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A facile domino protocol for the regioselective synthesis and discovery of novel 2-amino-5-arylthieno-[2,3-*b*]thiophenes as antimycobacterial agents

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ABSTRACT

A series of novel 2-amino-5-arylthieno[2,3-*b*]thiophenes has been synthesized regioselectively from the reaction of 5-aryldihydro-3(2*H*)-thiophenones with ethyl cyanoacetate/malononitrile and sulfur powder in the presence of morpholine under thermal as well as microwave irradiation conditions. This transformation presumably occurs *via* domino Gewald reaction–dehydrogenation sequence. The 2-amino-5-arylthieno[2,3-*b*]thiophenes were evaluated for their *in vitro* activity against *Mycobacterium tuberculosis* H37Rv (MTB) and multi-drug resistant *M. tuberculosis* (MDR-TB). Among 12 compounds screened, ethyl 2-amino-5-(1-naphthyl)thieno[2,3-*b*]thiophene-3-carboxylate was found to be the most active compound with MIC of 1.1 μM against MTB and MDR-TB.

One of the most convenient and well-established protocols for the synthesis of 2-aminothiophenes is Gewald's method,[1] which involves the three-component domino reactions of a ketone with an activated nitrile and elemental sulfur in the presence of morpholine. These 2-aminothiophenes serve as important intermediates in dye preparations and pharmaceutical industry.[2] In particular, they act as antimitotic agents,[3] kinesin spindle protein (KSP) inhibitors,[4] adenosine A1 receptor allosteric enhancers,[5] inhibitors of hepatitis C virus NS5B polymerase,[6] protein-tyrosine phosphatases (PTPs) 1B inhibitors[7], and human leukocyte elastase.[8] The basic framework of these compounds is prevalent in a variety of natural products,[9] besides serving as a building block for more complex structures which display inhibitory properties in a variety of biological targets.[8,10–15]

The World Health Organization estimates that 2 billion people (about one-third of the world population) are infected with *Mycobacterium tuberculosis*, among which 8 million develop active tuberculosis (TB) and nearly 2 million die each year, especially in developing countries.[16] In addition, the rising number of people who contract TB, because their immune systems are compromised by immunosuppressive drugs or substance abuse or HIV/AIDS, is a great impediment to TB control and prevention. There is currently a growing concern about the development and spread of multi-drug and extensively drug-resistant tuberculosis (MDR/XDR-TB), which has the potential to paralyze TB care programs. It is also a serious threat to industrialized nations where individual care and treatment costs and larger social and economic disruptions could become major public policy issues.[17] In the last 50 years, only a few drugs have been approved by the Food and Drug Administration (FDA) to treat TB, which reflects the difficulties rampant in the discovery and clinical testing of new candidates and the lack of pharmaceutical industry research in this area. Hence, the discovery of fast-acting new drugs to effectively cure TB, including MDR-TB, is imperative.

We have recently embarked on a research program to (i) evolve new methodologies employing tandem/domino multi-component reactions for the construction of novel heterocycles[18] in view of their distinct advantages of convergence, economy, efficiency, and eco-friendliness and (ii) unearth new lead molecules with antimycobacterial activities.[19] In this context, we were prompted to employ Gewald reaction–dehydrogenation domino reactions for the synthesis of 2-amino-5-arylthieno[2,3-*b*]thiophenes comprising two thiophene rings, screen them for antimycobacterial activities, and report the results in this Letter. That these 2-amino-5-arylthieno[2,3-*b*]thiophenes could be significant from

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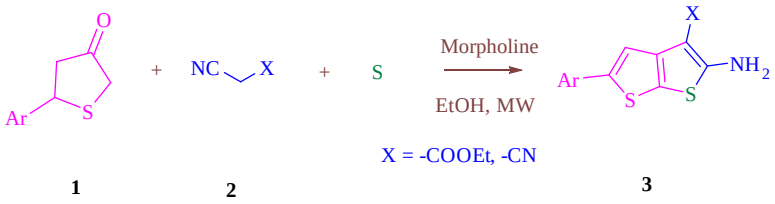


Scheme 1. Synthesis of 2-amino-5-arylthieno[2,3-*b*]thiophenes **3**.

Table 1
Synthesis of 2-amino-5-arylthieno[2,3-*b*]thiophenes **3**

Compd	Ar	X	Reaction time		Yield of 3 (%)		MIC (μM)	
			Reflux[a] (80 °C) (h)	MW[b] (140 °C) (min)	Reflux[c]	MW[c]	MTB	MDR-TB
3a	C_6H_5	CO_2Et	12	25	65	77	20.6	41.2
3b	*p*-MeC_6H_4	CO_2Et	12	25	60	74	4.9	4.9
3c	*p*-ClC_6H_4	CO_2Et	12	25	62	75	9.3	18.5
3d	*p*-$Pr^iC_6H_4$	CO_2Et	12	25	65	70	2.3	2.3
3e	*o,p*-$Cl_2C_6H_3$	CO_2Et	12	25	63	69	8.4	4.2
3f	1-Naphthyl	CO_2Et	12	25	67	72	1.1	1.1
3g	C_6H_5	CN	15	30	68	73	97.5	>97.5
3h	*p*-MeC_6H_4	CN	15	30	62	71	23.1	23.1
3i	*p*-ClC_6H_4	CN	15	30	67	76	43.0	21.5
3j	*p*-$Pr^iC_6H_4$	CN	15	30	61	68	20.9	20.9
3k	*o,p*-$Cl_2C_6H_3$	CN	15	30	58	65	30.4	19.2
3l	1-Naphthyl	CN	15	30	57	69	10.2	5.1
Isoniazid							0.4	11.4
Rifampicin							0.1	3.8
Ethambutol							7.6	61.2
Pyrazinamide							50.8	406.1

[a] Refluxed in ethanol.
[b] Irradiated with ethanol.
[c] Isolated yield after purification by column chromatography.

biological and industrial perspectives emerges from the fact that thieno[2,3-*b*]thiophenes possess important biological activities, *viz.* antiproliferative activity,[20] inhibition of non-peptide GPIIb/IIIa[21], and topically active carbonic anhydrase inhibition,[22] besides showing good potential as conducting polymers[23a] and semiconductors.[23b]

In the present investigation, the reaction of 5-aryldihydro-3(2*H*)-thiophenones **1**[24] with ethyl cyanoacetate or malononitrile **2** and sulfur powder in the presence of morpholine under microwave irradiation and conventional thermal conditions afforded moderate yields of 2-amino-5-arylthieno[2,3-*b*]thiophenes **3** (Scheme 1, Table 1). The microwave reaction was performed in a focused microwave oven by irradiating the reaction mixture in a sealed vial at 140 °C at 40 W power level with 5 bar pressure for 25–30 min[25] given in Table 1. The data in Tables 2 and 3 disclose that morpholine catalyzes the reaction efficiently and that the reaction could be completed rapidly at 140 °C. The reaction vial after completion of the reaction was cooled and the product was purified by flash column chromatography. The thermal reaction was conducted by refluxing the reaction mixture in ethanol for 12–15 h at 80 °C.[25] The time for completion of the reactions was determined by monitoring the reaction by TLC. As the reactions were conducted under thermal and microwave irradiations at different temperatures, the special influence of microwaves, other than of heating, was not assessed. It is to be noted, however, that the microwave reaction affords a slightly higher yield of 2-amino-5-arylthieno[2,3-*b*]thiophenes **3** (65–77%) in much shorter reaction times than the thermal reaction (57–68%) under the conditions employed.

Table 3
Influence of temperature on the synthesis of **3a** under microwave irradiation

S.No.	Temperature (°C)	Irradiation time (min)	Yield[a] of **3a** (%)
1	100	75	64
2	120	45	66
3	140	25	77

[a] Isolated yield after purification by column chromatography.

Table 2
Synthesis of 2-amino-5-phenylthieno[2,3-*b*]thiophenes, **3a** using different bases

S.No.	Base	Reaction time		Yield (%)	
		MW (min)	Thermal (h)	MW[a]	Thermal[a]
1	Morpholine	25	12	77	70
2	Diethylamine	25	12	70	62
3	DBU	25	15	40	58
4	Piperidine	25	15	44	35
5	KF–Al_2O_3	15	10	72	60
6	K_2CO_3	15	10	35	40

[a] Isolated yield after purification by column chromatography.

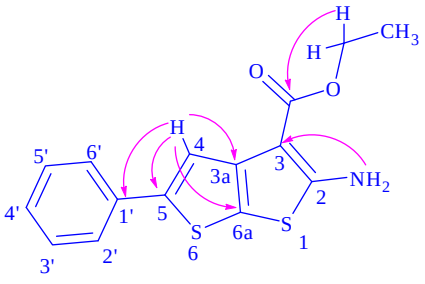
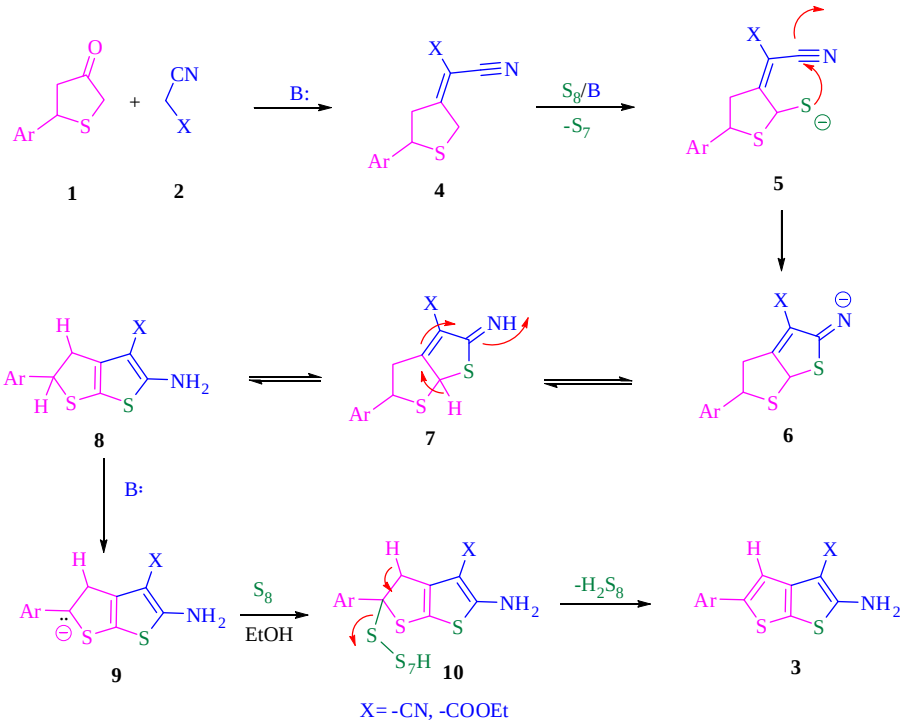


Figure 1. HMBC correlations in **3a**.



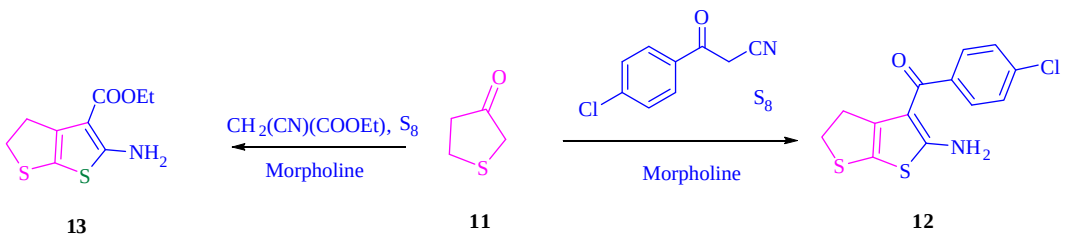
Scheme 2. Proposed mechanism for the formation of 2-amino-5-arylthieno-[2,3-*b*]thiophenes **3**.

The structure of the 2-amino-5-arylthieno[2,3-*b*]thiophenes **3** was established from ^{1}H, ^{13}C, and 2D NMR spectroscopic data as illustrated for a representative example **3a**. In the ^{1}H NMR spectrum of **3a**, the NH_2 protons appear as a singlet at 6.17 ppm, which shows a HMBC (Fig. 1) with the signal at 100.1 ppm due to C-3. The phenyl protons and the thiophene proton, H-4, overlap and occur in the range 7.26–7.62 ppm. The signal of H-4 can, however, be spotted as a tall peak at 7.59 ppm which has (i) a C,H COSY correlation with the signal at 117.7 ppm assignable to C-4 and (ii) HMBCs with carbon signals at 118.9, 134.8, 145.6, and 143.3 ppm ascribable to C-1′, C-3a, C-5, and C-6a which are not distinctly assigned (Fig. 1). The IR stretching frequencies of **3a**, *viz.* 1657 cm^{-1} for C=O and 3312 and 3419 cm^{-1} for NH_2, are diagnostic of the thiophene with a 2-amino and 3-ethyl ester functions, as evident from the comparison of these frequencies with that corresponding to the ester carbonyl at 1649 cm^{-1} and NH_2 at 3300 and 3403 cm^{-1} of the model system, *viz.* 2-amino-8*H*-indeno[2,1-*b*]thiophene-3-carboxylic acid ethyl ester[26] with the ester and amino groups at 3- and 2-positions of the thiophene ring.

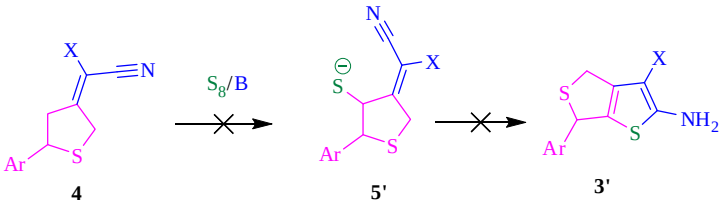
The domino reactions presumably proceed through an initial Knoevenagel condensation of 5-aryldihydro-3(2*H*)-thiophenones **1** with activated nitrile **2** yielding an α,β-unsaturated nitrile **4** (Scheme 2). This intermediate is then thiolated at the methylene carbon by sulfur, followed by ring closure to afford 2-amino-5-aryl-4,5-dihydrothieno[2,3-*b*]thiophenes **8** which further underwent dehydrogenation to afford the 2-amino-5-arylthieno [2,3-*b*]thiophenes **3**. This reaction when performed under N_2 atmosphere also led to **3,** thereby suggesting that the aromatization to **3** could have been effected by sulfur through dehydrogenation.

It is pertinent to note that only one report is available in the literature on the Gewald reaction of tetrahydrothiophen-3(2*H*)-one system, wherein **11** upon reaction with 3-(4-chlorophenyl)-3-oxopropanenitrile and sulfur furnished **12**[27] (Scheme 3). Similarly, the reaction of **11** with ethyl cyanoacetate and sulfur, in our laboratory, afforded ethyl 2-amino-4,5-dihydrothieno[2,3-*b*]thiophene-3-carboxylate **13** in 67% yield (Scheme 3). It is to be noted that both **12** and **13** have been formed without aromatization, while **3** has been formed with aromatization. This suggests that the presence of aryl ring in the intermediate **8** presumably facilitates the aromatization via dehydrogenation as shown in the mechanism (Scheme 2) by forming a stabilized carbanion. From the formation of **3**, it is evident that the reaction of **4** with base gives preferentially **5** instead of the other regioisomer **5′** (Scheme 4), as the carbanion formed by the abstraction of proton from the α-methylene adjacent to sulfur could be stabilized by conjugation with sulfur of the five-membered ring as well. This explains the regioselective formation of **3** in preference to **3′**.

All the newly synthesized compounds were screened for their in vitro antimycobacterial activity against MTB and MDR-TB by



Scheme 3. Gewald reactions of **11** with 3-(4-chlorophenyl)-3-oxopropanenitrile and ethyl cyanoacetate.



Scheme 4. Non-formation of regioisomer **3′** from **4**.

an agar dilution method and MICs of the synthesized compounds along with the standard drugs for comparison are reported (Table 1). In the first phase of screening against MTB, all the compounds showed good in vitro activity with MICs ranging from 1.1 to 97.5 μM. All compounds, except **3g**, were more active with MICs ranging from 1.1 to 43.0 μM than standard drug pyrazinamide (MIC: 50.8 μM). Three compounds (**3b**, **3d,** and **3f**) with MICs of 4.9, 2.3, and 1.1 μM were more potent than first line anti-TB drug, ethambutol (MIC: 7.6 μM). Ethyl 2-amino-5-(1-naphthyl)thieno[2,3-*b*]thiophene-3-carboxylate (**3f**), the most active compound in vitro with MIC of 1.1 μM against MTB, was 7 and 45 times more potent than ethambutol and pyrazinamide, respectively, but less active than isoniazid and rifampicin.

Subsequently, all the synthesized compounds were evaluated against MDR-TB which inhibited it with MICs ranging from 1.1 to >97.5 μM. Five compounds, **3b**, **3d**, **3e**, **3f,** and **3l**, with MICs of 4.0, 2.3. 4.2, 1.1, and 5.1 μM, respectively, were more potent against MDR-TB than the anti-TB drug isoniazid (MIC: 11.4 μM). Two compounds **3d** and **3f** with MICs of 2.3 and 1.1 μM showed greater activity against MDR-TB than rifampicin (MIC: 3.8 μM). Eleven compounds were found to be more active (1.5 - 55.5 times) than ethambutol (MIC: 61.2 μM), while all the twelve compounds screened were more active (4–370 times) than pyrazinamide (MIC: 406.1 μM). The compound **3f** displayed maximum activity *in vitro* with MIC of 1.1 μM against MDR-TB, which are 10 and 3 times more potent than isoniazid and rifampicin, respectively.

Two clear trends are discernible upon examination of the antitubercular activity of the compounds screened (Table 1) from structure–activity point of view.

(1) Compounds with X = COOEt (**3a–3f**) possess more activity against both MTB and MDR-TB than compounds with X = CN (**3g–3l**). In both these sets of compounds, **3f** and **3l** with 1-naphthyl ring displayed maximum activity against both MTB and MDR-TB.
(2) Among the aryl groups in both sets of compounds, the same order of activity *viz.* 1-naphthyl > *p*-Pr^{i}C$_6$H$_4$ > *p*-MeC$_6$H$_4$ > C$_6$H$_5$ is found against MTB as well as MDR-TB which probably indicates that the lipophilicity and/or steric bulk of the compounds is an important factor underlying the activity.

In conclusion, the present work describes a facile one-pot protocol for the regioselective synthesis of a new series of 2-amino-5-arylthieno[2,3-*b*]thiophenes **3** *via* domino Gewald reaction–dehydrogenation sequence. These reactions occur expediently under microwave irradiation affording a higher yield of the thienothiophenes than the thermal method. These 2-amino-5-arylthieno-[2,3-*b*]thiophenes also displayed good *in vitro* antimycobacterial activity against MTB and MDR-TB.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.085.

References and notes

1. Gewald, K.; Schink, E.; Bottcher, H. Z. *Chem. Ber.* **1966**, *99*, 94–100.
2. Sabnis, R. W.; Rangnekar, D. W.; Sonawane, N. D. *J. Heterocycl. Chem.* **1999**, *36*, 333–345.
3. Romagnoli, R.; Baraldi, P. G.; Carrion, M. D.; Cara, C. L.; Preti, D.; Fruttarolo, F.; Pavani, M. G.; Tabrizi, M. A.; Tolomeo, M.; Grimaudo, S.; Cristina, A. D. *J. Med. Chem.* **2007**, *50*, 2273–2277.
4. Pinkerton, A. B.; Lee, T. T.; Hoffman, T. Z.; Wang, Y.; Kahraman, M.; Cook, T. G.; Severance, D.; Gahman, T. C.; Noble, S. A.; Shiau, A. K.; Davis, R. L. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3562–3569.
5. Nikolakopoulos, G.; Figler, H.; Linden, J.; Scammells, P. J. *Bioorg. Med. Chem.* **2006**, *14*, 2358–2365.
6. LaPorte, M. G.; Lessen, T. A.; Leister, L.; Cebzanov, D.; Amparo, E.; Faust, C.; Ortlip, D.; Bailey, T. R.; Nitz, T. J.; Chunduru, S. K.; Young, D. C.; Burns, C. J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 100–103.
7. Andersen, H. S.; Olsen, O. H.; Iversen, L. F.; Sørensen, A. L. P.; Mortensen, S. B.; Christensen, M. S.; Branner, S.; Hansen, T. K.; Lau, J. F.; Jeppesen, L.; Moran, E. J.; Su, J.; Bakir, F.; Judge, L.; Shahbaz, M.; Collins, T.; Vo, T.; Newman, M. J.; Ripka, W. C.; Moller, N. P. H. *J. Med. Chem.* **2002**, *45*, 4443–4459.
8. Gutschow, M.; Kuerschner, L.; Neumann, U.; Pietsch, M.; Loser, R.; Koglin, N.; Eger, K. *J. Med. Chem.* **1999**, *42*, 5437–5447.
9. Koike, K.; Jia, Z.; Nikaido, T.; Liu, Y.; Zhao, Y.; Guo, D. *Org. Lett.* **1999**, *1*, 197–198.
10. Castanedo, G. M.; Sutherlin, D. P. *Tetrahedron Lett.* **2001**, *42*, 7181–7184.
11. Gottschlich, R.; Leibrock, J.; Noe, C. R.; Berger, M.; Buchstaller, H.-P. Eur. Pat. Appl. EP 717044, 1996; *Chem. Abstr.* **1996**, *125*, 114585.
12. Modica, M.; Santiagati, M.; Russo, F.; Parotti, L.; Gioia, L. D.; Selvaggini, C.; Salmona, M.; Mennini, T. *J. Med. Chem.* **1997**, *40*, 574–585.
13. Iversen, L. F.; Anderson, H. S.; Branner, S.; Mortensen, S. B.; Peters, G. H.; Norris, K.; Olsen, O. H.; Jeppesen, C. B.; Lundt, B. F.; Ripka, W.; Moller, K. B.; Moller, N. P. H. *J. Biol. Chem.* **2000**, *275*, 10300–10307.
14. Webb, T. R.; Melman, N.; Ji, X.; Jacobson, K. A. *Chem. Lett.* **2000**, *10*, 31.
15. Fujita, M.; Hirayama, T.; Ikeda, N. *Bioorg. Med. Chem.* **2002**, *10*, 3113–3122.
16. www.who.int/tb/publications/2007/factsheet.
17. http://www3.niaid.nih.gov/topics/tuberculosis/Research/PDF/MDRXDRTBResearchAgenda060607_tagged.pdf (June 2007).
18. (a) Indumathi, S.; Ranjith Kumar, R.; Perumal, S. *Tetrahedron* **2007**, *63*, 1411–1416; (b) Srinivasan, M.; Perumal, S. *Tetrahedron* **2007**, *63*, 2865–2874; (c) Kamal Nasar, M.; Ranjith Kumar, R.; Perumal, S. *Tetrahedron Lett.* **2007**, *48*, 2155–2158; (d) Karthikeyan, S. V.; Perumal, S. *Tetrahedron Lett.* **2007**, *48*, 2261–2265; (e) Ranjith Kumar, R.; Perumal, S. *Tetrahedron* **2007**, *63*, 12220–12231; (f) Savitha Devi, N.; Perumal, S. *Tetrahedron Lett.* **2007**, *48*, 5627–5629.
19. (a) Ranjith Kumar, R.; Perumal, S.; Senthilkumar, P.; Yogeeswari, P.; Sriram, D. *J. Med. Chem.* **2008**, *51*, 5731–5735; (b) Ranjith Kumar, R.; Perumal, S.; Senthilkumar, P.; Yogeeswari, P.; Sriram, D. *Tetrahedron* **2008**, *64*, 2962–2971; (c) Ranjith Kumar, R.; Perumal, S.; Senthilkumar, P.; Yogeeswari, P.; Sriram, D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6459–6462; (d) Karthikeyan, S. V.; Perumal, S.; Krithika, A. S.; Yogeeswari, P.; Sriram, D. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3006–3009; (e) Ranjith Kumar, R.; Perumal, S.; Manju, S. C.; Bhatt, P.; Yogeeswari, P.; Sriram, D. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3461–3465; (f) Ranjith Kumar, R.; Perumal, S.; Senthilkumar, P.; Yogeeswari, P.; Sriram, D. *Eur. J. Med. Chem.* **2009**, *44*, 3821–3829.
20. Egbertson, M. S.; Cook, J. J.; Bednar, B.; Prugh, J. D.; Bednar, R. A.; Gaul, S. L.; Gould, R. J.; Hartman, G. D.; Homnick, C. F.; Holahan, M. A.; Libby, L. A.; Lynch, J. J.; Sitko, G. R.; Stranieri, M. T.; Vassallo, L. M. *J. Med. Chem.* **1999**, *42*, 2409–2421.
21. Prugh, J. D.; Gould, R. J.; Lynch, R. J.; Zhang, G.; Cook, J. J.; Holahan, M. A.; Stranieri, M. T.; Sitko, G. R.; Gaul, S. L.; Bednar, R. A.; Bednar, B.; Hartman, G. D. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 865–870.

22. Prugh, J. D.; Hartman, G. D.; Mallorga, P. J.; McKeever, B. M.; Michelson, S. R.; Murcko, M. A.; Schwam, H.; Smith, R. L.; Sondey, J. M.; Springer, J. P.; Sugrue, M. F. *J. Med. Chem.* **1991**, *34*, 1805–1818.
23. (a) Lee, K.; Sotzing, G. A. *Macromolecules* **2001**, *34*, 5746–5747; (b) Heeney, M.; Bailey, C.; Genevicius, K.; Shkunov, M.; Sparrowe, D.; Tierney, S.; McCulloch, I. *J. Am. Chem. Soc.* **2005**, *127*, 1078–1079.
24. Karthikeyan, S. V.; Perumal, S. *Tetrahedron Lett.* **2007**, *48*, 6133–6136.
25. *General procedure for the synthesis of 2-amino-5-arylthieno[2,3-b]thiophenes* **3**:(1) *Conventional method*: a mixture of 5-aryldihydro-3(2*H*)-thiophenones (1 mmol), ethyl cyanoacetate or malononitrile (1 mmol), powdered sulfur (2 mmol), and morpholine (1.5 mmol) was refluxed in ethanol (10 ml) for the time mentioned in Table 1. The reaction mixture during reflux reached a maximum temperature of 80 °C, which was measured by inserting the thermometer inside the reaction mixture. After completion of the reaction as monitored by TLC, the reaction mixture was filtered to remove sulfur powder, the filtrate was concentrated under vacuum, and the residue was subjected to column chromatography using petroleum ether/ethyl acetate mixture (4:1) as eluent to afford the pure product **3**.
(2) *Microwave irradiation*: a mixture of 5-aryldihydro-3(2*H*)-thiophenones (1 mmol), ethyl cyanoacetate or malononitrile (1 mmol), and powdered sulfur (2 mmol) in ethanol (5 ml) was taken in a 10 ml quartz vial and placed in the Biotage microwave oven. After addition of morpholine (1.5 mmol), the vial was sealed and subjected to microwave irradiation. The irradiation was programed at 140 °C, 40 W, 5 bar for the time given in Table 1. After a period of 2–5 min, the temperature reached a plateau, 140 °C, and remained constant. After 25 min. the vial was gas jet cooled to room temperature (5 min), the reaction mixture was filtered to remove sulfur powder, the filtrate was concentrated under vacuum, and the residue was subjected to column chromatography using petroleum ether/ethyl acetate mixture (4:1) as eluent to afford the product **3**. Spectroscopic data for representative 2-amino-5-arylthieno[2,3-*b*]thiophene **3** are given below.
Ethyl 2-amino-5-phenylthieno[2,3-b]thiophene-3-carboxylate (**3a**):
(Table 1, entry, 1): isolated as pale yellow solid. Mp 149 °C, yield 77%. IR (KBr): 1657 cm^{-1} (C=O), 3312, 3419 cm^{-1} (NH_2); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.45 (t, 3H, J = 7.2 Hz, CH_3), 4.40 (q, 2H, J = 7.2 Hz, CH_2), 6.17 (s, 2H, NH_2), 7.26–7.62 (m, 6H, aromatic and H-4); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.6 (CH_3), 59.9 (CH_2), 100.1, 117.7, 118.9, 125.6, 127.5, 128.9, 134.8, 143.3, 145.6, 165.2 (aromatic), 165.8 (C=O). Anal. Calcd for $C_{15}H_{13}NO_2S_2$: C, 59.38; H, 4.32; N, 4.62%. Found: C, 59.42; H, 4.38; N, 4.67%.
2-Amino-5-(4-methylphenyl)thieno[2,3-b]thiophene-3-yl cyanide (**3h**):
(Table 1, entry, 8): Isolated as colorless solid. Mp 225 °C, yield 73%. IR (KBr): 2205 cm^{-1} (C≡N), 3320, 3422 cm^{-1} (NH_2); ^1H NMR ($CDCl_3$, 300 MHz): δ 2.29 (s, 3H CH_3), 7.11 (s, 2H, NH_2), 7.14–7.43 (m, 5H, aromatic and H-4); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.3 (CH_3), 111.8 (CN), 114.3, 116.5, 123.4, 128.0, 129.6, 135.6, 140.7, 144.4, 166.3 (aromatic). Anal. Calcd for $C_{14}H_{10}N_2S_2$: C, 62.19; H, 3.73; N, 10.36%. Found: C, 62.28; H, 3.80; N, 10.45%.
Ethyl 2-amino-4, 5 dihydrothieno[2,3-b]thiophene-3-carboxylate (**13**):
Isolated as a colorless solid. Mp 128 °C, yield 67%. IR (KBr): 1652 cm^{-1} (C=O), 3330, 3410 cm^{-1} (NH_2); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.32 (t, 3H, J = 5.1 Hz, CH_3), 3.99 (t, 2H, J = 3.9 Hz, CH_2), 4.14 (t, 2H, J = 3.6 Hz, CH_2), 4.25 (q, 2H, J = 7.5 Hz, CH_2), 5.99 (s, 2H, NH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.4 (CH_3), 33.4 (CH_2), 36.1 (CH_2), 59.7 CH_2), 102.0, 117.8, 139.3, (aromatic) 165.1 (C_2), 166.8 (C=O). Anal. Calcd for $C_9H_{11}NO_2S_2$: C, 47.14; H, 4.83; N, 6.11%. Found: C, 47.20; H, 4.89; N, 6.16%.
26. Fu, T. L.; Wang, I. J. *Dyes Pigments* **2008**, *76*, 590–595.
27. Romagnoli, R.; Baraldi, P. G.; Pavani, M. G.; Tabrizi, M. A.; Iaconinoto, M. A.; Carrion, M. D.; Cara, C. L.; Shryock, J. C.; Leung, E.; Moorman, A. R.; Gessi, S.; Merghi, S.; Borea, P. A. *Med. Chem. Res.* **2006**, *14*, 125–142.