A Novel Way to Tricyclic Heteroaromatics; Thiazolo[5,4-*b*]thieno[3,2-*e*]pyridine Derivatives

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Received: 15.03.2014; Accepted after revision: 27.04.2014

Abstract: Thiazolo[5,4-*b*]thieno[3,2-*e*]pyridine derivatives, novel tricyclic heteroaromatics, have been designed and synthesized by a one-pot reaction of diazepinethiones and aldehydes. This reaction is based on a novel rearrangement reaction of seven-membered 1,4-diazepine-2-thiones to six-membered 3-aminopyridine-2-thiols catalyzed by scandium(III) triflate.

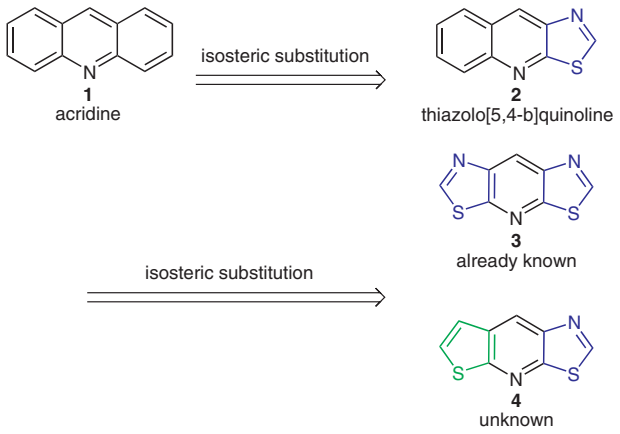
Key words: rearrangement, cyclization, heterocycles, Lewis acid, catalysis

Heterocycles are an important class of molecular space and constitute >50% of organic compounds.[2] The remarkable ability of heterocyclic nuclei to serve as both biomimetics and pharmacophores has largely contributed to their unique value as traditional key elements of numerous drugs.[3] However, our ability to predict the usefulness of new compounds before they are synthesized is still rudimentary, therefore, research directed toward the discovery of novel types of organic compounds continues at an unabated pace both in academia and pharmaceutical companies. Isosterism has often been an effective strategy and tactic to provide novel compounds to address stability, selectivity, toxicity, pharmacokinetics, and efficacy issues in drug discovery and development.[4]

It is well known that acridines **1** (Scheme 1), from isosterism of anthracenes, are significant as raw materials for the production of dyes and antitumor, antiparasitic, antibacterial, antifungal, antiviral agents, and multi-drug resistance modulators.[5]

Moreover, thiazolo[5,4-*b*]quinolines **2** (Scheme 1), which can be considered as isosterically substituted acridines, are also very useful as raw materials for the production of dyes[6] and bioactive agents.[5,7] However, very few compounds from further isosterism, with the exception of bisthiazolo[5,4-*b*:4′,5′-*e*]pyridines **3** that are useful for the treatment of diseases characterized by inhibiting excessive or anomalous cell proliferation,[8] have been reported. Accordingly, our aim was to synthesize novel tricyclic heteroaromatics analogous to compound **3**, but containing a thiazolo[5,4-*b*]thieno[3,2-*e*]pyridine moiety **4**.

As shown in Scheme 2, the key intermediate **6a** might be obtained from compound **11a** via two routes; compound **11a** is readily obtained by a three-component reaction of sulfur, 3-methylbutanal, and 3-(2-chlorophenyl)-3-oxopropanenitrile.

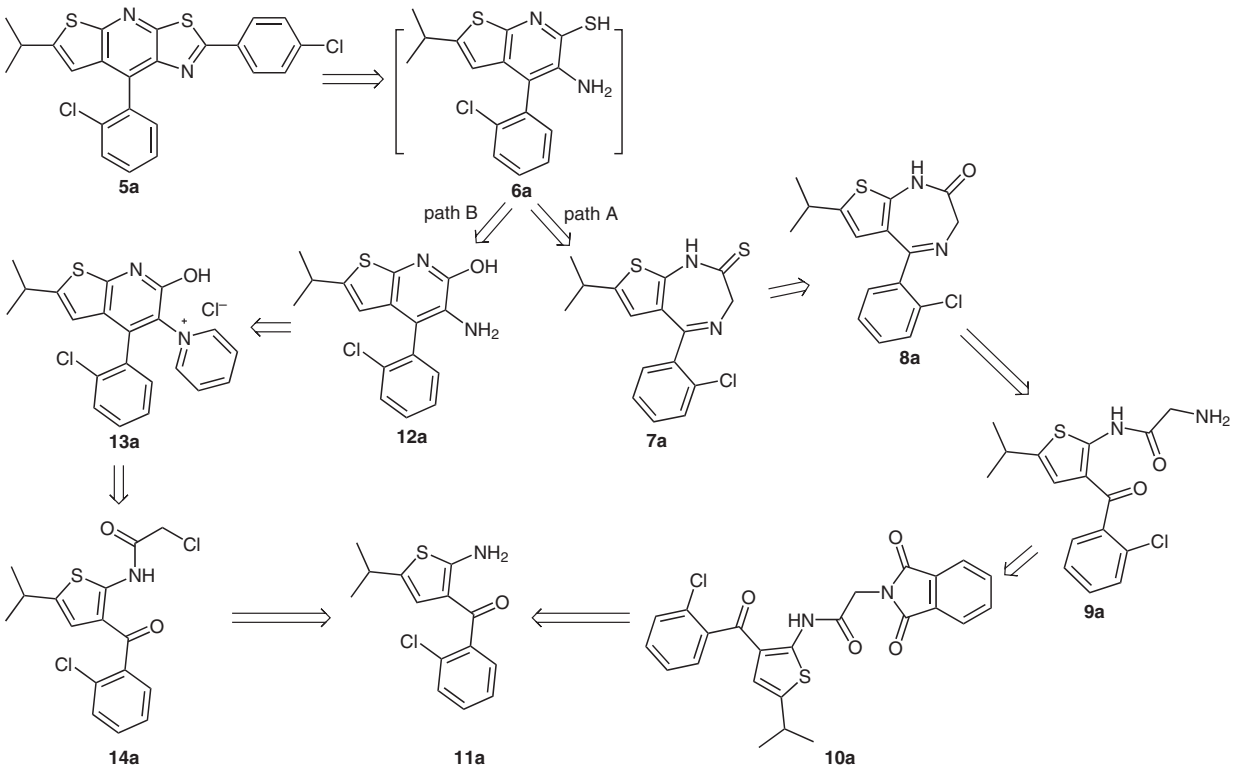


Scheme 1 The design of novel hetero tricycles

At first glance, path B appears to be a reliable shortcut to our key intermediate **6a**. We reasoned that **6a** could be accessed from compound **11a**, because aminoquinones have been readily prepared from 2-aminobenzophenones,[9] and a protocol for preparing 3-aminoquinoline-2-thiol from aminoquinones has been successfully established,[9c] which provide similar transformations for the preparation of **6a** from **11a**.

On the other hand, path A should be an alternative way from **11a** to **6a**. As is well known, a great number of methods for the synthesis of thienodiazepinones **8a** have been established.[10] Moreover, Kovač et al.[11a] obtained 3-amino-6-bromo-4-(2-pyridyl)quinolin-2-one from the rearrangement of corresponding bromazepam with manganese(III) acetate as a catalyst in glacial acetic acid. Hence, we reasoned that **12a** could be accessed from compound **8a**. The conversion of **7a** to **6a** would be more practical, because thienodiazepinethione derivatives such as **7a** would be more reactive than **8a** to perform a rearrangement to form **6a** with Lewis acids as catalysts. The rule of 'hard-soft acid-base' should provide a good answer, as it is well known that the donor atom, S, is of lower electronegativity and higher polarizability than the donor atom, O. Hence, the thiol group will bound more tightly to the soft metal ions of the common used Lewis acids, which will facilitate the rearrangement of **7a**. Moreover, thieno-

SYNTHESIS 2014, 46, 2317–2326
Advanced online publication: 12.06.2014
DOI: 10.1055/s-0033-1339138; Art ID: ss-2014-f0184-op



Scheme 2 Two routes of retrosynthesis of representative compound **5a**

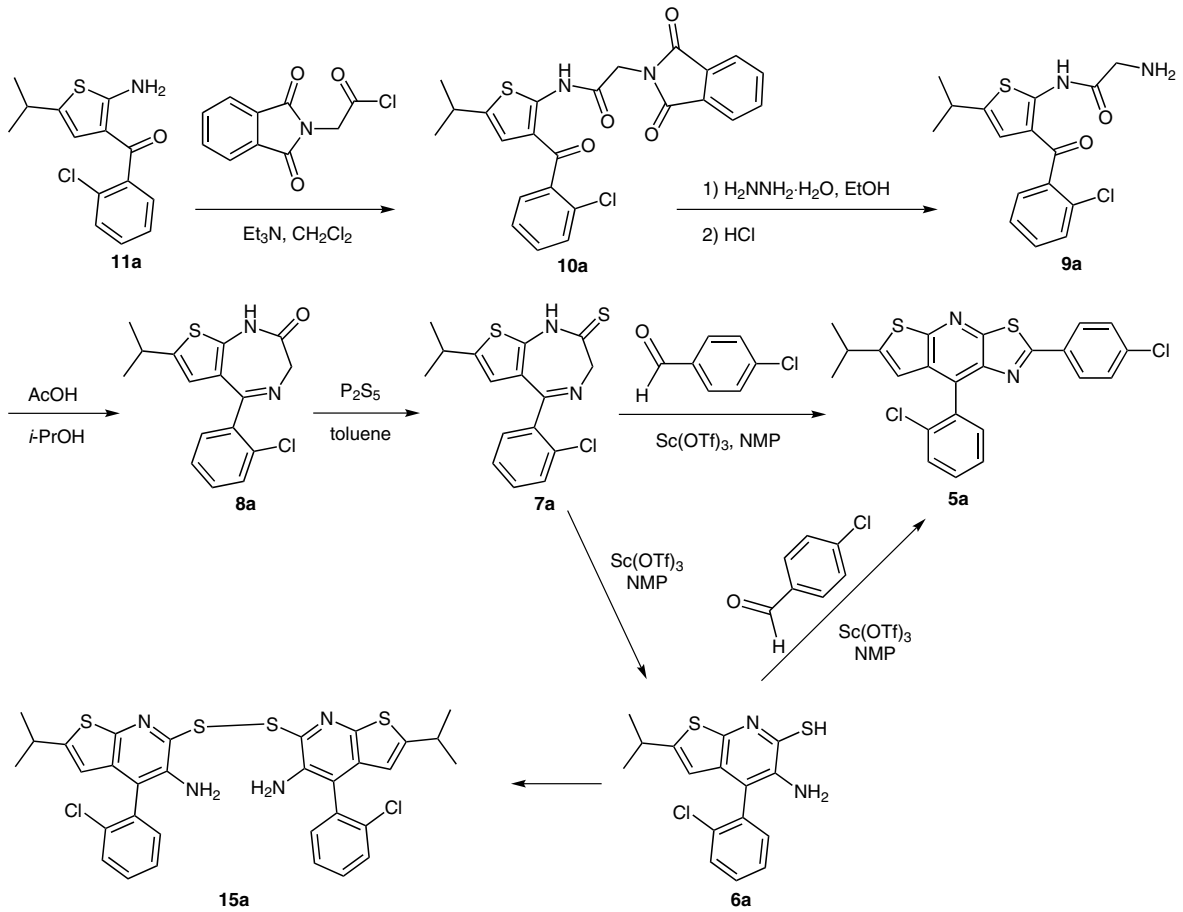
diazepinethione **7a** could be easily provided from the reaction of the corresponding thienodiazepinone **8a** with phosphorus pentasulfide[12] or Lawesson's reagent.[13] Accordingly, **6a** could react with various aldehydes to provide the desired thiazolo[5,4-*b*]thieno[3,2-*e*]pyridine derivatives.

To overcome the obvious drawback of path B (that is, largely using anhydrous pyridine at reflux) and to challenge a novel type of rearrangement, we carried out the reaction according to the path A (Scheme 3).

As expected, **8a** was readily prepared according to the reported method with slight modification (using morpholine as base instead of triethylamine) from 3-(2-chlorophenyl)-3-oxopropanenitrile in four steps with a total yield of 23%.[12c] It is intriguing that a rearrangement similar to that in literature[11] did not take place on treatment of **8a** with manganese(III) acetate in glacial acetic acid. After sulfuration of **8a** with phosphorus pentasulfide, compound **7a** was obtained in 90% isolated yield. Unfortunately, only a small amount of 5-amino-4-(2-chlorophenyl)-2-isopropylthieno[2,3-*b*]pyridine-6-thiol (**6a**) was obtained when **7a** was treated with manganese(III) acetate in glacial acetic acid. Otherwise, some byproducts (e.g., **15a**) appeared, which encouraged us to pursue a more concise and straightforward route (i.e., a one-pot route with treatment by 4-chlorobenzaldehyde) directly toward our target compound **5a**. In this case, **5a** was successfully obtained from **7a** on reaction with 4-chlorobenzaldehyde in 39% isolated yield. This encouraging result led us to screen other Lewis acids [e.g., $CuSO_4$, $Bi(OTf)_3$, $Sc(OTf)_3$, $AlCl_3$ and $TiCl_4$] and we found that scandium(III) triflate was the best choice because of its efficacy and water tolerance;[14] we obtained **5a** in 60% isolated yield at 150 °C in *N*,*N*-dimethylformamide. In addition to **5a**, we also obtained an interesting byproduct **5b**, which thought to arise from the reaction of **6a** with *N*,*N*-dimethylformamide, although the mechanism is not clear. To overcome this drawback, the use of other solvents was examined and finally *N*-methylpyrrolidin-2-one was identified as the best choice. As shown in Table 1, using *N*-methylpyrrolidin-2-one as the solvent gave a faster reaction rate and the isolated yield was up to 80%.

To explore the scope of the one-pot reaction, a variety of aldehydes were tested under the optimized reaction conditions [i.e., thienodiazepinethione (0.3 mmol), aldehyde (0.6 mmol), $Sc(OTf)_3$ (1 mol%), NMP (2 mL), 150 °C]. As shown in Table 1, arylaldehydes with electron-donating (entries 5–8) or also electron-withdrawing substituents (entries 9–11) afforded the desired products **5e**–**k** in very good yields. Furthermore, an *ortho*-substituted arylaldehyde (entry 12) resulting in a good outcome indicated no obvious stereohindrance effect. More importantly, heteroarylaldehydes performed the reaction very well (entries 13 and 14), which would lead to important bioactive molecules. In the example of an alkylaldehyde, interestingly, the desired product **5c** was also obtained in very good yield comparable to their aromatic counterparts (entry 3).

To understand further the one-pot reaction, especially to confirm the intermediate **6a**, we ran the model reaction



Scheme 3 One-pot and stepwise synthesis of **5a**

without the addition of 4-chlorobenzaldehyde under the optimized conditions. After the complete consumption of **7a** as shown by TLC, **6a** was isolated and identified (EI, ^{1}H NMR and HRMS). It is hardly surprising that ^{13}C NMR analysis indicated some level of conversion of **6a** to **15a**, which was also found in the reaction mixture as a by-product; it is well known that its analogues, 2-aminobenzenethiols, are readily transformed into diaryl disulfide.[15] Considering its HRMS analysis result {HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{32}H_{28}Cl_2N_4S_4$: 666.0568; found: 666.0570}, the byproduct was thought to be **15a**. Further, tandem mass analysis was applied to unequivocally identify the structure of **15a**. Moreover, **6a** reacted with 4-chlorobenzaldehyde to afford **5a** in 70% isolated yield. Hence, all evidence pointed to **6a** as the product of this rearrangement, which was readily oxidized to **15a**.

It should be noted that we have successfully synthesized two other thiazolo[5,4-*b*]thieno[3,2-*e*]pyridine derivatives **5o**,**p** (entries 15 and 16) using this novel protocol, replacing the isopropyl group by a phenyl group and also the 2-chlorophenyl group by a phenyl group in good yields from readily available starting materials. This result partially confirmed our protocol to be useful for the preparation of a variety of thiazolothienopyridine derivatives.

We confirmed the structure of the target products by X-ray single crystal diffraction techniques because not enough information could be drawn from NMR spectra. Hence, the structure of **5a** was determined by using X-ray single crystal diffraction (Figure 1), MS, and NMR techniques, while the structures of its analogues were identified only by MS and NMR techniques.

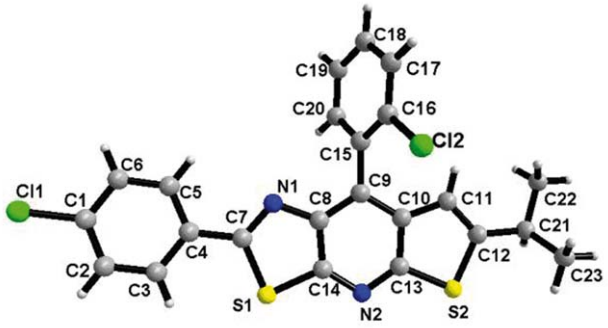
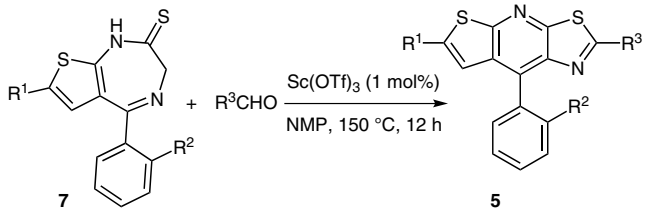


Figure 1 Single crystal structure of **5a**[16]

Considering these compounds containing a linear polycyclic aromatic moiety, which might be a toxicophore due to its potent cytotoxicity, we selected compound **5a** and **5b** for cytotoxicity assay with the MTT method on the HEK293 cell line. The preliminary tests indicated that

Table 1 The Reactions and Isolate Yields of Thienodiazepinethiones with Different Aldehydes



Entry	R^1	R^2	R^3	Product	Yield (%)
1	*i*-Pr	Cl	4-ClC_6H_4	**5a**	79
2	*i*-Pr	Cl	H	**5b**	58
3	*i*-Pr	Cl	*i*-Bu	**5c**	67
4	*i*-Pr	Cl	Ph	**5d**	66
5	*i*-Pr	Cl	4-MeC_6H_4	**5e**	83
6	*i*-Pr	Cl	4-$MeOC_6H_4$	**5f**	74
7	*i*-Pr	Cl	4-HOC_6H_4	**5g**	91
8	*i*-Pr	Cl	4-*i*-PrC_6H_4	**5h**	74
9	*i*-Pr	Cl	4-$F_3CC_6H_4$	**5i**	67
10	*i*-Pr	Cl	4-NCC_6H_4	**5j**	70
11	*i*-Pr	Cl	4-AcC_6H_4	**5k**	70
12	*i*-Pr	Cl	2-ClC_6H_4	**5l**	66
13	*i*-Pr	Cl	2-furyl	**5m**	72
14	*i*-Pr	Cl	2-thienyl	**5n**	77
15	*i*-Pr	H	4-ClC_6H_4	**5o**	70
16	Ph	Cl	4-ClC_6H_4	**5p**	52

these compounds do not show obvious cytotoxicity even at the concentration of 250 μg/mL.

We have developed an effective one-pot method based on a novel rearrangement reaction for the construction of novel thiazolo[5,4-*b*]thieno[3,2-*e*]pyridine derivatives. Their structure was confirmed by using X-ray single crystal diffraction, MS, and NMR techniques. This novel tricyclic heteroaromatic family is expected to be attractive to medicinal chemists and material scientists.

All reagents were purchased from commercial sources and used without further treatment, unless otherwise indicated. Toluene was treated with metal Na; CH_2Cl_2 was dried with molecular sieves (4 Å) and the others reagents were used as received. Flash column chromatography was performed on silica gel (200–300 mesh). TLC was carried out with Merck silica gel GF_{254} plates. ^1H NMR and ^{13}C NMR spectra were recorded at r.t. on a Mercury-Plus 300, a Bruker Avance 400 and a Bruker Avance 500 instrument with TMS as an internal reference. LC/MS was run on a LCMS-2010A or a LCQ DECA XP instrument. MS/MS was run on a LCQ DECA XP instrument. EI mass spectra were recorded on the Thermo DSQ mass spectrometer. HRMS were performed on a Thermo MAT95XP mass spectrometer or a Bruck APEX IV mass spectrometer. IR spectra were recorded on an EQUINOX 55 Fourier transformation infrared spectrophotometer coupled with an infrared microscope. Single-crystal X-ray diffraction data was collected at 150(2) K on an Agilent Technologies Gemini a Ultra system, with Cu-Kα radiation (λ = 1.54178 Å). Melting points were determined on a WRS-1B digital melting point apparatus and are uncorrected.

(2-Aminothiophen-3-yl)(phenyl)methanone Derivatives 11; General Procedure 1 (GP-1)

To a 30-mL vial was added nitrile (1.0 equiv), sulfur (1.0 equiv), aldehyde (1.0 equiv), morpholine (1.0 equiv), and EtOH (1.0 M) and the vial was sealed. The reaction was stirred in an oil bath at 100 °C for 6 h. The mixture was cooled to r.t., and then it was diluted by EtOAc (200 mL). The organic phase was washed with H_2O (3 × 40 mL) and brine, dried (anhyd Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel) to afford the desired compound.

(2-Amino-5-isopropylthiophen-3-yl)(2-chlorophenyl)methanone (11a)

According to GP-1 using 3-(2-chlorophenyl)-3-oxopropanenitrile (1.8 g, 10 mmol), sulfur (320 mg, 10 mmol), 3-methylbutanal (860 mg, 10 mmol), and morpholine (870 mg, 10 mmol) in EtOH (10 mL) gave **11a** (2.2 g, 78%) as a yellow oil.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.24 (m, 6 H, H_{Ar}, NH_2), 6.05 (s, 1 H, H_{Ar}), 2.81 (sept, *J* = 6.8 Hz, 1 H, CH), 1.15 (d, *J* = 6.8 Hz, 6 H, 2 CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 188.6, 166.1, 140.6, 133.7, 130.7, 130.4, 130.1, 128.6, 126.8, 120.2, 114.9, 29.9, 24.4.

MS (EI): *m*/*z* (%) = 279 (55) [M^+], 281 (20) [M + 2]$^+$, 264 (100).

(2-Amino-5-isopropylthiophen-3-yl)(phenyl)methanone (11b)

According to GP-1 using 3-oxo-3-phenylpropanenitrile (1.45 g, 10 mmol), sulfur (320 mg, 10 mmol), 3-methylbutanal (860 mg, 10 mmol), and morpholine (870 mg, 10 mmol) in EtOH (10 mL) gave **11b** (1.8 g, 75%) as a yellow oil.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.67–7.64 (m, 2 H, H_{Ar}), 7.50–7.40 (m, 3 H, H_{Ar}), 6.93 (br s, 2 H, NH_2), 6.51 (s, 1 H, H_{Ar}), 2.92 (sept, *J* = 6.8 Hz, 1 H, CH), 1.23 (d, *J* = 6.8 Hz, 6 H, 2 CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.0, 165.1, 141.3, 133.4, 130.7, 128.3, 128.2, 121.0, 114.6, 30.0, 24.5.

MS (EI): *m*/*z* (%) = 245 (55) [M^+], 230 (100).

(2-Amino-5-phenylthiophen-3-yl)(2-chlorophenyl)methanone (11c)

According to GP-1 using 3-(2-chlorophenyl)-3-oxopropanenitrile (1.8 g, 10 mmol), sulfur (320 mg, 10 mmol), 2-phenylacetaldehyde (1.2 g, 10 mmol), and morpholine (870 mg, 10 mmol) in EtOH (10 mL) gave **11c** (2.0 g, 65%) as a yellow solid; mp 165–166 °C.

IR (KBr): 3393, 3283, 3059, 1578, 1551, 1454, 1427, 1273, 1200, 1155, 1053, 1028, 941, 759, 692, 646, 611, 491, 454 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.44 (m, 1 H, H_{Ar}), 7.42–7.37 (m, 2 H, H_{Ar}), 7.37–7.33 (m, 2 H, H_{Ar}), 7.33–7.30 (m, 2 H, H_{Ar}), 7.29–7.27 (m, 1 H, H_{Ar}), 7.23–7.15 (m, 3 H, H_{Ar}, NH_2), 6.68 (s, 1 H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 189.3, 166.1, 140.2, 133.8, 130.8, 130.7, 130.2, 129.0, 128.6, 127.1, 126.9, 125.0, 124.6, 122.3, 116.9.

MS (EI): *m*/*z* (%) = 313 (100) [M^+], 315 (40) [M + 2]$^+$, 278 (85).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{17}H_{12}ONClS$: 313.0323; found: 313.0324.

***N*-[3-(2-Chlorobenzoyl)-5-isopropylthiophen-2-yl]-2-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)acetamide (10a); Typical Procedure**

To a 30-mL vial was added *N*-phthaloylglycine (2.05 g, 10 mmol) and $SOCl_2$ (8 mL) and the vial was sealed. The reaction was stirred in an oil bath at 60 °C for 8 h. The mixture was cooled to r.t., the

$SOCl_2$ was removed in vacuo, hexane (10 mL) was added, and the mixture was stirred for 10 min resulting in white solid. After filtration, the solid (2.0 g, 90%) was washed with hexane and used directly in the next reaction. Phthaloylglycyl chloride (2.0 g, 9.0 mmol) in CH_2Cl_2 (8 mL) was added dropwise to the solution of **11a** (2.2 g, 7.9 mmol) and Et_3N (3.0 mL) in CH_2Cl_2 (50 mL). The mixture was stirred at r.t. until completion of the reaction, then diluted with CH_2Cl_2 (150 mL). The organic phase was washed with H_2O (3 × 40 mL) and brine, dried (anhyd Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel) to afford **10a** (3.2 g, 89%) as a yellowish solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.19 (br s, 1 H, NH), 7.92–7.84 (m, 2 H, H_{Ar}), 7.76–7.69 (m, 2 H, H_{Ar}), 7.45–7.30 (m, 4 H, H_{Ar}), 6.34 (s, 1 H, H_{Ar}), 4.70 (s, 2 H, CH_2), 2.96 (sept, *J* = 6.8 Hz, 1 H, CH), 1.21 (d, *J* = 6.8 Hz, 6 H, 2 CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.4, 167.6, 164.3, 149.1, 143.4, 139.3, 134.5, 132.2, 131.2, 130.8, 130.3, 128.6, 126.9, 123.9, 121.1, 119.8, 41.2, 29.9, 24.6.

MS (ESI$^+$): *m*/*z*: 489 (80) $[M + Na]^+$, 491 (30) $[M + 2 + Na]^+$, 521 (100) $[M + MeOH + Na]^+$.

N-(3-Benzoyl-5-isopropylthiophen-2-yl)-2-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)acetamide (10b)

Following the typical procedure for **10a** gave **10b** (2.9 g, 90%) as a yellow solid; mp 209–210 °C.

IR (KBr): 3432, 2961, 1778, 1720, 1617, 1531, 1422, 1395, 1325, 1241, 1171, 1114, 952, 814, 739, 707, 662 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.33 (br s, 1 H, NH), 7.91–7.88 (m, 2 H, H_{Ar}), 7.75–7.72 (m, 2 H, H_{Ar}), 7.68–7.65 (m, 2 H, H_{Ar}), 7.56–7.44 (m, 3 H, H_{Ar}), 6.75 (s, 1 H, H_{Ar}), 4.68 (s, 2 H, CH_2), 3.03 (sept, *J* = 6.8 Hz, 1 H, CH), 1.27 (d, *J* = 6.8 Hz, 6 H, 2 CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.9, 167.6, 164.1, 148.8, 143.1, 139.9, 134.4, 132.2, 131.8, 128.7, 128.5, 123.9, 120.6, 120.4, 41.2, 30.0, 24.7.

MS (EI): *m*/*z* (%) = 432 (55) $[M^+]$, 230 (100), 160 (70), 245 (65).

HRMS (EI): *m*/*z* $[M^+]$ calcd for $C_{24}H_{20}O_4N_2S$: 432.1138; found: 432.1139.

N-[3-(2-Chlorobenzoyl)-5-phenylthiophen-2-yl]-2-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)acetamide (10c)

Following the typical procedure for **10a** gave **10c** (2.8 g, 90%) as a yellow solid; mp 201–202 °C.

IR (KBr): 3430, 1777, 1722, 1616, 1546, 1526, 1470, 1416, 1392, 1319, 1271, 1234, 1197, 1157, 1110, 1086, 1037, 949, 848, 815, 756, 713, 693, 648 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.27 (br s, 1 H, NH), 7.94–7.91 (m, 2 H, H_{Ar}), 7.77–7.75 (m, 2 H, H_{Ar}), 7.50–7.38 (m, 6 H, H_{Ar}), 7.33–7.28 (m, 2 H, H_{Ar}), 7.24–7.21 (m, 1 H, H_{Ar}), 6.88 (s, 1 H, H_{Ar}), 4.75 (s, 2 H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.6, 167.5, 164.4, 150.1, 138.9, 134.4, 134.4, 133.1, 132.0, 131.23, 130.7, 130.3, 129.0, 128.5, 127.8, 126.8, 125.6, 123.8, 122.3, 120.9, 40.9.

MS (EI): *m*/*z* (%) = 500 (45) $[M^+]$, 502 (15) $[M + 2]^+$, 313 (70), 160 (100).

HRMS (EI): *m*/*z* $[M^+]$ calcd for $C_{27}H_{17}O_4N_2ClS$: 500.0592; found: 500.0591.

2-Amino-*N*-[3-(2-chlorobenzoyl)-5-isopropylthiophen-2-yl]acetamide (9a); Typical Procedure

In a 250-mL round bottom flask, **10a** was dispersed in EtOH (150 mL) and cooled by an ice bath. Hydrazine hydrate (430 mg, 2 equiv) was added dropwise and the reaction was stirred for 8 h then allowed to warm to r.t. HCl (36%, 2.5 mL) was added and the mixture stirred at r.t. for 2 h. The insoluble mass was filtered off and the filtrate was neutralized with sat. aq $NaHCO_3$. After removal of solvent, CH_2Cl_2 (200 mL) was added to the residue and the organic phase was washed with H_2O (3 × 40 mL) and brine, dried (anhyd Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel) to afford **9a** (1.4 g, 61%) as a yellow solid.

IR (KBr): 3400, 3340, 3230, 3060, 2970, 2910, 1680, 1640, 1510, 1430, 1310, 1230, 1160, 1080, 1030, 945, 810, 762, 696, 644, 590, 434 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.84 (br s, 1 H, NH), 7.47–7.32 (m, 4 H, H_{Ar},), 6.36 (s, 1 H, H_{Ar}), 3.66 (s, 2 H, CH_2), 3.00 (sept, *J* = 6.8 Hz, 1 H, CH), 1.80 (br s, 2 H, NH_2), 1.26 (d, *J* = 6.8 Hz, 6 H, 2 CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.7, 171.5, 148.9, 142.5, 139.7, 130.8, 130.7, 130.8, 128.5, 126.7, 120.9, 119.8, 45.0, 29.8, 24.5.

MS (EI): *m*/*z* (%) = 336 (10) $[M^+]$, 338 (3) $[M + 2]^+$, 264 (100).

2-Amino-*N*-(3-benzoyl-5-isopropylthiophen-2-yl)acetamide (9b)

Following the typical procedure for **9a** gave **9b** (1.2 g, 60%) as a yellow solid; mp 88–89 °C.

IR (KBr): 3411, 3194, 2964, 1677, 1608, 1522, 1450, 1411, 1363, 1307, 1273, 1241, 1162, 1061, 1020, 803, 736, 710, 662 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.87 (br s, 1 H, NH), 7.74–7.71 (m, 2 H, H_{Ar}), 7.57–7.44 (m, 3 H, H_{Ar}), 6.77 (s, 1 H, H_{Ar}), 3.67 (s, 2 H, CH_2), 3.07 (sept, *J* = 6.8 Hz, 1 H, CH), 1.97 (br s, 2 H, NH_2), 1.31 (d, *J* = 6.8 Hz, 6 H, 2 CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.4, 171.2, 148.5, 142.3, 140.0, 131.6, 128.6, 128.3, 120.3, 120.3, 44.8, 29.6, 24.4.

MS (EI): *m*/*z* (%) = 302 (10) $[M^+]$, 230 (100).

HRMS (EI): *m*/*z* $[M^+]$ calcd for $C_{16}H_{18}O_2N_2S$: 302.1084; found: 302.1083.

2-Amino-*N*-[3-(2-chlorobenzoyl)-5-phenylthiophen-2-yl]acetamide (9c)

Following the typical procedure for **9a** gave **9c** (1.0 g, 50%) as a yellow solid; mp 147–148 °C.

IR (KBr): 3412, 3171, 1718, 1679, 1620, 1539, 1506, 1428, 1409, 1290, 1238, 1161, 1080, 1036, 941, 799, 754, 692, 641, 478 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.99 (br s, 1 H, NH), 7.49–7.47 (m, 3 H, H_{Ar}), 7.42–7.36 (m, 3 H, H_{Ar}), 7.34–7.29 (m, 2 H, H_{Ar}), 7.23–7.21 (m, 1 H, H_{Ar}), 6.89 (s, 1 H, H_{Ar}), 3.70 (s, 2 H, CH_2), 1.78 (br s, 2 H, NH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.0, 171.9, 150.1, 139.5, 133.6, 133.5, 131.1, 130.7, 130.2, 128.9, 128.5, 127.6, 126.8, 125.60, 122.2, 121.1, 44.8.

MS (EI): *m*/*z* (%) = 370 (20) $[M^+]$, 372 (7) $[M + 2]^+$, 337 (45), 313 (100), 139 (88).

HRMS (EI): *m*/*z* $[M^+]$ calcd for $C_{19}H_{15}O_2N_2ClS$: 370.0537; found: 370.0535.

5-(2-Chlorophenyl)-7-isopropyl-1,3-dihydro-2*H*-thieno[2,3-*e*][1,4]diazepin-2-one (8a); Typical Procedure

To a 30-mL vial was added **9a** (1.4 g, 4.4 mmol), AcOH (800 mg), and *i*-PrOH (6 mL) and the vial was sealed. The reaction was stirred in an oil bath at 70 °C for 8 h. The mixture was cooled to r.t., CH_2Cl_2 (150 mL) was added, and the organic solvent was washed with sat. aq $NaHCO_3$ (3 × 40 mL) and H_2O, brine, dried (anhyd Na_2SO_4), and concentrated in vacuo. The residue was crystallized (EtOAc) to give **8a** (0.85 g, 61%) as a yellowish solid.

IR (KBr): 3180, 3080, 2960, 1670, 1550, 1500, 1430, 1350, 1230, 1200, 1010, 982, 877, 833, 754, 631, 582, 523, 461 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.61 (br s, 1 H, NH), 7.45–7.27 (m, 4 H, H_{Ar}), 6.18 (s, 1 H, H_{Ar}), 4.49 (s, 2 H, CH_2), 2.98 (sept, *J* = 6.8 Hz, 1 H, CH), 1.23 (d, *J* = 6.8 Hz, 6 H, 2 CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.2, 166.6, 145.1, 142.6, 138.3, 133.0, 130.7, 130.4, 129.9, 126.8, 126.3, 120.1, 57.6, 30.1, 24.5.

MS (EI): *m*/*z* (%) = 318 (85) [M^+], 320 (30) [M + 2]$^+$, 289 (100), 275 (65).

7-Isopropyl-5-phenyl-1,3-dihydro-2*H*-thieno[2,3-*e*][1,4]diazepin-2-one (8b)
Following the typical procedure for **8a** gave **8b** (677 mg, 60%) as a yellow solid; mp 188–189 °C.

IR (KBr): 3430, 3095, 2964, 1677, 1592, 1546, 1495, 1368, 1226, 1058, 1007, 873, 773, 723, 700 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.53 (br s, 1 H, NH), 7.62–7.59 (m, 2 H, H_{Ar}), 7.42–7.34 (m, 3 H, H_{Ar}), 6.47 (s, 1 H, H_{Ar}), 4.42 (s, 2 H, CH_2), 3.03 (sept, *J* = 6.7 Hz, 1 H, CH), 1.27 (d, *J* = 6.8 Hz, 6 H, 2 CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.4, 167.4, 144.9, 143.4, 138.8, 130.5, 129.5, 128.4, 126.3, 121.4, 57.8, 30.3, 24.7.

MS (EI): *m*/*z* (%) = 284 (95) [M^+], 255 (100), 241 (50), 149 (60).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{16}H_{16}ON_2S$: 284.0978; found: 284.0977.

5-(2-Chlorophenyl)-7-phenyl-1,3-dihydro-2*H*-thieno[2,3-*e*][1,4]diazepin-2-one (8c)
Following the typical procedure for **8a** gave **8c** (523 mg, 55%) as a yellow solid; mp 219–220 °C.

IR (KBr): 3180, 3097, 2925, 1677, 1596, 1550, 1504, 1478, 1434, 1374, 1339, 1253, 1219, 1076, 1045, 1006, 948, 908, 875, 841, 795, 757, 735, 692, 520 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.22 (br s, 1 H, NH), 7.53–7.20 (m, 9 H, H_{Ar}), 7.13–7.08 (m, 1 H, H_{Ar}), 4.33 (s, 2 H, CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.7, 171.3, 139.6, 139.1, 131.9, 131.5, 130.5, 129.9, 128.4, 127.4, 123.5, 121.5, 57.1.

MS (EI): *m*/*z* (%) = 352 (60) [M^+], 354 (20) [M + 2]$^+$, 323 (100).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{19}H_{13}ON_2ClS$: 352.0432; found: 352.0430.

5-(2-Chlorophenyl)-7-isopropyl-1,3-dihydro-2*H*-thieno[2,3-*e*][1,4]diazepine-2-thione (7a);[10e,12c] Typical Procedure
Compound **8a** (300 mg), P_2S_5 (1.5 g), and toluene (30 mL) were added to a three-necked round-bottom flask under a N_2 atmosphere. The mixture was stirred under reflux for 16 h. After removal of the solvent, sat. aq $NaHCO_3$ (30 mL) was added to the residue and the mixture was stirred for 3 h. Filtration and washing with H_2O gave **7a** (270 mg, 90%) as a yellow solid; mp 175–176 °C.

IR (KBr): 3442, 3129, 3064, 2960, 2925, 2867, 1924, 1594, 1562, 1483, 1434, 1348, 1315, 1168, 1078, 1037, 991, 808, 781, 738, 655, 603, 460 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53–7.29 (m, 4 H, H_{Ar}), 6.23 (s, 1 H, H_{Ar}), 4.91 (s, 2 H, CH_2), 3.02 (sept, *J* = 6.6 Hz, 1 H, CH), 1.25 (d, *J* = 6.8 Hz, 6 H, 2 CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.7, 166.7, 146.7, 144.4, 137.5, 133.3, 131.2, 131.1, 130.2, 128.5, 127.1, 120.9, 64.3, 30.3, 24.6.

MS (EI): *m*/*z* (%) = 334 (80) [M^+], 336 (30) [M + 2]$^+$, 319 (100).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{16}H_{15}N_2ClS_2$: 334.0360; found: 334.0361.

7-Isopropyl-5-phenyl-1,3-dihydro-2*H*-thieno[2,3-*e*][1,4]diazepine-2-thione (7b)
Following the typical procedure for **7a** gave **7b** (657 mg, 92%) as a yellow solid; mp 162–163 °C.

IR (KBr): 3436, 3130, 3094, 3033, 2963, 1592, 1557, 1519, 1482, 1448, 1355, 1314, 1285, 1234, 1193, 1166, 1077, 1054, 1028, 993, 875, 809, 763, 717, 697, 674, 599, 549 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61–7.59 (m, 2 H, H_{Ar}), 7.46–7.39 (m, 3 H, H_{Ar}), 6.52 (s, 1 H, H_{Ar}), 4.83 (s, 2 H, CH_2), 3.06 (sept, *J* = 6.9 Hz, 1 H, CH), 1.30 (d, *J* = 6.7 Hz, 6 H, 2 CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 195.7, 165.0, 145.7, 139.8, 133.7, 131.0, 130.8, 129.1, 128.3, 121.6, 65.2, 29.5, 24.5.

MS (EI): *m*/*z* (%) = 300 (75) [M^+], 299 (100).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{16}H_{16}N_2S_2$: 300.0749; found: 300.0748.

5-(2-Chlorophenyl)-7-phenyl-1,3-dihydro-2*H*-thieno[2,3-*e*][1,4]diazepine-2-thione (7c)
Following the typical procedure for **7a** gave **7c** (492 mg, 90%) as a brown solid; mp 199–200 °C.

IR (KBr): 3397, 1608, 1567, 1493, 1473, 1434, 1380, 1352, 1317, 1164, 1076, 1037, 999, 948, 843, 809, 757, 710, 691, 655 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.45 (br s, 1 H, NH), 7.58–7.57 (m, 1 H, H_{Ar}), 7.42–7.35 (m, 6 H, H_{Ar}), 7.24–7.13 (m, 3 H, H_{Ar}), 4.56 (s, 2 H, CH_2).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 200.6, 171.0, 169.8, 140.6, 140.2, 139.7, 139.3, 132.2, 131.5, 131.3, 131.0, 129.9, 128.9, 128.4, 125.0, 122.1, 64.7.

MS (EI): *m*/*z* (%) = 368 (100) [M^+], 370 (40) [M + 2]$^+$, 333 (85).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{19}H_{13}N_2ClS_2$: 368.0203; found: 368.0202.

5-Amino-4-(2-chlorophenyl)-2-isopropylthieno[2,3-*b*]pyridine-6-thiol (6a)
To a 10-mL vial was added **7a** (100 mg, 0.3 mmol), $Sc(OTf)_3$ (1.5 mg, 0.003 mmol), and NMP (2.0 mL) and the vial was sealed. The reaction was stirred in an oil bath preheated to 150 °C for 12 h. The mixture was cooled to r.t., and it was dilute with EtOAc (120 mL). The organic phase was washed with sat. aq NH_4Cl (3 × 30 mL), H_2O, and brine, dried (anhyd Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel) to afford crude **6a** (36 mg, 36%) as a yellow solid; mp 143–144 °C.

IR (KBr): 3450, 3350, 3190, 3050, 2960, 2920, 2850, 1720, 1600, 1510, 1430, 1350, 1290, 1120, 1050, 827, 750, 698, 638, 594, 451 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59–7.56 (m, 1 H, H_{Ar}), 7.43–7.40 (m, 2 H, H_{Ar}), 7.32–7.28 (m, 1 H, H_{Ar}), 6.26 (s, 1 H, H_{Ar}), 3.12 (sept, *J* = 6.9 Hz, 1 H, CH), 1.31 (d, *J* = 6.8 Hz, 6 H, 2 CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.9, 156.8, 150.4, 138.6, 138.5, 133.7, 131.5, 131.4, 130.4, 130.2, 127.7, 127.6, 114.4, 31.3, 24.1, 24.0.

MS (EI): *m*/*z* (%) = 334 (90) [M^+], 336 (40) [M + 2]$^+$, 319 (100).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{16}H_{15}N_2ClS_2$: 334.0360; found: 334.0361.

Thiazolo[5,4-*b*]thieno[3,2-*e*]pyridine Derivatives 5a–n; General Procedure 2 (GP-2)
To a 10-mL vial was added compound **7a** (100 mg, 0.3 mmol), $Sc(OTf)_3$ (1.5 mg, 0.003 mmol), aldehyde (0.6 mmol), and NMP (2.0 mL) and the vial was sealed. The reaction was stirred in an oil bath preheated to 150 °C for 12 h. The mixture was cooled to r.t., and it was dilute with EtOAc (120 mL). The organic phase was washed with sat. aq NH_4Cl (3 × 30 mL), water, and brine, dried (anhyd Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel) to afford the desired compound.

8-(2-Chlorophenyl)-2-(4-chlorophenyl)-6-isopropylthiazolo[5,4-*b*]thieno[3,2-*e*]pyridine (5a)

From **7a**: According to GP-2 using **7a** and 4-chlorobenzaldehyde (84 mg, 0.6 mmol) gave **5a** (108 mg, 79%) as a white solid; mp 152–153 °C.

From **6a**: To 10-mL vial was added **6a** (36 mg, 0.108 mmol), $Sc(OTf)_3$ (0.5 mg, 0.001 mmol), 4-chlorobenzaldehyde (30 mg, 0.216 mmol), and NMP (2.0 mL) and the vial was sealed. The reaction was stirred in an oil bath preheated to 150 °C for 12 h. The mixture was cooled to r.t., it was dilute with EtOAc (50 mL). The organic phase was washed with sat. aq NH_4Cl (3 × 15 mL), H_2O, and brine, dried (anhyd Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel) to afford **5a** (34 mg, 70%) as a white solid.

IR (KBr): 3053, 3021, 2965, 2894, 2869, 1552, 1519, 1477, 1315, 1283, 1211, 1179, 1038, 958, 948, 811, 734, 706 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 8.6 Hz, 2 H, H_{Ar}), 7.65–7.59 (m, 1 H, H_{Ar}), 7.54–7.43 (m, 3 H, H_{Ar}), 7.38 (d, *J* = 8.6 Hz, 2 H, H_{Ar}), 6.73 (s, 1 H, H_{Ar}), 3.24 (sept, *J* = 6.8 Hz, 1 H, CH), 1.40 (d, *J* = 6.8 Hz, 6 H, 2 CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.2, 159.5, 155.6, 154.9, 143.2, 137.5, 134.7, 133.8, 132.5, 132.1, 131.7, 130.1, 129.3, 129.0, 126.7, 115.5, 31.7, 24.4, 24.4.

MS (EI): *m*/*z* (%) = 454 (75) $[M^+]$, 456 (50) $[M + 2]^+$, 439 (100), 419 (95), 202 (70).

HRMS (EI): *m*/*z* $[M^+]$ calcd for $C_{23}H_{16}N_2Cl_2S_2$: 454.0126; found: 454.0127.

8-(2-Chlorophenyl)-6-isopropylthiazolo[5,4-*b*]thieno[3,2-*e*]pyridine (5b)

From **7a** *in NMP*: According to GP-2 using **7a** and paraformaldehyde (54 mg, 0.6 mmol) in NMP (2 mL) gave **5b** (60 mg, 58%) as a yellow oil.

From **7a** *in DMF*: According to GP-2 using **7a** and 4-chlorobenzaldehyde (84 mg, 0.6 mmol) in DMF (2 mL) gave **5b** (31 mg, 30%) as a byproduct as a yellow oil.

IR (KBr): 3063, 2963, 2926, 2869, 1720, 1671, 1549, 1452, 1303, 1281, 1052, 871, 835, 749, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 9.03 (s, 1 H, CH), 7.67–7.56 (m, 1 H, H_{Ar}), 7.52–7.42 (m, 3 H, H_{Ar}), 6.73 (s, 1 H, H_{Ar}), 3.25 (sept, *J* = 6.8 Hz, 1 H, CH), 1.40 (d, *J* = 6.8 Hz, 6 H, 2 CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.3, 155.4, 154.3, 154.0, 141.8, 135.2, 134.5, 133.6, 131.6, 131.5, 130.4, 130.3, 127.0, 115.3, 31.7, 24.4, 24.3.

MS (EI): *m*/*z* (%) = 344 (55) $[M^+]$, 346 (25) $[M + 2]^+$, 329 (100), 309 (65).

HRMS (EI): *m*/*z* $[M^+]$ calcd for $C_{17}H_{13}N_2ClS_2$: 344.0203; found: 344.0202.

8-(2-Chlorophenyl)-2-isobutyl-6-isopropylthiazolo[5,4-*b*]thieno[3,2-*e*]pyridine (5c)

According to GP-2 using **7a** and 3-methylbutanal (52 mg, 0.6 mmol) gave **5c** (80 mg, 67%) as a yellow oil.

IR (KBr): 2964, 2927, 2869, 1556, 1471, 1302, 1276, 1170, 1086, 1049, 879, 827, 754, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.62–7.55 (m, 1 H, H_{Ar}), 7.50–7.38 (m, 3 H, H_{Ar}), 6.68 (s, 1 H, H_{Ar}), 3.22 (sept, *J* = 6.8 Hz, 1 H, CH), 2.95 (d, *J* = 7.2 Hz, 2 H, CH_2), 2.26–2.17 (m, 1 H, CH), 1.38 (d, *J* = 6.8 Hz, 6 H, 2 CH_3), 1.02 (d, *J* = 6.6 Hz, 6 H, 2 CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.6, 158.8, 156.0, 154.4, 142.3, 134.9, 134.0, 133.8, 131.8, 131.2, 130.2, 130.1, 126.8, 115.4, 44.4, 31.7, 29.9, 24.5, 24.4, 22.7, 22.7.

MS (EI): *m*/*z* (%) = 400 (25) $[M^+]$, 402 (10) $[M + 2]^+$, 385 (30), 358 (100), 343 (25), 307 (25).

HRMS (EI): *m*/*z* $[M^+]$ calcd for $C_{21}H_{21}N_2ClS_2$: 400.0829; found: 400.0828.

8-(2-Chlorophenyl)-6-isopropyl-2-phenylthiazolo[5,4-*b*]thieno[3,2-*e*]pyridine (5d)

According to GP-2 using **7a** and benzaldehyde (64 mg, 0.6 mmol) gave **5d** (83 mg, 66%) as a yellow solid; mp 175–176 °C ($CHCl_3$–hexane).

IR (KBr): 2961, 2925, 2872, 1607, 1519, 1472, 1311, 1278, 1169, 1051, 960, 836, 803, 754, 699, 679 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.05–7.98 (m, 2 H, H_{Ar}), 7.66–7.58 (m, 1 H, H_{Ar}), 7.56–7.34 (m, 6 H, H_{Ar}), 6.74 (s, 1 H, H_{Ar}), 3.24 (sept, *J* = 6.8 Hz, 1 H, CH), 1.40 (d, *J* = 6.8 Hz, 6 H, 2 CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6, 159.3, 155.7, 154.7, 143.3, 134.8, 134.6, 134.0, 133.8, 132.2, 131.6, 131.4, 130.1, 130.1, 129.1, 127.9, 126.8, 115.6, 31.7, 24.5, 24.4.

MS (EI): *m*/*z* (%) = 420 (80) $[M^+]$, 422 (35) $[M + 2]^+$, 405 (95), 385 (100), 185 (85).

HRMS (EI): *m*/*z* $[M^+]$ calcd for $C_{23}H_{17}N_2ClS_2$: 420.0516; found: 420.0514.

8-(2-Chlorophenyl)-6-isopropyl-2-(*p*-tolyl)thiazolo[5,4-*b*]thieno[3,2-*e*]pyridine (5e)

According to GP-2 using **7a** and 4-tolualdehyde (72 mg, 0.6 mmol) gave **5e** (108 mg, 83%) as a yellow solid; mp 160–161 °C ($CHCl_3$–hexane).

IR (KBr): 2962, 2927, 2869, 1594, 1556, 1516, 1471, 1385, 1302, 1276, 1085, 1049, 827, 754 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.1 Hz, 2 H, H_{Ar}), 7.66–7.59 (m, 1 H, H_{Ar}), 7.57–7.42 (m, 3 H, H_{Ar}), 7.23 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 6.73 (s, 1 H, H_{Ar}), 3.24 (sept, *J* = 6.8 Hz, 1 H, CH), 2.40 (s, 3 H, CH_3), 1.40 (d, *J* = 6.8 Hz, 6 H, 2 CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7, 159.0, 155.8, 154.5, 143.3, 141.9, 134.8, 134.3, 133.8, 132.2, 131.5, 131.3, 130.1, 130.0, 129.8, 127.8, 126.7, 115.6, 31.7, 24.5, 24.4, 22.0.

MS (EI): *m*/*z* (%) = 434 (55) $[M^+]$, 436 (25) $[M + 2]^+$, 419 (70), 399 (100), 192 (60).

HRMS (EI): *m*/*z* $[M^+]$ calcd for $C_{24}H_{19}N_2ClS_2$: 434.0673; found: 434.0674.

8-(2-Chlorophenyl)-6-isopropyl-2-(4-methoxyphenyl)thiazolo[5,4-*b*]thieno[3,2-*e*]pyridine (5f)

According to GP-2 using **7a** and 4-methoxybenzaldehyde (81 mg, 0.6 mmol) gave **5f** (100 mg, 74%) as a yellow solid; mp 132–133 °C.

IR (KBr): 3056, 2960, 2923, 2852, 1604, 1551, 1518, 1474, 1308, 1281, 1210, 1173, 1050, 1021, 958, 829, 811, 757, 733, 698, 678 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.9 Hz, 2 H, H_{Ar}), 7.64–7.60 (m, 1 H, H_{Ar}), 7.55–7.42 (m, 3 H, H_{Ar}), 6.94 (d, *J* = 8.9 Hz, 2 H, H_{Ar}), 6.72 (s, 1 H, H_{Ar}), 3.85 (s, 3 H, CH_3), 3.23 (sept, *J* = 6.8 Hz, 1 H, CH), 1.39 (d, *J* = 6.8 Hz, 6 H, 2 CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 162.3, 158.8, 155.8, 154.5, 143.4, 134.9, 134.0, 133.8, 132.2, 131.4, 130.1, 129.9, 129.5, 126.9, 126.7, 115.5, 114.4, 55.6, 31.4, 24.3, 24.2.

MS (EI): *m*/*z* (%) = 450 (45) $[M^+]$, 452 (20) $[M + 2]^+$, 435 (55), 415 (100), 200 (55).

HRMS (EI): *m*/*z* $[M^+]$ calcd for $C_{24}H_{19}ON_2ClS_2$: 450.0622; found: 450.0623.

4-[8-(2-Chlorophenyl)-6-isopropylthiazolo[5,4-*b*]thieno[3,2-*e*]pyridin-2-yl]phenol (5g)

According to GP-2 using **7a** and 4-hydroxybenzaldehyde (73 mg, 0.6 mmol) gave **5g** (119 mg, 91%) as a white solid; mp 154–155 °C.

IR (KBr): 3060, 2961, 2929, 2869, 1607, 1474, 1278, 1168, 1051, 960, 835, 754, 700 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 8.5 Hz, 2 H, H_{Ar}), 7.64–7.55 (m, 1 H, H_{Ar}), 7.52–7.38 (m, 3 H, H_{Ar}), 6.82 (d, *J* = 8.5 Hz, 2 H, H_{Ar}), 6.70 (s, 1 H, H_{Ar}), 3.23 (sept, *J* = 6.7 Hz, 1 H, CH), 1.38 (d, *J* = 6.8 Hz, 6 H, 2 CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 159.4, 158.6, 155.4, 154.7, 143.5, 134.7, 134.3, 133.8, 132.0, 131.7, 130.1, 129.7, 126.8, 126.3, 116.2, 115.5, 31.4, 24.4, 24.2.

MS (EI): *m*/*z* (%) = 436 (85) $[M^+]$, 438 (40) $[M + 2]^+$, 421 (100), 401 (95), 193 (90).

HRMS (EI): *m*/*z* $[M^+]$ calcd for $C_{23}H_{17}ON_2ClS_2$: 436.0465; found: 436.0464.

8-(2-Chlorophenyl)-6-isopropyl-2-(4-isopropylphenyl)thiazolo[5,4-*b*]thieno[3,2-*e*]pyridine (5h)

According to GP-2 using **7a** and 4-isopropylbenzaldehyde (89 mg, 0.6 mmol) gave **5h** (102 mg, 74%) as a white solid; mp 108–109 °C.

IR (KBr): 3063, 3021, 2959, 2929, 2869, 1608, 1549, 1517, 1472, 1309, 1278, 1183, 1151, 961, 836, 754, 732, 700 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 7.2 Hz, 2 H, H_{Ar}), 7.67–7.56 (m, 1 H, H_{Ar}), 7.55–7.38 (m, 3 H, H_{Ar}), 7.29 (d, *J* = 7.6 Hz, 2 H, H_{Ar}), 6.72 (s, 1 H, H_{Ar}), 3.23 (sept, *J* = 6.1 Hz, 1 H, CH), 2.95 (sept, *J* = 6.1 Hz, 1 H, CH), 1.40 (d, *J* = 6.1 Hz, 6 H, 2 CH_3), 1.27 (d, *J* = 6.1 Hz, 6 H, 2 CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7, 159.0, 155.8, 154.5, 152.8, 143.4, 134.9, 134.3, 133.8, 132.2, 131.7, 131.5, 130.1, 130.0, 128.0, 127.2, 126.7, 115.6, 34.5, 31.7, 24.5, 24.4, 24.1.

MS (EI): *m*/*z* (%) = 462 (30) $[M^+]$, 464 (10) $[M + 2]^+$, 447 (45), 427 (100).

HRMS (EI): *m*/*z* $[M^+]$ calcd for $C_{26}H_{23}N_2ClS_2$: 462.0986; found: 462.0985.

8-(2-Chlorophenyl)-6-isopropyl-2-[4-(trifluoromethyl)phenyl]thiazolo[5,4-*b*]thieno[3,2-*e*]pyridine (5i)

According to GP-2 using **7a** and 4-(trifluoromethyl)benzaldehyde (104 mg, 0.6 mmol) gave **5i** (98 mg, 67%) as a white solid; mp 125–126 °C.

IR (KBr): 2974, 2932, 2879, 1657, 1459, 1427, 1381, 1325, 1089, 1046, 876 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 7.69 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 7.66–7.60 (m, 1 H, H_{Ar}), 7.56–7.42 (m, 3 H, H_{Ar}), 6.75 (s, 1 H, H_{Ar}), 3.25 (sept, *J* = 6.8 Hz, 1 H, CH), 1.41 (d, *J* = 6.7 Hz, 6 H, 2 CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.6, 159.9, 155.4, 155.1, 143.1, 136.9, 134.9, 134.4, 133.7, 132.7 (q, *J* = 32.7 Hz), 131.9, 131.7, 130.1, 128.0, 126.7, 125.9, 123.8 (q, *J* = 271.5 Hz), 115.4, 31.4, 24.1, 24.0.

MS (EI): *m*/*z* (%) = 488 (40) $[M^+]$, 490 (18) $[M + 2]^+$, 473 (85), 453 (100), 437 (45), 423 (30), 219 (45).

HRMS (EI): *m*/*z* $[M^+]$ calcd for $C_{24}H_{16}N_2ClF_3S_2$: 488.0390; found: 488.0391.

4-[8-(2-Chlorophenyl)-6-isopropylthiazolo[5,4-*b*]thieno[3,2-*e*]pyridin-2-yl]benzonitrile (5j)

According to GP-2 using **7a** and 4-cyanobenzaldehyde (78 mg, 0.6 mmol) gave **5j** (93 mg, 70%) as a white solid; mp 224–225 °C.

IR (KBr): 3067, 2966, 2932, 2869, 1552, 1469, 1449, 1312, 1210, 1063, 1038, 961, 827, 733, 721, 699, 678 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 7.69 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 7.66–7.60 (m, 1 H, H_{Ar}), 7.55–7.39 (m, 3 H, H_{Ar}), 6.74 (s, 1 H, H_{Ar}), 3.25 (sept, *J* = 6.6 Hz, 1 H, CH), 1.40 (d, *J* = 6.7 Hz, 6 H, 2 CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.9, 160.3, 155.4, 143.1, 137.7, 135.2, 134.5, 133.7, 132.8, 132.0, 130.3, 130.2, 128.2, 126.8, 118.4, 115.5, 114.5, 31.7, 24.4, 24.4.

MS (EI): *m*/*z* (%) = 445 (65) $[M^+]$, 447 (27) $[M + 2]^+$, 430 (100), 410 (60), 198 (55).

HRMS (EI): *m*/*z* $[M^+]$ calcd for $C_{24}H_{16}N_3ClS_2$: 445.0469; found: 445.0469.

1-{4-[8-(2-Chlorophenyl)-6-isopropylthiazolo[5,4-*b*]thieno[3,2-*e*]pyridin-2-yl]phenyl}ethanone (5k)

According to GP-2 using **7a** and 4-acetylbenzaldehyde (88 mg, 0.6 mmol) gave **5k** (97 mg, 70%) as a white solid; mp 173–174 °C.

IR (KBr): 2973, 2929, 2897, 1455, 1406, 1381, 1084, 1045, 879 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 8.5 Hz, 2 H, H_{Ar}), 8.00 (d, *J* = 8.6 Hz, 2 H, H_{Ar}), 7.66–7.60 (m, 1 H, H_{Ar}), 7.55–7.43 (m, 3 H, H_{Ar}), 6.74 (s, 1 H, H_{Ar}), 3.25 (sept, *J* = 6.8 Hz, 1 H, CH), 2.64 (s, 3 H, CH_3), 1.40 (d, *J* = 6.8 Hz, 6 H, 2 CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.4, 165.0, 156.0, 155.6, 155.1, 143.3, 138.9, 137.8, 135.0, 134.6, 133.8, 132.1, 131.8, 130.2, 129.0, 128.0, 126.8, 115.5, 31.7, 27.2, 24.5, 24.4.

MS (EI): *m*/*z* (%) = 462 (40) $[M^+]$, 464 (15) $[M + 2]^+$, 447 (70), 427 (100).

HRMS (EI): *m*/*z* $[M^+]$ calcd for $C_{25}H_{19}ON_2ClS_2$: 462.0622; found: 462.0621.

2,8-Bis(2-chlorophenyl)-6-isopropylthiazolo[5,4-*b*]thieno[3,2-*e*]pyridine (5l)

According to GP-2 using **7a** and 2-chlorobenzaldehyde (84 mg, 0.6 mmol) gave **5l** (90 mg, 66%) as a yellow solid; mp 146–147 °C.

IR (KBr): 3053, 2965, 2922, 2869, 1552, 1520, 1478, 1316, 1211, 1180, 1038, 958, 812, 706 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.17–8.09 (m, 1 H, H_{Ar}), 7.66–7.59 (m, 1 H, H_{Ar}), 7.56–7.42 (m, 4 H, H_{Ar}), 7.39–7.29 (m, 2 H, H_{Ar}), 6.76 (s, 1 H, H_{Ar}), 3.25 (sept, *J* = 6.8 Hz, 1 H, CH), 1.41 (d, *J* = 6.8 Hz, 6 H, 2 CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.0, 159.9, 156.4, 154.9, 141.5, 134.8, 134.7, 133.8, 133.0, 132.5, 132.1, 131.6, 131.6, 131.0, 130.2, 130.2, 127.3, 126.8, 115.5, 31.7, 24.5, 24.4.

MS (EI): *m*/*z* (%) = 454 (60) $[M^+]$, 456 (45) $[M + 2]^+$, 439 (85), 419 (100), 202 (55).

HRMS (EI): *m*/*z* $[M^+]$ calcd for $C_{23}H_{16}N_2Cl_2S_2$: 454.0126; found: 454.0124.

8-(2-Chlorophenyl)-2-(furan-2-yl)-6-isopropylthiazolo[5,4-*b*]thieno[3,2-*e*]pyridine (5m)

According to GP-2 using **7a** and furan-2-carbaldehyde (58 mg, 0.6 mmol) gave **5m** (88 mg, 72%) as a beige solid; mp 167–168 °C.

IR (KBr): 2973, 2929, 2883, 1452, 1420, 1381, 1332, 1275, 1088, 1046, 880 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.65–7.39 (m, 5 H, H_{Ar}), 7.18–7.03 (m, 1 H, H_{Ar}), 6.70 (s, 1 H, H_{Ar}), 6.58–6.45 (m, 1 H, H_{Ar}), 3.23 (sept, *J* = 6.9 Hz, 1 H, CH), 1.39 (d, *J* = 6.8 Hz, 6 H, 2 CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0, 156.1, 155.1, 154.6, 148.9, 145.0, 142.9, 134.5, 134.2, 133.6, 132.0, 131.5, 130.0, 129.9, 126.7, 115.4, 112.6, 112.3, 31.5, 24.3, 24.2.

MS (EI): *m*/*z* (%) = 410 (70) $[M^+]$, 412 (25) $[M + 2]^+$, 395 (80), 375 (100).

HRMS (EI): *m*/*z* $[M^+]$ calcd for $C_{21}H_{15}ON_2ClS_2$: 410.0309; found: 410.0307.

8-(2-Chlorophenyl)-6-isopropyl-2-(thiophen-2-yl)thiazolo[5,4-*b*]thieno[3,2-*e*]pyridine (5n)
According to GP-2 using **7a** and thiophene-2-carbaldehyde (67 mg, 0.6 mmol) gave **5n** (98 mg, 77%) as a beige solid; mp 163–164 °C.

IR (KBr): 2961, 2922, 2869, 1604, 1551, 1472, 1278, 1051, 754 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.72–7.39 (m, 6 H, H_{Ar}), 7.15–7.04 (m, 1 H, H_{Ar}), 6.72 (s, 1 H, H_{Ar}), 3.24 (sept, *J* = 6.7 Hz, 1 H, CH), 1.40 (d, *J* = 6.8 Hz, 6 H, 2 CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.8, 159.0, 155.4, 154.5, 142.8, 137.8, 134.5, 134.0, 133.6, 132.0, 131.5, 129.9, 129.8, 129.0, 128.0, 126.6, 115.5, 31.5, 24.3, 24.2.

MS (EI): *m*/*z* (%) = 426 (65) [M^+], 428 (30) [M + 2]$^+$, 411 (90), 391 (100).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{21}H_{15}N_2ClS_3$: 426.0080; found: 426.0083.

2-(4-Chlorophenyl)-6-isopropyl-8-phenylthiazolo[5,4-*b*]thieno[3,2-*e*]pyridine (5o)
According to GP-2 using **7b** and 4-chlorobenzaldehyde (84 mg, 0.6 mmol) gave **5o** (98 mg, 70%) as a white solid; mp 181–182 °C.

IR (KBr): 3433, 2961, 2924, 1594, 1546, 1496, 1468, 1402, 1311, 1280, 1090, 964, 880, 830, 730, 707 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.3 Hz, 2 H, H_{Ar}), 7.85–7.78 (m, 2 H, H_{Ar}), 7.64–7.50 (m, 3 H, H_{Ar}), 7.41 (d, *J* = 8.3 Hz, 2 H, H_{Ar}), 7.09 (s, 1 H, H_{Ar}), 3.25 (sept, *J* = 6.8 Hz, 1 H, CH), 1.42 (d, *J* = 6.8 Hz, 6 H, 2 CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ =164.6, 160.0, 155.9, 154.4, 142.6, 137.3, 137.1, 135.3, 132.3, 130.9, 130.7, 129.2, 128.7, 128.3, 115.4, 31.4, 24.1.

MS (EI): *m*/*z* (%) = 420 (50) [M^+], 422 (20) [M + 2]$^+$, 405 (100).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{23}H_{17}N_2ClS_2$: 420.0516; found: 420.0510.

8-(2-Chlorophenyl)-2-(4-chlorophenyl)-6-phenylthiazolo[5,4-*b*]thieno[3,2-*e*]pyridine (5p)
According to GP-2 using **7c** and 4-chlorobenzaldehyde (84 mg, 0.6 mmol) gave **5p** (69 mg, 52%) as a yellow solid; mp >250 °C.

IR (KBr): 3060, 2962, 2925, 2872, 1471, 1278, 1049, 960, 835, 755, 704 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$–TFA): δ = 7.99–7.92 (m, 1 H, H_{Ar}), 7.82–7.39 (m, 12 H, H_{Ar}), 7.34 (s, 1 H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$–TFA): δ = 161.9 (q, *J* = 43.3 Hz), 133.4, 132.7, 132.6, 132.4, 132.0, 131.9, 131.8, 131.4, 131.1, 130.8, 130.5, 130.0, 129.6, 127.8, 127.5, 127.1, 115.7, 114.4 (q, *J* = 284.1 Hz).

MS (EI): *m*/*z* (%) = 488 (50) [M^+], 490 (40) [M + 2]$^+$, 453 (100), 226 (90).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{26}H_{14}N_2Cl_2S_2$: 487.9970; found: 487.9969.

Cytotoxicity Experiment
The toxicity of compound **5a** and compound **5b** were evaluated by MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay. Briefly, HEK293 cells were seeded on 96-well plates, diluted with fresh medium to yield cell densities of 2.5 × 10^4 cells/mL of culture. After 20 h culture, different concentrations [250, 125, 63, 31, 16, 8, 4, 2, 1, 0.500, 0.250, 0.125 (μg/mL)] of the drugs were added to each well for 18 h. Then, MTT (20 μL) was added to each well, and incubated at 37 °C for 3 h for the formation of formazan crystals. The medium was then removed and DMSO (150 μL) was added to each well to dissolve the formazan crystals produced by living cells. The absorbance of the solution was measured at 570 nm on a microplate reader (Bio-Rad). Cells with no drug treatment were used as a negative control group, and cells with melittin added were used as a positive control group.

Acknowledgment

This work was supported financially by grants from the National Natural Science Foundation of China 21272287.

Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000084.

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(16) Structural and other crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 989476 for compound **5a**. A copy of the data can be obtained, free of charge, by applying to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk].

