO-d_6) δ: 168.6; 139.7; 136.6; 130.0; 129.7; 126.7; 126.5; 125.4; 125.2; 122.7; 119.7 (m); 115.2 (m); 37.5 ppm; IV ν_{max} (cm^{-1}; KBr pellets): 1669 (CO); *compound **10**:* *N*-(3-nitrophenyl)-2-thiophen-2-ylacetamide; yield: 100%; mp: 96–97 °C; CG/MS: *m/z* $[M]^{+\cdot}$: 262; ^1H NMR [500.00 MHz (FIDRES ± 0.15 Hz), DMSO-d_6] δ: 10.67 (1H; s; NH); 8.62 (s; 1H; H2′); 7.91 (dd; 2H; *J* = 8.5

and 2.5 Hz; H4′6′); 7.61 (t; 1H; J = 8.0 Hz; H5′); 7.40 (dd; 1H; J = 5.0 and 1.5 Hz; H1); 7.01–6.98 (m; 2H; H2,3); 3.93 (s, 2H, CH_2CO) ppm. ^{13}C NMR (125.0 MHz, $CDCl_3$) δ: 168.1; 148.6; 138.5; 134.8; 129.9; 128.1; 127.9; 126.5; 125.5; 119.2; 114.6; 38.5; IVν_{max} (cm^{-1}; KBr pellets): 1673 (CO); *compound* ***11****: N*-(4-methylphenyl)-2-thiophen-2-ylacetamide; yield: 88%; mp: 121–123 °C; CG/MS: *m/z* $[M]^{+\cdot}$: 231; ^1H NMR [500.00 MHz (FIDRES ± 0.15 Hz), $CDCl_3$] δ: 9.37 (1H; s; N*H*); 7.24 (d; 2H; J = 9.0 Hz; H3′,5′); 7.27; (t; 1H; J = 3.5 Hz; H1); 7.01–6.98 (m; 2H; H2,3); 7.26 (d; 2H; J = 9.0 Hz; H2′,6′); 3.77 (s, 2H, CH_2CO); 2.26 (s, 3H, CH_3) ppm. ^{13}C NMR (125.0 MHz, $CDCl_3$) δ: 176.8; 139.6; 136.8; 135.0; 132.6; 129.5; 128.7; 118.0; 40.3; 20.4.; IV ν_{max} (cm^{-1}; KBr pellets): 1670 (CO); *compound* ***12****: N*-(4-fluorophenyl)-2-thiophen-2-ylacetamide; yield: 98%; mp: 104–106 °C; CG/MS: *m/z* $[M]^{+\cdot}$: 235; ^1H NMR [500.00 MHz (FIDRES ± 0.15 Hz), DMSO-d_6] δ: 10.12 (1H; s; N*H*); 7.61 (dd; 2H; J = 8.5 and 3.5 Hz; H3′,5′); 7.37 (dd; 1H; J = 4.5 and 2.0 Hz; H1); 7.13; (t; 2H; J = 8.5 Hz; H2′,6′); 6.98–6.96 (m; 2H; H2,3); 3.86 (s, 2H, CH_2CO) ppm. ^{13}C NMR (125.0 MHz, DMSO-d_6) δ: 167.8; 158.0 (238 Hz); 136.9; 135.3; 126.6; 126.3; 124.9; 120.8 (J = 8 Hz); 115.2 (J = 22 Hz); 37.3 ppm; IVν_{max} (cm^{-1}; KBr pellets): 1665 (CO); *compound* ***13****: N*-(4-bromophenyl)-2-thiophen-2-ylacetamide; yield: 96%; mp: 138–139 °C; CG/MS: *m/z* $[M]^{+\cdot}$: 297; ^1H NMR [500.00 MHz (FIDRES ± 0.15 Hz), DMSO-d_6] δ: 10.30 (1H; s; N*H*); 7.56 (d; 2H; J = 9.0 Hz; H3′,5′); 7.48 (d; 2H; J = 9.0 Hz; H2′,6′); 7.38; (dd; 1H; J = 4.5 and 2.0 Hz; H1); 6.98–6.96 (m; 2H; H2,3); 3.87 (s, 2H, CH_2CO) ppm. ^{13}C NMR (125.0 MHz, DMSO-d_6) δ: 168.1; 138.3; 136.8; 131.5; 126.6; 126.3; 125.0; 121.3; 114.8; 37.4 ppm; IV ν_{max} (cm^{-1}; KBr pellets): 1660 (CO); *compound* ***14****: N*-(4-methoxyphenyl)-2-thiophen-2-ylacetamide; yield: 86%; mp: 138–139 °C; CG/MS: *m/z* $[M]^{+\cdot}$: 247; ^1H NMR [500.00 MHz (FIDRES ± 0.15 Hz), DMSO-d_6] δ: 10.00 (1H; s; N*H*); 7.48 (d; 2H; J = 9.0 Hz; H3′,5′); 7.37; (t; 1H; J = 3.5 Hz; H1); 6.97–6.96 (m;2H; H2,3); 6.87 (d; 2H; J = 9.0 Hz; H2′,6′); 3.82 (s, 2H, CH_2CO); 3.71 (s, 3H, OCH_3) ppm. ^{13}C NMR (125.0 MHz, DMSO-d_6) δ: 167.5; 155.2; 150.6; 142.3; 137.3; 132.2; 114.5; 113.8; 55.2; 37.4 ppm; IV ν_{max} (cm^{-1}; KBr pellets): 1679 (CO); *compound* ***15****: N*-(4-chlorophenyl)-2-thiophen-2-ylacetamide; yield: 76%; mp: 114–116 °C; CG/MS: *m/z* $[M]^{+\cdot}$: 251; ^1H NMR [500.00 MHz (FIDRES ± 0.15 Hz), DMSO-d_6] δ: 10.30 (1H; s; N*H*); 7.62 (d; 2H; J = 9.0 Hz; H3′,5′); 7.38; (dd; 1H; J = 5.0 and 2.0 Hz; H1); 7.34 (d; 2H; J = 9.0 Hz; H2′,6′); 6.98–6.96 (m; 2H; H2,3); 3.87 (s, 2H, CH_2CO) ppm. ^{13}C NMR (125.0 MHz, DMSO-d_6) δ: 168.1; 137.9; 136.8; 128.6; 126.8; 126.6; 126.3; 125.0; 120.6; 37.4 ppm; IV ν_{max} (cm^{-1}; KBr pellets): 1658 (CO); *compound* ***16****: N*-(4-nitrophenyl)-2-thiophen-2-ylacetamide; yield: 92%; mp: 125–127 °C; CG/MS: *m/z* $[M]^{+\cdot}$: 262; ^1H NMR [500.00 MHz (FIDRES ± 0.15 Hz), DMSO-d_6] δ: 10.78 (1H; s; N*H*); 8.22 (d; 2H; J = 7.5 Hz; H3′,5′); 7.84 (d; 2H; J = 7.5 Hz; H2′,6′); 7.39; (dd; 1H; J = 5.0 and 0.5 Hz; H1); 7.0–6.97 (m; 2H; H2,3); 3.96 (s, 2H, CH_2CO) ppm. ^{13}C NMR (125.0 MHz, DMSO-d_6) δ: 169.0; 145.2; 142.3; 136.3; 126.8; 126.7; 125.4; 118.9; 37.6 ppm; IV ν_{max} (cm^{-1}; KBr pellets): 1683 (CO); *compound* ***17****: N*-(2,5-dimethylphenyl)-2-thiophen-2-ylacetamide; yield: 90%; mp: 132–133 °C; CG/MS: *m/z* $[M]^{+\cdot}$: 245; ^1H NMR [500.00 MHz (FIDRES ± 0.15 Hz), DMSO-d_6] δ: 9.46 (1H; s; NH); 7.38 (dd; 1H; J = 6.5 and 2.0 Hz; H1); 7.05–6.97 (m; 5H; H3,2,2′-5′); 3.82 (s; 2H; CH_2CO); 2.09 (s; 6H; 2CH_3) ppm. ^{13}C NMR (125.0 MHz, DMSO-d_6) δ: 167.7; 137.6; 135.1; 134.8; 127.6; 126.6; 126.4; 126.2; 124.8; 36.5; 17.9 ppm; IV ν_{max} (cm^{-1}; KBr pellets): 1644 (CO); *compound* ***18****: N*-(2,5-dichlorophenyl)-2-thiophen-2-ylacetamide; yield: 76%; mp: 138–140 °C; CG/MS: *m/z* $[M]^{+\cdot}$: 285; ^1H NMR [500.00 MHz (FIDRES ± 0.15 Hz), DMSO-d_6] δ: 10.07 (1H; s; NH); 7.53 (d; 2H; J = 8.0 Hz; H3′,5); 7.38 (dd; 1H; J = 5.0 and 0.5 Hz; H1); 7.34 (t; 1H; J = 8.0; H4′); 7.02–6.97 (m; 2H; H2,3); 3.92 (s; 2H; CH_2CO) ppm. ^{13}C NMR (125.0 MHz, DMSO-d_6) δ: 168.0; 142.0; 136.7; 132.8; 128.5; 126.6; 125.2; 116.9; 36.1 ppm; IV ν_{max} (cm^{-1}; KBr pellets): 1671 (CO); *compound* ***19****: N*-(2,4-chlorofluorophenyl)-2-thiophen-2-ylacetamide; yield: 97%; mp: 113–114 °C; CG/MS: *m/z* $[M]^{+\cdot}$: 269; ^1H NMR [500.00 MHz (FIDRES ± 0.15 Hz), DMSO-d_6] δ: 9.76 (1H; s; N*H*); 7.67 (dd; 1H; J = 8.5 and 5.5 Hz; H3′); 7.48 (dd; 1H; J = 8.5 and 3.0 Hz; H5′); 7.38 (dd; 1H; J = 5.0 and 0.5 Hz; H1); 7.21 (ddd; 1H; J = 8.5; 5.0 and 3.0 Hz; H6′); 7.02–6.97 (m; 2H; H2,3); 3.92 (s; 2H; CH_2CO) ppm. ^{13}C NMR (125.0 MHz, DMSO-d_6) δ: 168.4; 158.7 (J = 244 Hz); 136.8; 131.4; 131.3; 127.8-127.7 (m); 126.6; 126.4; 125.0; 116.5 (J = 25.6 Hz); 114.4 (J = 22.0 Hz); 36.6 ppm; IV ν_{max} (cm^{-1}; KBr pellets): 1662 (CO); *compound* ***20****: N*-(2,4-fluorochlorophenyl)-2-thiophen-2-ylacetamide; yield: 98%; mp: 111–113 °C; CG/MS: *m/z* $[M]^{+\cdot}$: 269; ^1H NMR [500.00 MHz (FIDRES ± 0.15 Hz), DMSO-d_6] δ: 10.05 (1H; s; N*H*); 7.93 (t; 1H; J = 9.0 Hz; H3′); 7.47 (dd; 1H; J = 10 and 2.5 Hz; H5′); 7.38 (dd; 1H; J = 4.5 and 1.5 Hz; H1); 7.24 (d; 1H; J = 10 Hz; H6′); 6.98–6.96 (m; 2H; H2,3); 3.95 (s; 2H; CH_2CO) ppm. ^{13}C NMR (125.0 MHz, DMSO-d_6) δ: 168.5; 153.0 (J = 247 Hz) 136.7; 128.1 (J = 23 Hz); 126.6; 126.4; 126.2; 125.0; 124.8; 124.5; 124.4; 116.0 (J = 95 Hz); 36.8 ppm; IV ν_{max} (cm^{-1}; KBr pellets): 1668 (CO); *compound* ***21****: N*-(2,5-dimethoxyphenyl)-2-thiophen-2-ylacetamide; yield: 70%; mp: 97–99 °C; CG/MS: *m/z* $[M]^{+\cdot}$: 277; ^1H NMR [500.00 MHz (FIDRES ± 0.15 Hz), DMSO-d_6] δ: 9.25 (1H; s; N*H*); 7.71 (d; 1H; J = 5.0 Hz; H5); 7.38 (dd; 1H; J = 5.0 and 1.5 Hz; H4); 6.98–6.93 (m; 3H; H3′,4′,6′); 6.61 (dd; 1H; J = 5.0 and 1.5 Hz; H3); 3.99 (s; 2H; CH_2CO); 3.68 (s; 3H; OCH_3); 3.67 (s; 3H; OCH_3) ppm. ^{13}C NMR (125.0 MHz, DMSO-d_6) δ: 168.3; 152.8; 143.3; 137.1; 127.9; 126.6; 126.4; 125.0; 111.7; 108.0; 107.8; 56.1; 55.2; 37.1 ppm; IV ν_{max} (cm^{-1}; KBr pellets): 1685 (CO); *compound* ***22****: N*-(1,3-benzodioxol-5-yl-)-2-thiophen-2-ylacetamide; yield: 72%; mp: 105–108 °C; CG/MS: *m/z* $[M]^{+\cdot}$: 261; ^1H NMR [500.00 MHz (FIDRES ± 0.15 Hz), $CDCl_3$] δ: 10.6 (1H; s; N*H*); 7.30 (d; 1H; J = 4.0 Hz; H5); 7.28–7.16 (m; 4H; H4; Harom.) 7.04 (ls; 1H; H3); 5.90 (s; 2H; O–CH_2–O); 3.88 (s; 2H; CH_2CO) ppm. ^{13}C NMR (125.0 MHz, $CDCl_3$) δ: 167.8; 147.8; 144.5; 135.6; 131.6; 127.9; 127.6; 126.7; 126.1; 113.2; 108.0; 102.9; 101.3; 38.4 ppm; IV ν_{max} (cm^{-1}; KBr pellets): 1665 (CO).

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