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Unprecedented convergent synthesis of the fused tricyclic thiophenes via Friedel-Crafts cycliacylation reactions

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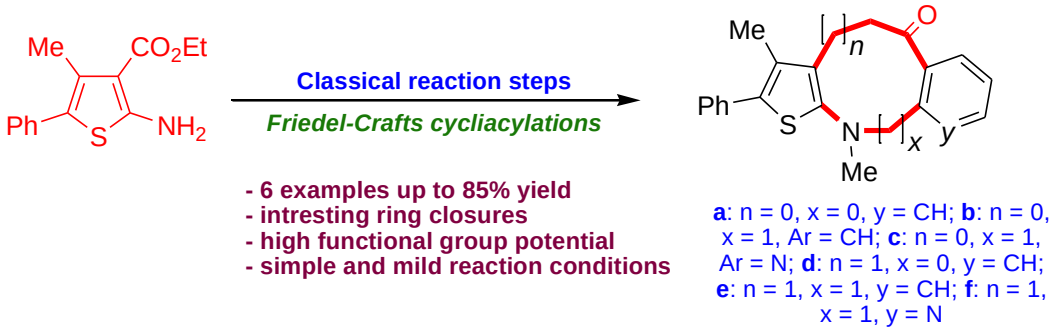
Abstract

An efficient and concise procedure toward benzo-and pyridothieno[2,3-*b*] fused N-heterocycles from readily available substrates is described. The process involves Lewis and Bronsted acids-mediated Friedel-Crafts cyclizations of the synthesized thiophene-based carboxylic acid precursors into new tricyclic thiophenes. The method efficiently achieves the promising pharmaceutically polycyclic thiophenes in good yields.



Keywords: Friedel-Crafts cycliacylations, thiophenes, thienoazocines, heteropolycycles

Introduction

Thiophenes and their fused heterocyclic derivatives have garnered much attention in the organic synthetic community due to their wide abundance in many biological active natural products[1] and pharmaceutical drugs[2] e.g. olanzapine, ticarcillin, urothione, biotin, clopidogrel, tienopramine and pizotifen (Fig 1). Both natural and synthetic thiophene architectures are particularly noted for their immense biological properties[3] like anticonvulsant, anticholinergic, potent analgesic, antipsychotic, anti-inflammatory, antihistaminic, antidepressant, antidiabetic and anti-HIV activities. Moreover, functionalized thiophenes have also found application in industry as luminescent and light-emitting materials,[4] conducting polymers[5] and antioxidant.[6]

Some of the most relevant synthetic approaches applied in the synthesis of fused thiophenes include well known examples of Paal-Knorr synthesis,[7] Gewald reaction,[8] Fiesselmann synthesis,[9] Lawesson's reagent[10] and Hinsberg synthesis.[11] Most of the reported methods imply a stepwise introduction of the fused five or six-membered heterocyclic rings in a multistep synthesis. As a result of the structural diversity and astonishing biological profile of thiophene-based heterocycles, synthetic chemists have sought to organize and design versatile methods towards the discovery of novel drug architectures.[12]

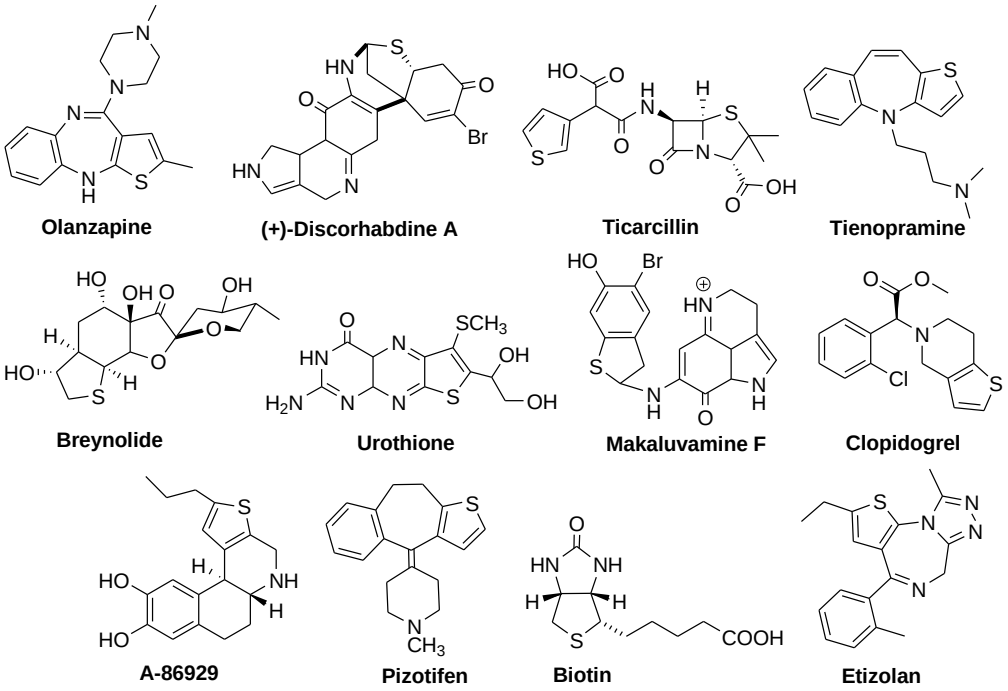


Figure 1. Examples of drugs containing fused thiophenes core structures.

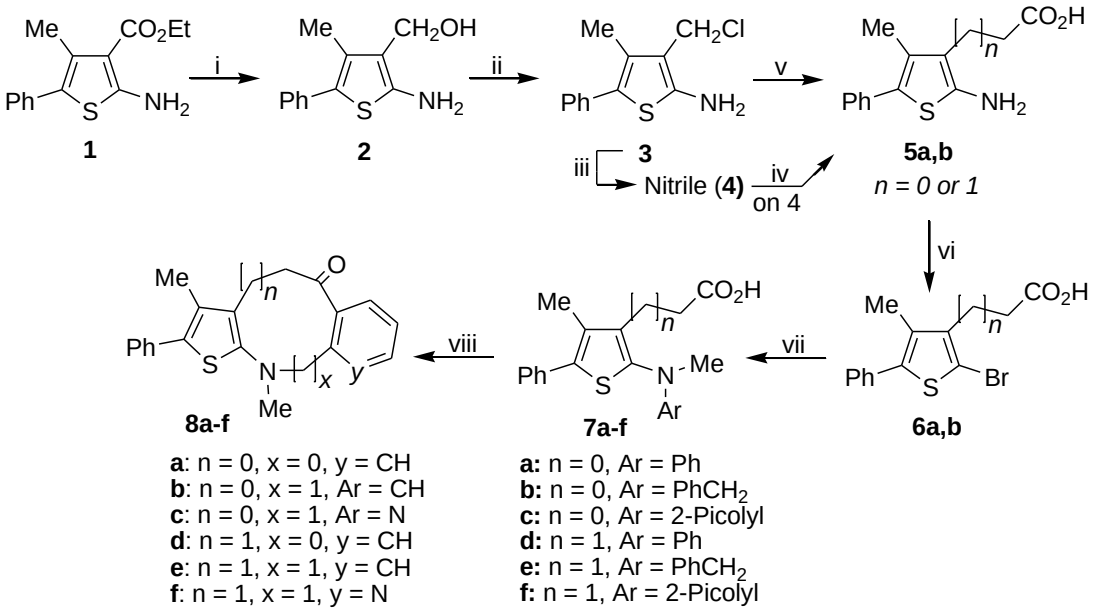
Of particular interest is the formation of hetero-fused thiophene compounds such as thienoquinoline and thienoazepine regioisomers are associated with diverse pharmacological activities.[13] A literature search of the general applied approaches for the synthesis of these scaffolds revealed that, a variety of robust methods for synthesizing and selective functionalization of substituted thienoquinolines with different fusion positions have been reported.[14] Literately, limited work has been carried out on the synthesis of fused thienoazepines. Whereas thiophenes fused with eight or higher-membered N-heterocyclic rings are thereof not reported in the literature. Synthetic methodologies have been developed to generate thienoazepines and can be divided into three major classes, namely, stepwise construction of thiophene nucleus or fused seven membered *N*-hetero-rings via cyclizations of acyclic chain elements of appropriate substrates,[15] photochemical reactions of

appropriately heterocyclic substrates[16] and ring expansion reactions of the pre-constructed fused thiophene substrates.[17]

In continuation of our research interests regarding sophistications of an efficient and divergent procedures for synthesis and functionalization of heterocycles,[18] it was considered worthwhile to synthesize certain new polycyclic thiophenes in moderate to high yields incorporating two bioactive moieties, thiophene and medium sized N-heterocycles in a single molecular designs *via* $AlCl_3/CH_3NO_2$ or PPA or P_2O_5-mediated Friedel-Crafts[19] cyclizations on thiophene-based carboxylic acids.

Results and Discussion

We describe herein the synthesis of benzo-and pyrido fused thieno[2,3-*b*]azepinones, thieno[2,3-*b*]azocinones and thieno[2,3-*b*]azoninones **8a-f** from the functionalized thiophene carboxylic acids **7a-f** (Schemes 1). For the synthesis of target compounds, first, the substituted thiophene-3-carboxylate **1**[20] was prepared by the literature Gewald's procedure[21] from ethyl cyanoacetate with phenylacetone in the presence of diethylamine to afford substituted 2-aminothiophene **1**.

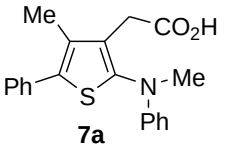
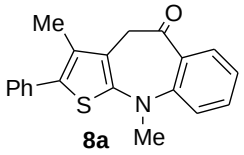
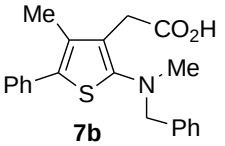
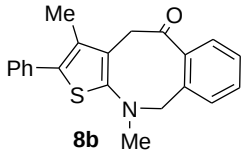
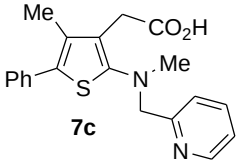
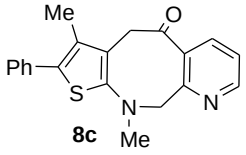
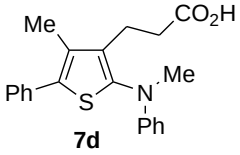
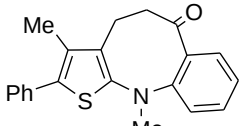
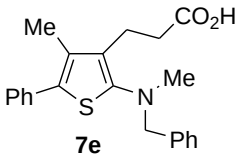
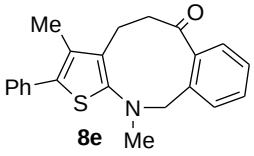
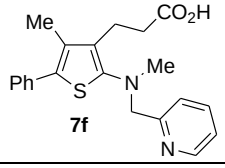
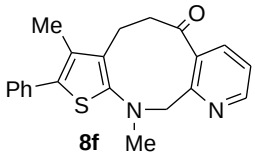


Scheme 1. Reagents and conditions: (i) $LiAlH_4$/THF-Et_2O, reflux, 6h, NaOH, 84%, (ii) $SOCl_2/Et_2O$, 2h, reflux, 90%, (iii) KCN/EtOH, 6h, reflux, 80%, (iv) EtOH/NaOH, 10h, reflux, AcOH, 82%, (v) *a.* $NaCH(COOEt)_2$, KOH, 7h, reflux, *b.* heated at 170-180 °C, 10 min., 75%, (vi) HCl/$NaNO_2$/KBr, 1h, 90-100 °C, 70-74%, (vii) Arylations with aromatic amines (*N*-methylaniline *or N*-benzylmethylamine or 2-picolylmethylamine)/K_2CO_3/DMF, 120-130 °C, 10h, (viii) Cycliacylations by $AlCl_3/CH_3NO_2$ or PPA or P_2O_5 catalysts (Table 1).

Reduction of compound **1** with $LiAlH_4$ in THF/Et_2O afforded alcohol **2**. This alcohol was converted into the corresponding chloride **3** using $SOCl_2$. Both acids **5a** and **5b** were obtained starting from chloride **3** via two synthetic routes outlined in Scheme 1. Hence, chloride **3** was converted into nitrile **4** with KCN in ethanol followed by hydrolysis of resulting nitrile with NaOH to afford the corresponding acetic acid **5a**.

On the other hand, chloride **3** underwent alkylation of malonic ester with EtONa in EtOH to give propionic acid **5b**. Once the key intermediates acids **5a,b** were obtained, they can be transformed into bromo-acids **6a,b** by reaction with $NaNO_2$/HCl/KBr. Lastly, arylations of the resulted bromo-acids **6a,b** with aromatic amines (PhNHMe or $MeNHCH_2Ph$ or 2-picolylmethylamine) in the presence of K_2CO_3 in DMF afforded thiophene-based alkanoic acids **7a-f** in good overall yields. The structures of all products were appropriately established by both elemental and spectral analyses. We next attempted to create tricyclic scaffolds **8a-f** by performing intramolecular Friedel-Crafts acylations on heterocyclic acids **7a-f**. We thought this would be an interesting cyclization due to the diverse potential regiochemical outcomes (Table 1).

Table 1. Efforts to optimize Friedel-Crafts cyclizations on substrates **7a-f**

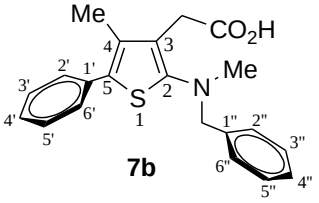
Entry	Substrate	Product	Conditions	Yield (%)[a]
1	 **7a**	 **8a**	$AlCl_3/CH_3NO_2$[b], DCM[c], 14 h, rt	81
			P_2O_5[d], DCE[e], 14 h, reflux	78
			PPA[f], 6 h, 190-200 °C	73
2	 **7b**	 **8b**	$AlCl_3/CH_3NO_2$, DCM, 13 h, rt	84
			P_2O_5, DCE, 11 h, reflux	80
			PPA, 7 h, 190-200 °C	75
3	 **7c**	 **8c**	$AlCl_3/CH_3NO_2$, DCM, 12 h, rt	78
			P_2O_5, DCE, 16 h, reflux	72
			PPA, 8 h, 190-200 °C	70
4	 **7d**	 **8d**	$AlCl_3/CH_3NO_2$, DCM, 11 h, rt	79
			P_2O_5, DCE, 14 h, reflux	81
			PPA, 10 h, 190-200 °C	75
5	 **7e**	 **8e**	$AlCl_3/CH_3NO_2$, DCM, 20 h, rt	83
			P_2O_5, DCE, 15 h, reflux	74
			PPA, 9 h, 190-200 °C	75
6	 **7f**	 **8f**	$AlCl_3/CH_3NO_2$, DCM, 18 h, rt	85
			P_2O_5, DCE, 18 h, reflux	80
			PPA, 8 h, 190-200 °C	73

[a]Isolated yields. [b]With $AlCl_3/CH_3NO_2$–catalyst reactant proportions were: acid (2 mmol), $AlCl_3$ (10 mmol) in CH_3NO_2 (80 mmol), solvent (10 mL). [c]Dichloromethane. [d]With P_2O_5 catalyst reactant proportions were: acid (0.5 g) and P_2O_5 (5 g) in anhydrous solvent (10 mL). [e]Dichloroethane. [f]With PPA catalyst reactant proportions were: acid (0.5 g) and PPA (5 g).

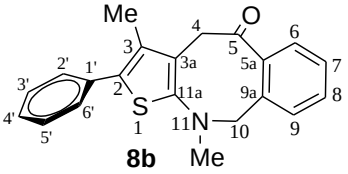
Initially, attempts to perform cyclization of **7a** were carried out using $AlCl_3/CH_3NO_2$-catalyst for 30 min at room temperature. The product composition was examined by TLC and a flash chromatographed sample (0.5g) of the cyclization reaction leading to product **8a** was subjected to column chromatography (silica,

column; 1×25 cm, *n*-hexane/EtOAc 7:3). Unfortunately, the content of reaction product was found by GC to contain cyclic product **8a** (0.12g, 24%) and starting acid **7a** (0.34g, 70%) respectively. Attempts to improve the effectiveness of the ring closure reactions and by examining the efficacy of other catalysts to effect this cyclization process were studied. For example, cyclization of substrate **7a** was carried out with $AlCl_3/CH_3NO_2$ for longer reaction time (14h) at room temperature gave product **8a** in 81% yield. While cyclization of **7a** in the presence of PPA-catalyst at 190-200 °C for in 6h, led to an increase in yield to 73% of **8a**. When the reaction was allowed to go longer time (14h) with P_2O_5 it furnished the corresponding cyclized product **8a** in 78% yield (entry 1).

Encouraged by this result, attempts were conducted to control the outcome of the cyclization of precursors **8a-f** under more vigorous conditions. Out of several variations tried, the results in Table 1 and Scheme 1, illustrate the successful cyclizations that provided the polycyclic thiophenes in good yields. The formation of cyclic products were unambiguously confirmed by spectral techniques. Notably, these results exploiting the importance of electrophilic inhibition generated by a Lewis or Brønsted acid catalyst which determines the regioselectivity in Friedel-Crafts cyclizations to heterocyclic compounds.[22] It seemed reasonable, therefore, that the catalyst inhibition created by coordinating of an electron-deficient species ($AlCl_3$ or proton) of the catalyst on heteroatoms in substrate, would decrease the rate of ring closures of heteroarenes **7a-f** under normal conditions. This suggested that the rate of the cyclization process strongly depends on the strength of Lewis or Brønsted catalysts. Thus, we deduced that the poor catalysts are unable to coordinate effectively with the heteroatoms present in the substrate. Consequently, the mild catalysts mentioned are suitable for optimization of cyclization reactions in order to bring about ring closure completely. Cyclization processes could be achieved by optimizing the reaction conditions using more than a stoichiometric of such mild catalyst, high temperatures and long reaction times.



2-(2-(*N*-benzyl-*N*-methylamino)-4-methyl-5-phenylthiophen-3-yl)acetic acid



4,5,10-Trihydro-3,11-dimethyl-2-phenyl-benzo[*f*]thieno[2,3-*b*]azocin-5 (11*H*)-one

Figure 2. Structures of tricyclic thiophene **8b** and its precursor acid **7b.**

A plausible mechanism[23] to account for transformations of heterocyclic acids **7a-f** into fused tricyclic thiophenes **8a-f** is realized on the generation of acyl–carbocation[24] by loss of water upon treatment of the acid precursors **7a-f** with acidic catalysts. The resulting acyl–carbocation underwent ring closures to substituted tricyclic ketones in overall good yields. In the IR spectrum of **7b**, absorption bands at 2612 and 1725 cm^{-1} attributed to the O-H and carbonyl stretching frequencies, respectively. The ^1H NMR spectrum of **7b** exhibited five singlet signals at 2.33, 2.92, 3.87, 4.60 and 10.45 ppm, respectively, related to CH_3, N-CH_3, CαH_2, Ph-CH_2 and COOH groups, while ten aromatic protons appeared at an average of δ 7.08 - 7.37 ppm with multiplicity of different values of coupling constants. On the other hand, the structure of cyclic product **8b** was deduced from NMR spectroscopic data, as described for **7b** as a representative example (Fig. 2). The ^1H NMR spectra for tricyclic **9a** displayed several distinct signals for four groups as CH_3 at 2.33 ppm, N-CH_3 at 3.10 ppm, C^4H_2 at

3.67 ppm and $C^{10}H_2$ at 4.53 ppm. Meanwhile, aromatic protons appeared in the rang of 7.08-7.85 ppm, which showed the inner signals overlapping.

In this context, it is worth mentioning that despite more than 130 years of history, the Friedel-Crafts reactions promoted by Brønsted and Lewis acids are still in the forefront of organic synthesis and become one of the most commonly used methodologies for the construction of carbo-and heterocyclic compounds. Nowadays, the Friedel-Crafts processes constitute an essential synthetic step in a wide number of industry processes regarding to the production of natural products and biologically active drug skeletons (Fig. 3).[25-30]

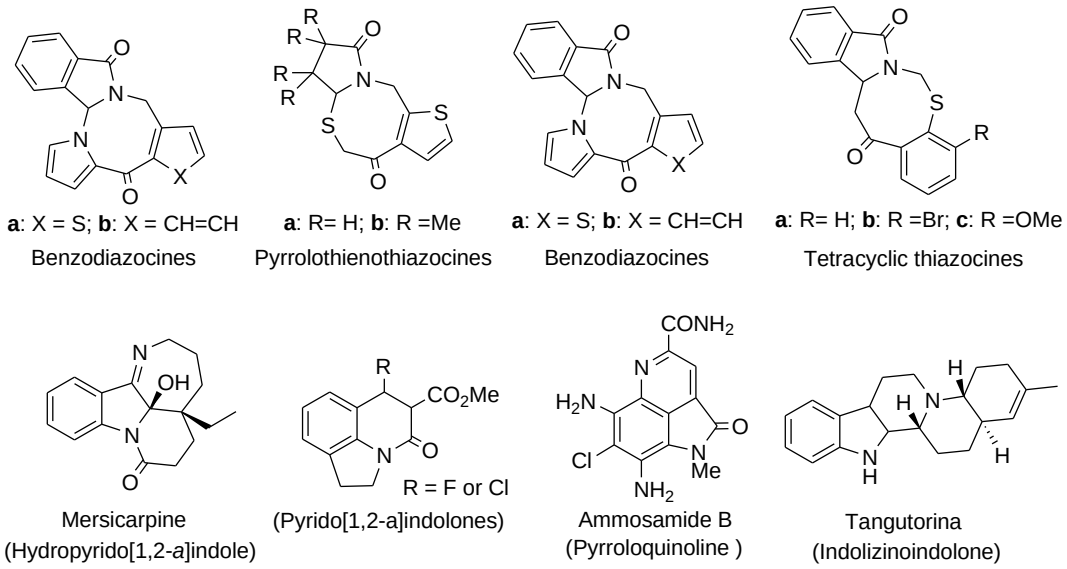


Figure 3. Some of condensed heterocyclic skeletons synthesized by Friedel–Crafts processes.

The scope, limitation and the great versatility of inter-and intramolecular Friedel–Crafts acylation and alkylation reactions are expanding rapidly and the actual contribution of classic and asymmetric Friedel–Crafts approaches on aromatics (benzene and more electron rich aromatics) as well as electron-rich heteroaromatics (thiophene, indole, quinoline) constitutes the major area of synthetic community. In doing this, many comprehensive reviews and books are leaving more detailed descriptions of applications, orientations, mechanisms and outcomes of Friedel-Crafts reactions concerning synthesis and functionalization of polycyclic systems are described.[31-36] As reported,[37] Friedel–Crafts reactions are macrocyclization strategies featured by small enthalpic and relatively large entropic barriers in the transition state. Apart from elimination of transannular interactions, Baeyer and Pitzer strains are also involved in dealing with medium-ring compounds formation. To overcome of these disappointingly impediments encountered in ring closure step, cyclizations could carried out under more drastic conditions catalyzed by mild catalyst-type which would allow ring closing process to occur.

Conclusions

We have developed expedient and efficient procedures for the constructions of fused tricyclic thiophenes via intramolecular Friedel-Crafts cycliacylations. This protocol allows easy access to functionalized thiophene fused with medium sized N-heterocyclic ring systems (*e.g.* benzo-and pyrido fused thieno[2,3-*b*]azepinones,

thieno[2,3-*b*]azocinones and thieno[2,3-*b*]azoninones) in good yields by ring closures of heterocyclic carboxylic acids **7a-f**. The ease of workup and wide variability of the method, simplifies the construction of condensed thiophene-based scaffolds of sound promising pharmaceutical applicability.

Experimental Section

General. Commercially available reagents were used without further purification unless otherwise stated; solvents were dried by standard procedures. Melting points were measured by a digital Gallenkamp capillary melting point apparatus and are uncorrected. IR spectra were determined on a Shimadzu 470 Infrared spectrophotometer using KBr wafer technique (ν cm^{-1}). The ^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL LA 400 MHz FT-NMR (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR) and on a Varian NMR (90 MHz) spectrometers using $CDCl_3$ solvent with TMS as internal standard. Chemical shifts are given in parts per million (δ), and the coupling constants (*J*) are given in Hertz. Mass spectra were performed by JEOL JMS 600 spectrometer at under electron impact at 70 eV. Elemental analyses were performed using a GmbH Vario EL III, 2400, CHNS-elemental analyzer and halogens were determined manually at microanalytical unit. The reaction progress monitoring was accomplished by thin layer chromatography (TLC; silica-gel 60 F254 plates, *n*-hexane/ethyl acetate) and plates were visualized by UV light (at 254 and/or 360 nm). Flash column chromatography was prepared from Aldrich silica gel, 70–230 mesh. Substituted ethyl 2-aminothiophene-3-carboxylate **1** used in this work was obtained as yellow crystals (88% yield), mp 98–99 °C (Lit.[20] mp 94–96°C) by heating a mixture of ethyl cyanoacetate, sulfur, phenyl acetone and diethyl amine in ethanol for 10 hours.

3-(Chloromethyl)-4-methyl-5-phenylthiophen-2-amine (**3**). This intermediate compound was obtained in two reaction steps starting with ethyl 2-amino-4-methyl-5-phenylthiophene-3-carboxylate (**1**). A summary of the steps is given in the following:

(i) A solution of the ester **1** (3.9 g, 15 mmol) in dry THF (20 mL) was added dropwise over 20 min to an ice-cold suspension of $LiAlH_4$ (0.9 g, 25 mmol) in THF (40 mL) and the reaction was stirred for 2 h at 0-5 °C. The reaction mixture was refluxed for 4h, cooled to 0°C and then quenched by dropwise addition and stirring of water (5 mL) followed by NaOH solution (25 mL, 20%). The resulting mixture was filtered and the filtrate was basified with NaOH (2 M) until pH 10, then it was extracted with EtOAc (3×40 mL). The combined organic layer was washed, dried over Na_2SO_4, filtered and the solvent was evaporated in *vacuo* to afford the crude alcohol. Crystallization from ethanol gave (2.7 g, 84%) of pure (2-amino-4-methyl-5-phenylthiophen-3-yl)methanol **(2)** as yellow crystals, mp 126-129 °C; IR (KBr) ν_{max} 3434, 3390, 3080, 2960, 1590, 1470, 1445, 1330 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.37 (3H, s, CH_3), 4.61 (2H, s, CH_2O), 7.10 (1H, tdd, *J* 7.7, 1.9, 1.6 Hz), 7.29-7.42 (4H, m, phenyl), 6.25 (2H, s, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 58.4 (1C, -CH_3), 64.7 (1C, -CH_2), 127.1 (2C, Ar., C-2', C-6'), 128.9 (1C, Ar., C-4'), 129.0 (2C, Ar., C-3', C-5'), 129.2 (1C, Ar., C-1'), 133.0 (1C, Ar., C-3), 133.1 (1C, Ar., C-4), 137.5 (1C, Ar., C-5), 163.0 (1C, Ar., C-2). Anal. Calcd. for $C_{12}H_{13}NOS$ (219); C, 65.75; H, 5.93; N, 6.39; S, 14.61. Found; C, 65.90; H, 5.84; N, 6.44; S, 14.50%.

(ii) To a solution of alcohol **2** (3.5 g, 16 mmol) in dry diethyl ether (30 mL) was added $SOCl_2$ (4.8 g, 40 mmol) and the reaction was refluxed on a water bath for 2h. The reaction mixture was then poured with efficient stirring into cold water (70 mL) and extracted with ether (3×40 mL). The combined organic layers were washed with $NaHCO_3$ solution (20 mL, 30%), washed with water and dried over anhydrous $MgSO_4$. Filtration and the solvent removed in *vacuo* to afford (3.4 g, 90%) of 3-(chloromethyl)-4-methyl-5-phenylthiophen-2-amine (**3**) as brown solid mp 85-87 °C, which was used without further purification. IR (KBr) ν_{max} 3410, 3347, 3050, 3062,

2970, 1585, 1470, 1380 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, δ, ppm): 2.4 (3H, s, CH_3), 4.8 (2H, s, CH_2Cl), 6.60 (2H, s, NH_2), 6.5-7.9 (5H, m, phenyl). Anal. Calcd. for $C_{12}H_{13}ClNOS$ (237.5); C, 60.63; H, 5.05; Cl, 14.94; N, 5.89; S, 13.47. Found; C, 60.90; H, 5.16; Cl, 14.80; N, 5.85; S, 13.29%.

Substituted thiophene alkanoic acids (5a,b). These acids were synthesized via two different pathways (*path a* and *path b*) starting from chloride **3**. A summary of the steps is given in the following:

Path A. Synthesis of 2-(2-amino-4-methyl-5-phenylthiophen-3-yl)acetic acid (**5a**) starting from chloride **3** via two reaction steps.

(i) A mixture of chloride **3** (3.3 g, 14 mmol) and KCN (2.6 g, 40 mmol) in ethanol (25 mL) was refluxed for 6 h. Afterwards, the excess solvent was removed in *vacuo* and the residue was diluted with water (50 mL). The product was extracted with ether (3×30 mL) and the combined ether extracts washed with water, dried and concentrated *in vacuo* to yield the crude cyanide. Crystallization from benzene gave (2.5 g, 80%) of pure 2-(2-amino-4-methyl-5-phenylthiophen-3-yl)acetonitrile (**4**) as white needles; mp 90-92 °C; IR (KBr) ν_{max} 3430, 3370, 3033, 2950, 2248, 1590, 1490, 1365, 1283 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, δ, ppm): 2.3 (3H, s, CH_3), 4.2 (2H, s, CH_2CN), 6.2 (2H, s, NH_2), 6.7-8.0 (5H, m, phenyl). Anal. Calcd. for $C_{13}H_{12}N_2S$ (228); C, 68.42; H, 5.26; N, 12.28; S, 14.03. Found; C, 68.47; H, 5.24; N, 12.41; S, 13.84%.

(ii) A mixture of nitrile **4** (4.5 g, 20 mmol), NaOH (3.2 g, 80 mmol), in ethanol (30 mL) was refluxed for 10h. The reaction was concentrated to dryness and the residue was dissolved in water (20 mL), neutralized by addition of AcOH (10%) until pH 6-7, and finally it was extracted with AcOEt (3×40 mL). The combined extract was separated, washed with water, dried, and the solvent was evaporated in *vacuo* to give of crude product. Crystallization from benzene gave (3.9 g, 82%) of pure 2-(2-amino-4-methyl-5-phenylthiophen-3-yl)acetic acid (**5a**) as white needles; mp 158-60°C; IR (KBr) ν_{max} 3410, 3360, 3065, 2968, 2255, 1590, 1480, 1385, 1272 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.36 (3H, s, CH_3), 3.88 (2H, s, CαH_2), 5.91 (2H, s, NH_2), 7.10 (1H, tdd, *J* 7.7, 1.9, 1.6 Hz), 7.29-7.42 (4H, m, phenyl), 9.60 (1H, s, COOH); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 14.2 (1C, -CH_3), 32.6 (1C, -CH_2), 127.1 (2C, Ar., C-2', C-6'), 128.9 (1C, Ar., C-4'), 129.0 (2C, Ar., C-3', C-5'), 132.1 (1C, Ar., C-1'), 133.0 (1C, Ar., C-3), 133.1 (1C, Ar., C-4), 137.5 (1C, Ar., C-5), 163.0 (1C, Ar., C-2), 174.0 (1C, -COOH). Anal. Calcd. for $C_{13}H_{13}NO_2S$ (247); C, 63.15; H, 5.26; N, 5.66; S, 12.95. Found; C, 63.09; H, 5.33; N, 5.49; S, 13.08%.

Path B. 3-(2-Amino-4-methyl-5-phenylthiophen-3-yl)propanoic acid (5b). A solution of chloride **3** (3.5 g, 15 mmol) in dry benzene (20 mL) was added dropwise over 10 min to an ice-cold suspension of sodio-malonic ester prepared from Na (0.8 g. atom, 35 mmol) and diethyl malonate (4.8 g, 30 mmol) in absolute ethanol (30 mL). After complete addition, the reaction mixture was refluxed for 6h and the solvent was removed in *vacuo*. The residue was then refluxed for 1h with KOH solution (20 mL, 30%). The reaction mixture was cooled and acidified with HCl solution (40 mL, 30%). The precipitate was filtered, washed with water and dried. This resulted dibasic acid was heated at 170-180 °C on an oil bath with stirring for 10 min and the melted residue was poured into acetone (40 mL). To the acetone solution was added charcoal (0.5 g), warmed, filtered and the solvent was evaporated in vacuo to give the crude acid. Crystallization from acetone gave (2.8 g, 75%) of pure aminoacid **5b** as pale yellow crystals, mp 144-147 °C (acetone); IR (KBr) ν_{max} 3410, 3370, 3045, 2955, 2540, 1730, 1600, 1590, 1460, 1445, 1335 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.33 (3H, s, CH_3), 2.62 (2H, t, *J* 7.4 Hz, CβH_2), 2.94 (2H, t, *J* 7.4 Hz, CαH_2), 6.55 (2H, s, NH_2), 7.10 (1H, tdd, *J* 7.7, 1.9, 1.6 Hz), 7.29-7.42 (4H, m, phenyl), 10.38 (1H, s, COOH); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 14.2 (1C, -CH_3), 30.0 (1C, -$C\beta H_2$), 34.2 (1C, -$C\alpha H_2$), 127.1 (2C, Ar., C-2', C-6'), 128.9 (1C, Ar., C-4'), 129.0 (2C, Ar., C-3', C-5'), 132.1 (1C, Ar., C-1'), 133.0 (1C, Ar., C-3), 133.1 (1C, Ar., C-4), 137.5 (1C, Ar., C-5), 163.0 (1C, Ar., C-2), 177.7 (1C, -COOH). Anal. Calcd. for $C_{14}H_{15}NO_2S$ (261); C, 64.36; H, 5.74; N, 5.36; S, 12.26. Found; C, 64.44; H, 5.80; N, 5.48; S, 12.14%.

General procedure for the synthesis of bromo-alkanoic acid (6a,b). To a suspension of acid **5a** or **5b** (15 mmol) in water (20 mL) was added concentrated HCl (15 mL) and the whole mixture was warmed on a water bath until solids was dissolved. The solution was cooled in an ice bath and a solution of $NaNO_2$ (1.4 g, 20 mmol) in water (15 mL) was added slowly with stirring. The resulting solution was stirred for 10 min while a solution of KBr (3.0 g, 25 mmol) in water (15 mL) was added with occasional shaking. The reaction was then heated on water bath for 1h. The reaction mixture was cooled to room temperature and the resulting precipitate was filtered, washed with water and dried to give the crude product. Purifications, yields and spectral data are given in the following:

2-(2-Bromo-4-methyl-5-phenylthiophen-3-yl)acetic acid (6a). Light brown solid; 74%, mp 180-83 ºC (AcOEt); IR (KBr) ν_{max} 3020, 2943, 2640, 1723, 1600, 1580, 1470, 1440, 1375 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 2.41 (3H, s, CH_3), 3.90 (2H, s, CH_2), 7.27-7.48 (5H, m, phenyl), 10.42 (1H, s, COOH); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 14.2 (1C, -CH_3), 32.6 (1C, -*C*αH_2), 108.4 (1C, Ar., C-3), 127.1 (2C, Ar., C-2', C-6'), 128.9 (1C, Ar., C-4'), 129.0 (2C, Ar., C-3', C-5'), 129.2 (1C, Ar., C-1'), 133.0 (1C, Ar., C-4), 133.1 (1C, Ar., C-5), 137.5 (1C, Ar., C-2), 174.0 (1C, -COOH). Anal. Calcd. for $C_{13}H_{11}BrO_2S$ (311); C, 50.16; H, 3.53; Br, 25.72; S, 10.28. Found; C, 50.30; H, 3.62; Br, 25.78; S, 10.02%.

3-(2-Bromo-4-methyl-5-phenylthiophen-3-yl)propanoic acid (6b). Yellow crystals; 70%, mp 154-56 ºC (AcOEt); IR (KBr) ν_{max} 3030, 2955, 2580, 1720, 1590, 1468, 1445, 1377 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 2.39 (3H, s, CH_3), 2.65 (2H, t, *J* 7.4 Hz, CβH_2), 3.15 (2H, t, *J* 7.4 Hz, CαH_2), 7.27-7.48 (5H, m, phenyl), 10.91 (1H, s, COOH); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 14.2 (1C, -CH_3), 30.0 (1C, -*C*βH_2), 34.0 (1C, -*C*αH_2), 108.4 (1C, Ar., C-3), 127.1 (2C, Ar., C-2', C-6'), 128.9 (1C, Ar., C-4'), 129.00 (2C, Ar., C-3', C-5'),129.2 (1C, Ar., C-1'), 133.0 (1C, Ar., C-4), 133.1 (1C, Ar., C-5), 137.5 (1C, Ar., C-2), 177.7 (1C, -COOH). Anal. Calcd. for $C_{14}H_{13}BrO_2S$ (325); C, 51.69; H, 4.00; Br, 24.61; S, 9.84. Found; C, 51.91; H, 3.85; Br, 24.90; S, 9.77%.

General procedure for arylation of bromo-thiophene carboxylic acids (6a,b). A mixture of carboxylic acids **6a** or **6b** (10 mmol), K_2CO_3 (2.7 g, 20 mmol), amine; PhNHMe *or* $PhCH_2NHMe$ or 2-picolylmethylamine (14 mmol) and CuCl (0.3 g) in DMF (20 mL) was heated with efficient stirring for 10 h at 120-130 °C. The progress of the reaction was monitored by TLC (hexane:AcOEt; 8:2). After the completion of the reaction, the reaction mixture was decomposed with aqueous NaOH solution (100 mL, 10%). Afterwards, decolorizing carbon (2 g) was added and the mixture was heated for 10 min and filtered on hot. The cold filtrate was acidified with aqueous HCl solution (40 mL, 20%) and the formed precipitate was filtered, washed and dried to give the crude acids **7a-f**. The crude acids were purified by flash chromatography (basic alumina, EtOAc/*n*-hexane, 1/1). Further purifications, yields and spectral data of acids **7a-f** are given in the following:

2-(2-(*N*-Methyl-*N*-phenylamino)-4-methyl-5-phenylthiophen-3-yl)acetic acid (7b). Colourless crystals; 72%, mp 141-43 ºC (AcOEt); IR (KBr) ν_{max} 3035, 2950, 2564, 1720, 1580, 1440, 1382, 1277 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 2.32 (3H, s, CH_3), 3.15 (3H, s, N-CH_3), 3.90 (2H, s, CαH_2), 6.89 (1H, tt, *J* 8.1, 1.2 Hz), 7.08 (2H, dtd, *J* 8.2, 1.2, 0.5 Hz), 7.13 (1H, tdd, *J* 7.7, 2.0, 1.6 Hz), 7.27 (2H, dddd, *J* 8.2, 8.1, 1.4, 0.5 Hz), 7.34 (2H, dddd, *J* 7.9, 7.7, 1.3, 0.6 Hz), 7.47 (2H, dddd, *J* 7.9, 1.9, 1.6, 0.5 Hz), 11.14 (1H, s, COOH); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 14.2 (1C, -CH_3), 32.6 (1C, -*C*αH_2), 52.9 (1C, N-CH_3), 122.1 (2C, Ar., C-2'', C-6''), 124.7 (1C, Ar., C-3), 127.1 (2C, Ar., C-2', C-6'), 128.9 (1C, Ar., C-4'), 129.0 (2C, Ar., C-3', C-5'), 129.2 (2C, Ar., C-3'', C-5''), 132.1 (1C, Ar., C-4''), 133.0 (1C, Ar., C-1'), 133.1 (1C, Ar., C-4), 137.5 (1C, Ar., C-5), 140.1 (1C, Ar., C-2), 144.7 (1C, Ar., C-1''), 174.0 (1C, -COOH); MS (EI, 70 eV) *m/z* (%), 338 (M^++1, 52), 337 (M^+, 34), 292 (100), 278 (62), 200 (45), 172 (92), 106 (20), 77 (18). Anal. Calcd. for $C_{20}H_{19}NO_2S$ (337); C, 71.12; H, 5.63; N, 4.15; S, 9.49. Found; C, 70.94; H, 5.60; N, 4.18; S, 9.74%.

2-(2-(*N*-Benzyl-*N*-methylamino)-4-methyl-5-phenylthiophen-3-yl)acetic acid (7). Colourless plates; 74%, mp 120-23 ºC (AcOH); IR (KBr) ν_{max} 3070, 2930, 2612, 1725, 1590, 1580, 1440, 1384, 1248 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 2.33 (3H, s, CH_3), 2.92 (3H, s, N-CH_3), 3.87 (2H, s, CαH_2), 4.60 (2H, s, Ph-CH_2), 7.08 (1H, dddd, *J* 8.1, 7.9, 2.0, 1.6 Hz), 7.17-7.31 (7H, m), 7.37 (2H, dddd, *J* 7.9, 1.8, 1.6, 0.5 Hz), 10.45 (1H, s, COOH); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 14.2 (1C, -CH_3), 32.6 (1C, -*C*αH_2), 44.8 (1C, N-CH_3), 53.6 (1C, Ph*C*H_2), 127.1(2C, Ar., C-2'', C-6''), 127.9 (2C, Ar., C-2', C-6'), 128.5 (2C, Ar., C-3'', C-5''), 128.9 (2C, Ar., C-4', C-4''), 129.0 (2C, Ar., C-3', C-5'), 132.1 (1C, Ar., C-1'), 133.0 (1C, Ar., C-3), 133.1 (1C, Ar., C-4), 136.7 (1C, Ar., C-5), 137.5 (1C, Ar., C-2), 140.1 (1C, Ar., C-1''), 174.0 (1C, -COOH); MS (EI, 70 eV) *m/z* (%), 351 (M^+, 22), 306 (100), 292 (50), 263 (30), 171 (80), 105 (41), 77 (8). Anal. Calcd. for $C_{21}H_{21}NO_2S$ (351); C, 71.79; H, 5.98; N, 3.98; S, 9.11. Found; C, 71.64; H, 6.19; N, 4.11; S, 8.85%.

2-(2-(*N*-Methyl-*N*-((pyridin-2-yl)methyl)amino)-4-methyl-5-phenylthiophen-3-yl)acetic acid (7c). Yellow crystals; 77%; mp 204 *dec.*ºC, (AcOH); IR (KBr) ν_{max} 3070, 2948, 2740, 1715, 1600, 1570, 1455, 1330, 1245 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 2.33 (3H, s, CH_3), 3.02 (3H, s, N-CH_3), 3.87 (2H, s, CαH_2), 4.81 (2H, s, Ph-CH_2), 7.09 (1H, dddd, *J* 8.1, 7.9, 2.0, 1.6 Hz), 7.17-7.29 (4H, m), 7.37 (2H, dddd, *J* 7.9, 1.8, 1.6, 0.5 Hz), 7.63 (1H, ddd, *J* 7.6, 7.4, 1.9 Hz), 8.51 (1H, ddd, *J* 4.5, 1.9, 0.5 Hz), 10.52 (1H, s, COOH); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 14.2 (1C, -CH_3), 32.6(1C, -*C*αH_2), 44.8 (1C, N-CH_3), 49.2 (1C, pyridyl-*C*H_2), 123.3 (1C, Ar., C-4'), 123.5 (1C, Ar., C-4''), 127.1 (2C, Ar., C-2', C-6'), 128.9 (1C, Ar., C-2''), 129.0 (2C, Ar., C-3', C-5'), 132.1 (1C, Ar., C-3''), 133.0 (1C, Ar., C-1'), 133.1 (1C, Ar., C-3), 137.5 (1C, Ar., C-4), 137.7 (1C, Ar., C-5), 140.1 (1C, Ar., C-2), 149.0 (1C, Ar., C-5''), 160.1 (1C, Ar., C-1''), 174.0 (1C, -COOH); MS (EI, 70 eV) *m/z* (%), 354 (M^++2, 9), 353 (22), 337 (M^+, 29), 307 (100), 292 (32), 278 (27), 201 (42), 172 (70), 106 (55), 77 (27). Anal. Calcd. for $C_{20}H_{20}N_2O_2S$ (352); C, 68.18; H, 5.68; N, 7.95; S, 9.09. Found; C, 68.16; H, 5.92; N, 7.85; S, 9.27%.

3-(2-(*N*-Methyl-*N*-phenylamino)-4-methyl-5-phenylthiophen-3-yl)propanoic acid (7d). Colourless plates; 80%, mp 140-43 ºC (methanol); IR (KBr) ν_{max} 3110, 2974, 2642, 1723, 1600, 1585, 1440, 1374, 1230 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 2.29 (3H, s, CH_3), 2.64 (2H, t, *J* 7.4 Hz, CβH_2), 2.96 (2H, t, *J* 7.4 Hz, CαH_2), 3.14 (3H, s, N-CH_3), 6.89 (1H, tt, *J* 8.1, 1.2 Hz), 7.08 (2H, dtd, *J* 8.2, 1.2, 0.5 Hz), 7.12 (H, tdd, *J* 7.7, 2.0, 1.6 Hz),7.27 (2H, dddd, *J* 8.2, 8.1, 1.4, 0.5 Hz), 7.34 (2H, dddd, *J* 7.9, 7.7, 1.3, 0.6 Hz), 7.47 (2H, dddd, *J* 7.9, 1.9, 1.6, 0.5 Hz), 10.66 (1H, s, COOH);^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 14.2 (1C, -CH_3), 30.0 (1C, -*C*βH_2), 34.2 (1C, -*C*αH_2), 52.9 (1C, N-CH_3), 122.1 (2C, Ar., C-2'', C-6''), 124.7 (1C, Ar., C-4''), 127.1 (2C, Ar., C-2', C-6'), 128.9 (1C, Ar., C-4'), 129.0 (2C, Ar., C-3'', C-5''), 129.2 (2C, Ar., C-3', C-5'), 132.1 (1C, Ar., C-1'), 133.0 (1C, Ar., C-3), 133.1 (1C, Ar., C-4), 137.5 (1C, Ar., C-5), 140.1 (1C, Ar., C-2), 144.7 (1C, Ar., C-1''), 177.7 (1C, -COOH); MS (EI, 70 eV) *m/z* (%), 352 (M^++1, 18), 351 (M^+, 32), 306 (100), 292 (19), 278 (48), 172 (64), 106 (25), 77 (12). Anal. Calcd. for $C_{21}H_{21}NO_2S$ (351); C, 71.79; H, 5.98; N, 3.98; S, 9.11. Found; C, 71.88; H, 6.05; N, 3.90; S, 9.04%.

3-(2-(*N*-Benzyl-*N*-methylamino)-4-methyl-5-phenylthiophen-3-yl)propanoic acid (7e). Yellow crystals; 82%; mp 118-20 ºC (acetone); IR (KBr) ν_{max} 3065, 2970, 2550, 1710, 1600, 1590, 1440, 1338, 1280 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 2.30 (3H, s, CH_3), 2.54 (2H, t, *J* 7.4 Hz, CβH_2), 2.94 (2H, t, *J* 7.4 Hz, CαH_2), 2.92 (3H, s, N-CH_3), 4.60 (2H, s, Ph-CH_2), 7.08 (1H, tdd, *J* 8.1, 2.0, 1.6 Hz), 7.17-7.31 (7H, m), 7.37 (2H, dddd, *J* 7.9, 1.8, 1.6, 0.5 Hz), 11.08 (1H, s, COOH); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 14.2 (1C, -CH_3), 30.0 (1C, -*C*βH_2), 34.2 (1C, -*C*αH_2), 44.8 (1C, PhCH_2), 53.6 (1C, N-CH_3), 127.1 (2C, Ar., C-2', C-6'), 127.9 (2C, Ar., C-4', C-4''), 128.5 (2C, Ar., C-2'', C-6''), 128.9 (2C, Ar., C-3'', C-5''), 129.0 (2C, Ar., C-3', C-5'), 132.1 (1C, Ar., C-1'), 133.0 (1C, Ar., C-3), 133.1 (1C, Ar., C-4), 136.7 (1C, Ar., C-5), 137.5 (1C, Ar., C-2), 140.1 (1C, Ar., C-1''), 177.7 (1C, -COOH); MS (EI, 70 eV) *m/z* (%), 365 (M^+, 26), 364 (M^+-1, 14), 306 (100), 292 (19), 277 (40), 172 (45), 105 (27), 77 (10). Anal. Calcd. for $C_{22}H_{23}NO_2S$ (365); C, 72.32; H, 6.30; N, 3.83; S, 8.76. Found; C, 72.36; H, 6.44; N, 4.05; S, 8.64%.

3-(2-(*N*-Methyl-*N*-((pyridin-2-yl)methyl)amino)-4-methyl-5-phenylthiophen-3-yl)propanoic acid (7f). Colourless crystals; 75%; mp 185-88 ºC (AcOEt); IR (KBr) ν_{max} 3090, 2966, 2653, 1720, 1600, 1590, 1480, 1360,

1289 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 2.30 (3H, s, CH_3), 2.54 (2H, t, *J* 7.4 Hz, CβH_2), 2.94 (2H, t, *J* 7.4 Hz, CαH_2), 3.02 (3H, s, N-CH_3), 4.81 (2H, s, Ph-CH_2), 7.08 (1H, tdd, *J* 8.1, 2.0, 1.6 Hz), 7.20 (1H, ddd, *J* 7.4, 4.5, 1.2 Hz), 7.23 (2H, dddd, *J* 8.1, 7.9, 1.4, 0.5 Hz), 7.26 (1H, ddd, *J* 7.6, 1.2, 0.5 Hz), 7.37 (2H, dddd, *J* 7.9, 1.8, 1.6, 0.5 Hz), 7.63 (1H, ddd, *J* 7.6, 7.4, 1.9 Hz), 8.51 (1H, ddd, *J* 4.5, 1.9, 0.5 Hz), 10.52 (1H, s, COOH); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 14.2 (1C, -CH_3), 30.0 (1C, -*Cβ*H_2), 34.2 (1C, -*Cα*H_2), 44.8 (1C, N-CH_3), 49.2 (1C, Pyridyl-CH_3), 123.3 (1C, Ar., C-4'), 123.5 (1C, Ar., C-4''), 127.1 (2C, Ar., C-2', C-6'), 128.9 (1C, Ar., C-2''), 129.0 (2C, Ar., C-3', C-5'), 132.1 (1C, Ar., C-3''), 133.0 (1C, Ar., C-1'), 133.1 (1C, Ar., C-3), 137.5 (1C, Ar., C-4), 137.7 (1C, Ar., C-5), 140.1 (1C, Ar., C-2), 149.0 (1C, Ar., C-5''), 160.1 (1C, Ar., C-1''), 177.7 (1C, -COOH); MS (EI, 70 eV) *m/z* (%), 367 (M^++1, 8), 366 (M^+, 15), 365 (31), 307 (100), 293 (39), 278 (24), 171 (35), 105 (15), 77 (8). Anal. Calcd. for $C_{21}H_{22}N_2O_2S$ (366); C, 68.85; H, 6.01; N, 7.65; S, 8.74. Found; C, 69.04; H, 6.15; N, 7.53; S, 8.72%.

Cycliacylations procedures. Friedel-Crafts cyclization procedures[19] using $AlCl_3/CH_3NO_2$ or P_2O_5 or PPA were essentially followed. The crude products were purified by flash column chromatography (basic alumina, EtOAc/n-hexane, 1/1) and by crystallization from a suitable solvents. The conditions and yields for the products 8a-f are shown in Table 1, while the physical and spectral data of the products are given in the following.

4,5-Dihydro-3,10-dimethyl-2-phenyl-benzo[*f*]thieno[2,3-*b*]azepin-5(10*H*)-one (8a). Yellowish crystals; 80%; mp 168-71 ºC (acetone); IR (KBr) ν_{max} 3070, 2940, 1735, 1580, 1480, 1440, 1383, 1272 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 2.32 (3H, s, CH_3), 3.80 (3H, s, N-CH_3), 3.86 (2H, s, C^4H_2), 7.11 (1H, ddd, *J* 8.6, 1.2, 0.6 Hz), 7.14 (1H, tdd, *J* 7.7, 2.0, 1.6 Hz), 7.32 (1H, ddd, *J* 7.9, 7.5, 1.2 Hz), 7.34 (2H, dddd, *J* 7.9, 7.7, 1.3, 0.6 Hz), 7.38 (1H, ddd, *J* 7.9, 1.3, 0.6 Hz), 7.49 (2H, dddd, *J* 7.9, 1.9, 1.6, 0.5 Hz), 7.57 (1H, ddd, *J* 8.6, 7.5, 1.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 14.2 (1C, -CH_3), 44.7 (1C, -C^4H_2), 52.9 (1C, N-CH_3), 117.3 (1C, Ar., C-9), 122.2 (1C, Ar., C-7), 122.5 (1C, Ar., C-5a), 126.8 (1C, Ar., C-6), 127.1 (2C, Ar., C-2', C-6'), 128.9 (1C, Ar., C-4'), 129.0 (2C, Ar., C-3', C-5'), 131.7 (1C, Ar., C-8), 132.1 (1C, Ar., C-9a), 133.0 (1C, Ar., C-1'), 133.1 (1C, Ar., C-3), 137.5 (1C, Ar., C-10a), 140.1 (1C, Ar., C-2), 141.6 (1C, Ar., C-3a), 199.2 (1C, C=O, C-5); MS (EI, 70 eV) *m/z* (%), 320 (M^++1, 20), 319 (M^+, 40), 304 (100), 291 (62), 192 (77), 170 (41), 106 (8), 77 (17). Anal. Calcd. for $C_{20}H_{17}NOS$ (319); C, 75.23; H, 5.32; N, 4.38; S, 10.03. Found; C, 75.51; H, 5.17; N, 4.34; S, 10.14%.

4,5,10-Trihydro-3,11-dimethyl-2-phenyl-benzo[*f*]thieno[2,3-*b*]azocin-5(11*H*)-one (8b). Colourless plates; 82%; mp 162-65 ºC (methanol); IR (KBr) ν_{max} 3053, 2945, 1740, 1610, 1590, 1485, 1440, 1380, 1240 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.33 (3H, s, CH_3), 3.10 (3H, s, N-CH_3), 3.67 (2H, s, C^4H_2), 4.53 (2H, s, $C^{10}H_2$), 7.08 (1H, tdd, *J* 8.1, 2.0, 1.6 Hz), 7.22 (2H, dddd, *J* 8.1, 7.9, 1.4, 0.5 Hz), 7.26 (1H, ddd, *J* 8.0, 1.7, 0.5 Hz), 7.36 (1H, ddd, *J* 7.9, 7.3, 1.7 Hz), 7.37 (2H, dddd, *J* 7.9, 1.8, 1.6, 0.5 Hz), 7.49 (1H, ddd, *J* 8.0, 7.3, 1.3 Hz), 7.85 (1H, ddd, *J* 7.9, 1.3, 0.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 14.2 (1C, -CH_3), 44.7 (1C, -C^4H_2), 44.8 (1C, -$C^{10}H_2$), 53.6 (1C, N-CH_3), 125.8 (1C, Ar., C-9), 126.6 (1C, Ar., C-7), 127.0 (1C, Ar., C-6), 127.1 (2C, Ar., C-2', C-6'), 128.9 (1C, Ar., C-4'), 129.0 (2C, Ar., C-3', C-5'), 131.4 (1C, Ar., C-8), 132.1 (1C, Ar., C-9a), 132.3 (1C, Ar., C-1'), 133.0 (1C, Ar., C-3), 133.1 (2C, Ar., C-5a, C-2), 137.5 (1C, Ar., C-11a), 140.1 (1C, Ar., C-3a), 199.2 (1C, C=O, C-5); MS (EI, 70 eV) *m/z* (%), 334 (M^++1, 19), 333 (M^+, 40), 318 (100), 256 (51), 192 (63), 171 (74), 106 (19), 77 (11). Anal. Calcd. for $C_{21}H_{19}NOS$ (333); C, 75.67; H, 5.70; N, 4.20; S, 9.60. Found; C, 75.52; H, 5.55; N, 4.34; S, 9.82%.

5,6,11-Trihydro-7,10-dimethyl-8-phenyl-pyrido[3,2-*f*]thieno[2,3-*b*]azocin-5(10*H*)-one (8c). Pale brown crystals; 77%; mp 189 ºC *dec.* (acetone); IR (KBr) ν_{max} 3075, 2930, 1735, 1585, 1480, 1470, 1385,1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.33 (3H, s, CH_3), 3.20 (3H, s, N-CH_3), 3.66 (2H, s, C^6H_2), 4.91 (2H, s, $C^{11}H_2$), 7.09 (1H, dddd, *J* 8.1, 7.9, 2.0, 1.6 Hz), 7.22 (2H, tdd, *J* 7.9, 1.4, 0.5 Hz), 7.25 (1H, dd, *J* 7.9, 4.5 Hz), 7.37 (2H, dddd, *J* 7.9, 1.8, 1.6, 0.5 Hz), 7.88 (1H, dd, *J* 7.9, 1.9 Hz), 8.78 (1H, dd, *J* 4.5, 1.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 14.2 (1C, -CH_3), 44.7 (1C, -C^6H_2), 44.8 (1C, -$C^{11}H_2$), 49.2 (1C, N-CH_3), 126.7 (1C, Ar., C-3), 127.1 (2C, Ar., C-2',

C-6'), 128.2 (1C, Ar., C-4), 128.9 (1C, Ar., C-4'), 129.0 (2C, Ar., C-3', C-5'), 132.1 (1C, Ar., C-1'), 133.0 (1C, Ar., C-4a), 133.1 (1C, Ar., C-6a), 134.7 (1C, Ar., C-9a), 137.5 (1C, Ar., C-7), 140.1 (1C, Ar., C-8), 149.0 (1C, Ar., C-2), 155.8 (1C, Ar., C-11a), 199.2 (1C, C=O, C-5); MS (EI, 70 eV) *m/z* (%), 334 (M^+, 30), 319 (100), 304 (64), 257 (36), 190 (60), 172 (82), 106 (35), 77 (19). Anal. Calcd. for $C_{20}H_{18}N_2OS$ (334); C, 71.85; H, 5.38; N, 8.38; S, 9.58. Found; C, 71.68; H, 5.50; N, 8.15; S, 9.74%.

4,5,6-Trihydro-3,11-dimethyl-2-phenyl-benzo[*g*]thieno[2,3-*b*]azocin-6(11*H*)-one (8d). Pale yellow crystals; 80%; mp 145-48 ºC (acetone); IR (KBr) ν_{max} 3070, 2925, 1730, 1580, 1475, 1385, 1270 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.30 (3H, s, CH_3), 2.83 (2H, ddd, *J* 17.1, 7.4, 1.7 Hz, C^4H_2), 3.05 (2H, ddd, *J* 15.7, 7.4, 1.6 Hz, C^5H_2), 3.79 (3H, s, N-CH_3), 7.12 (1H, *app*-ddd, *J* 8.1, 1.2, 0.5 Hz), 7.14 (1H, *app*-tdd, *J* 7.7, 2.0, 1.6 Hz), 7.26-7.39 (4H, m), 7.48 (2H, dddd, *J* 7.9, 1.9, 1.6, 0.5 Hz), 7.64 (1H, ddd, *J* 8.1, 7.5, 1.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 14.2 (1C, -CH_3), 30.0 (1C, -C^4H_2), 38.7 (1C, -C^5H_2), 52.9 (1C, N-CH_3), 117.3 (1C, Ar., C-10), 122.2 (1C, Ar., C-8), 122.5 (1C, Ar., C-9), 126.8 (1C, Ar., C-6a), 127.1 (2C, Ar., C-2', C-6'), 128.9 (1C, Ar., C-4'), 129.0 (2C, Ar., C-3', C-5'), 131.7 (1C, Ar., C-7), 132.1 (1C, Ar., C-1'), 133.0 (1C, Ar., C-3), 133.1 (1C, Ar., C-2), 137.5 (1C, Ar., C-10a), 140.1 (1C, Ar., C-11a), 141.6 (1C, Ar., C-3a), 204.3 (1C, C=O, C-6); MS (EI, 70 eV) *m/z* (%), 335 (M^++2, 10), 333 (M^+, 26), 318 (100), 303 (43), 256 (62), 191 (20), 172 (52), 106 (30), 77 (10). Anal. Calcd. for $C_{21}H_{19}NOS$ (333); C, 75.67; H, 5.70; N, 4.20; S, 9.60. Found; C, 75.55; H, 5.68; N, 4.42; S, 9.41%.

4,5,6,11-Tetrahydro-3,12-dimethyl-2-phenyl-benzo[*g*]thieno[2,3-*b*]azonin-6(11*H*)-one (8e). Yellow plates; 78%; mp 160-63 ºC (methanol); IR (KBr) ν_{max} 3051, 2948, 1738, 1600, 1590, 1470, 1380, 1274 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.30 (3H, s, CH_3), 2.92-3.08 (7H, 2.98 (2H, *app*-ddd, *J* 16.8, 5.1, 3.0 Hz, C^4H_2), 3.01 (2H, *app*-ddd, *J* 13.1, 7.8, 5.1 Hz, C^5H_2), 3.01 (3H, s, N-CH_3), 4.79 (2H, d, *J* 14.4 Hz, $C^{11}H_2$), 7.08 (1H, tdd, *J* 8.1, 2.0, 1.6 Hz), 7.22 (2H, dddd, *J* 8.1, 7.9, 1.4, 0.5 Hz), 7.27 (1H, ddd, *J* 8.0, 1.5, 0.5 Hz), 7.37 (3H, m), 7.49 (1H, ddd, *J* 8.0, 7.5, 1.2 Hz), 7.82 (1H, ddd, *J* 7.9, 1.2, 0.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 14.2 (1C, -CH_3), 30.0 (1C, -C^4H_2), 38.7 (1C, -C^5H_2), 44.8 (1C, -$C^{11}H_2$), 53.6 (1C, N-CH_3), 125.8 (1C, Ar., C-7), 126.6 (1C, Ar., C-8), 127.0 (1C, Ar., C-10), 127.1 (2C, Ar., C-2', C-6'), 128.9 (1C, Ar., C-4'), 129.0 (2C, Ar., C-3', C-5'), 131.4 (1C, Ar., C-9), 132.1 (1C, Ar., C-1'), 132.3 (1C, Ar., C-3), 133.0 (1C, Ar., C-2), 133.1 (2C, Ar., C-3a, C-6a), 137.5 (1C, Ar., C-10a), 140.1 (1C, Ar., C-11a), 206.8 (1C, C=O, C-6); MS (EI, 70 eV) *m/z* (%), 348 (M^++1, 12), 347 (M^+, 30), 332 (33), 317 (100), 270 (48), 190 (23), 172 (45), 106 (33), 77 (21). Anal. Calcd. for $C_{22}H_{21}NOS$ (347); C, 76.08; H, 6.05; N, 4.03; S, 9.22. Found; C, 76.00; H, 6.24; N, 4.00; S, 8.94%.

5,6,7,12-Tetrahydro-8,11-dimethyl-9-phenyl-pyrido[3,2-*g*]thieno[2,3-*b*]azonin-5(11*H*)-one (8f). Yellow plates; 84%; mp 194 ºC *dec.* (methanol); IR (KBr) ν_{max} 3022, 2950, 1740, 1605, 1580, 1440, 1364, 1285 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.30 (3H, s, CH_3), 3.01 (2H, *app*-ddd, *J* 9.4, 7.1, 6.8 Hz, C^7H_2), 3.10 (2H, *app*-ddd, *J* 17.1, 6.8, 1.8 Hz, C^6H_2), 3.11 (3H, s, N-CH_3), 4.75 (2H, s, $C^{12}H_2$), 7.08 (1H, tdd, *J* 8.1, 2.0, 1.6 Hz), 7.22 (2H, dddd, *J* 8.1, 7.9, 1.4, 0.5 Hz), 7.26 (1H, dd, *J* 7.9, 4.6 Hz), 7.37 (2H, dddd, *J* 7.9, 1.8, 1.6, 0.5 Hz), 7.88 (1H, dd, *J* 7.9, 1.9 Hz), 8.65 (1H, dd, *J* 4.6, 1.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 14.2 (1C, -CH_3), 30.0 (1C, -C^7H_2), 38.7 (1C, -C^6H_2), 44.8 (1C, -$C^{12}H_2$), 49.2 (1C, N-CH_3), 126.7 (1C, Ar., C-3), 127.1 (2C, Ar., C-2', C-6'), 128.2 (1C, Ar., C-4), 128.9 (1C, Ar., C-4'), 129.0 (2C, Ar., C-3', C-5'), 132.1 (1C, Ar., C-1'), 133.0 (1C, Ar., C-4a), 133.1 (1C, Ar., C-10a), 134.7 (1C, Ar., C-8), 137.5 (1C, Ar., C-9), 140.1 (1C, Ar., C-7a), 149.0 (1C, Ar., C-2), 155.8 (1C, Ar., C-12a), 199.2 (1C, C=O, C-5); MS (EI, 70 eV) *m/z* (%), 350 (M^++2, 5), 348 (M^+, 16), 333 (25), 318 (100), 271 (63), 191 (20), 172 (50), 106 (30), 77 (18). Anal. Calcd. for $C_{21}H_{20}N_2OS$ (348); C, 72.41; H, 5.74; N, 8.04; S, 9.19. Found; C, 72.22; H, 5.84; N, 8.12; S, 9.35%.

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