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One-Pot Synthesis and Evaluation of Antileishmanial Activities of Functionalized *S*-Alkyl/Aryl Benzothiazole-2-carbothioate Scaffold

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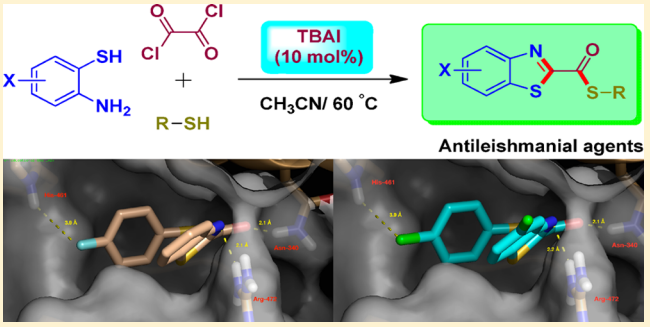
Supporting Information

ABSTRACT: The synthesis of hitherto unreported *S*-alkyl/aryl benzothiazole-2-carbothioate is reported from thiols, oxalyl chloride, and 2-aminothiophenols using 10 mol % *n*-tetrabutylammonium iodide (TBAI) as catalyst in acetonitrile through multicomponent reaction (MCR) strategy. The present protocol favored formation of benzothiazoles and thioesters via simultaneous formation of C−N and C−S bonds in good yields with a wide range of substrates. A few of the synthesized derivatives were evaluated for their antimicrobial activity against the protozoan parasite *Leishmania donovani*, a causative agent of visceral leishmaniasis (VL). Further, these compounds displayed no toxicity toward macrophage RAW 264.7 cells and are therefore nontoxic and effective antileishmanial leads. In silico docking studies were performed to understand the possible binding site interaction with trypanothione reductase (TryR).



INTRODUCTION

Protozoan parasites of the genus *Leishmania* are causative agents of human leishmaniasis. It is one of the world's most neglected diseases in terms of drug development, owing to its major prevalence among the poorest. It is projected that 12 million people worldwide are infected by over 20 species of leishmania and about 350 million people are at risk of infection in around 98 countries. Depending upon its species, leishmaniasis manifests as mild cutaneous lesions caused by *Leishmania major*, disfiguring mucocutaneous disease caused by *Leishmania braziliensis* or visceral form caused by *Leishmania donovani* which is often fatal, if left untreated.[1] Currently, organic antimonial drugs are the only chemotherapeutic agents widely used for its treatment and it is generally agreed that new agents with safe, inexpensive, and more effective profiles are urgently needed.

Benzothiazole derivatives are the most essential heterocyclic compounds found in a variety of natural products and pharmaceutical agents with a high degree of structural diversity.[2] These scaffolds are used as functional materials in ratiometric fluorescent pH indicators, as sensors and bioluminogenic probes, and as agrochemicals. Various marine and terrestrial natural products, namely erythrazoles A and B, isolated from mangrove sediments are useful intermediates for dyes and are versatile ligands for catalytic reactions.[3] It is well-known that amalgamation of benzothiazoles with other functionalities opens doors to design novel druglike molecules. Some substituted benzothiazoles are used as drugs: riluzole (an anticonvulsant drug), zopolrestat (to treat endotoxin-related inflammatory diseases, namely sepsis, asthma, and uveitis), and 5F203 and PMX 610 (exhibit antitumor properties). They are also used as imaging agents for Aβ plaques in cerebral amyloid angiopathy, radioactive β-amyloid imagining agents (^{11}C-PIB), γ-aminobutyric acid (GABA-A) inhibitors, inhibitors of fatty acid oxidation, aldose reductase inhibitors (ARIs), falcipain inhibitors, microsomal triglyceride transfer protein inhibitors (MTP), and fatty acid amide hydrolase (FAAH) inhibitors (Figure 1).[4] Giorgio et al. carried out structure−activity relationships (SARs) of position 2-substituted 6-nitro- and 6-aminobenzothiazoles and their corresponding anthranilic acid derivatives against *Leishmania infantum* and *Trichomonas vaginalis*. They also reported benzothiazole-substituted acridinone derivatives as potent antileishmanial agents with a promising selectivity index (SI). Fazal et al. studied antileishmanial activities of benzothiazole derivatives. Benzothiazole derivatives containing an electron-donating group were reported to enhance antileishmanial activity whereas an electron-withdrawing group made the compounds completely inactive.[5] Consequently,[6] our research group focused to develop new antileishmanial agents: benzothiazole-thioester derivatives.

Several approaches have been designed for the synthesis of benzothiazole derivatives. Most of these syntheses of

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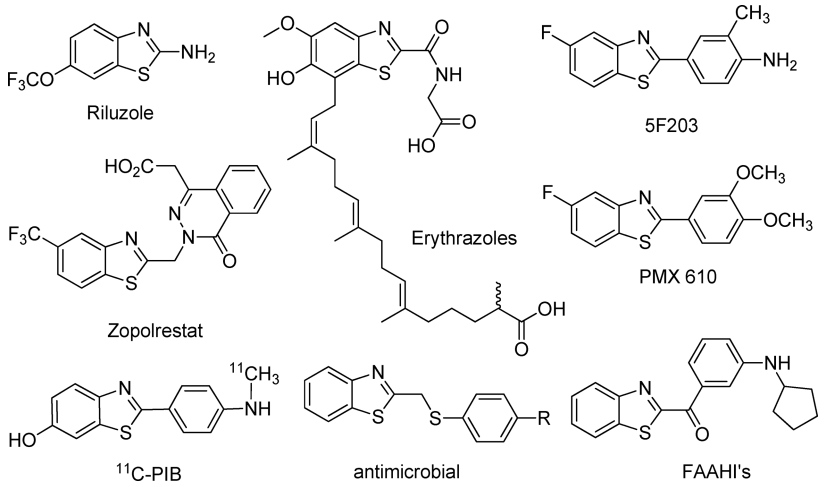


Figure 1. Structures of bioactive 2-substituted benzothiazoles.

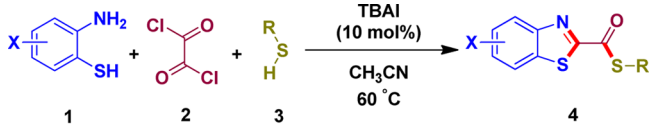
benzothiazole derivatives involve metal catalysis and are often expensive with tedious workup procedures and metallic toxic wastes as offshoots. Other protocols mainly include cyclization of different aromatic thiourea linkages, condensation of various *o*-haloanilides or their analogues with different thiocyanates and isothiocyanates, and condensation of 2-aminothiophenols and carbon disulfide/sodium sulfide/acids/acid chlorides/aldehydes/esters/nitriles/ketones/thioesters under mild conditions.[7] 2-arylbenzothiazole synthesis was extensively explored as compared to 2-acylbenzothiazoles.[8] Introducing an acyl group at the 2-position of benzothiazoles has been synthetically challenging. However, the synthesis of *S*-alkyl/aryl benzothiazole-2-carbothioate has yet to be reported.

The thioester moiety is another useful and versatile functional group in organic transformations because of less resonance stabilization, i.e., very poor overlap of the 3p orbital with the 2p orbitals of the carbonyl, resulting in high reactivity in the ground state. They are key intermediates used in *β*-lactam synthesis, carbocyclization, peptide coupling, natural product synthesis, acyl transfer reactions, functional group transformations, carbon−carbon bond formation, and biosynthetic reactions and in certain instances as protecting groups.[9]

The syntheses of thioesters by direct reaction of the corresponding thiols with a suitable acid chloride[10a] or acid anhydride[10b] are well-known methods. They have also been synthesized by transthioesterification of active carboxylic acid derivatives, esters,[10c] and *N*-acylbenzotriazoles[10d] with thiols under varied reaction conditions and catalysts.[10e] Recently *tert*-butyl-protected thiols have been utilized for the preparation of thioesters.[10f] The N−S acyl shift, mediated by attaching a thiol auxiliary residue to the peptide backbone, has been applied to peptide thioester syntheses.[10g] They have also been accessed from thiols and carbon monoxide by carbonylation of organic substrates catalyzed by transition metals such as Pt[10h] or Pd.[10i] The Dess−Martin periodinane (DMP)-mediated reaction of thiols and aldehydes[10j] and the coupling of aldehyde with disulfide or thiol via a free radical mechanism are other methods for the synthesis of thioesters.[11]

Herein we report an unprecedented synthesis of *S*-alkyl/aryl benzothiazole-2-carbothioate using one-pot three-component reaction between thiols, oxalyl chloride, and 2-aminothiophenols using *n*-tetrabutylammonium iodide[12] (TBAI) in acetonitrile (Scheme 1), and the activity of *S*-alkyl/aryl benzothiazole-2-carbothioate against promastigotes of *L. donovani* was evaluated.

Scheme 1. Synthesis of *S*-Alkyl/Aryl Benzothiazole-2-carbothioate



1 2 3 4

X = H (**1a**), 4-Cl (**1b**), 4-CF_3 (**1c**), 5-OCH_3 (**1d**), 5-CH_2CH_3 (**1e**)

R = 4-MeC_6H_4 (**3a**), 4-$MeOC_6H_4$ (**3b**), 4-ClC_6H_4 (**3c**), 4-BrC_6H_4 (**3d**), 4-OHC_6H_4 (**3e**), 4-FC_6H_4 (**3f**), 3-$MeOC_6H_4$ (**3g**), 3-ClC_6H_4 (**3h**), 2-MeC_6H_4 (**3i**), 2-ClC_6H_4 (**3j**), 2-BrC_6H_4 (**3k**), C_6H_5 (**3l**), 2-Naphthalene (**3m**), $C_6H_4CH_2$ (**3n**), 2-$ClC_6H_4CH_2$ (**3o**), CH_3CH_2 (**3p**), $CH_3CH_2CH_2$ (**3q**), -$CH_3(CH_2)_{10}CH_2$ (**3r**)

RESULTS AND DISCUSSION

We started with the reaction of 4-methylthiophenol and oxalyl chloride with 2-aminothiophenol in acetonitrile at room temperature in the absence of catalyst, and no desired product was obtained (Table 1, entry 1). When the reaction mixture was subjected to heating at 60 °C, the desired product was isolated in 15% yield (Table 1, entry 2). To increase the efficiency of the reaction, the same reaction was examined using 10 mol % *n*-tetrabutylammonium iodide (TBAI), and the desired product was obtained in 75% yield. No significant increase in yield was noted when the reaction was carried out with 20 mol % catalyst (Table 1, entry 4). Further, the yield of the desired product dropped to 40% (Table 1, entry 5) when the reaction was carried out with 5 mol % catalyst. A lower yield was observed when the reaction temperatures exceeded 70 °C. Various other salts of iodine such as sodium iodide, potassium iodide, and molecular iodine, as well as other quaternary ammonium salts, namely *n*-tetrabutylammonium chloride (TBACl) and *n*-tetrabutylammonium bromide (TBABr), were examined under similar reaction conditions (Table 1, entries 6−10). TBAI was found to provide the best yields. The choice of solvent was next examined by carrying out reactions in 1,2-dichloroethane, ethanol, methanol, dichloromethane, and tetrahydrofuran. 1,2-Dichloroethane furnished the desired product in comparable yield as with acetonitrile, while other solvents were found ineffective (Table 1, entries 11−15).

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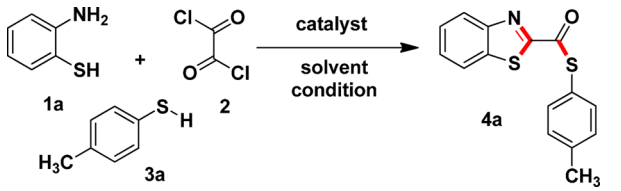
Table 1. Optimization for Reaction Conditions[a]



entry	catalyst (mol %)	solvent	time (h)	yield (%)
1	no catalyst	CH_3CN	12	0
2	no catalyst	CH_3CN	12	15[b]
3	TBAI (10)	CH_3CN	4.0	75
4	TBAI (20)	CH_3CN	4.0	77
5	TBAI (5)	CH_3CN	4.0	40
6	NaI (10)	CH_3CN	4.0	24
7	KI (10)	CH_3CN	4.0	28
8	I_2 (10)	CH_3CN	4.0	20
9	TBACl (10)	CH_3CN	4.0	30
10	TBABr (10)	CH_3CN	4.0	40
11	TBAI (10)	DCE	4.5	72
12	TBAI (10)	C_2H_5OH	6.0	≤10
13	TBAI (10)	CH_3OH	6.0	<10
14	TBAI (10)	DCM	6.0	<20
15	TBAI (10)	THF	6.0	≤15

[a]All the reactions were carried out in 1 mmol scale. [b]The reaction was carried out at 60 °C.

After optimization of reaction conditions, the substrate scope was explored using various substituted thiols and substituted 2-aminothiophenols. At first, 2-aminothiophenol (**1a**) was treated with a set of aromatic thiols bearing both electron-donating and electron-withdrawing substituents, and the corresponding products were obtained in good yields. The substrates with 4-methyl (**3a**) and 4-methoxy (**3b**) substituents underwent reactions to give *S*-aryl benzothiazole-2-carbothioates **4a** and **4b** (Table 2), respectively, in high yields. The substrates with 4-chloro (**3c**), 4-bromo (**3d**), 4-hydroxyl (**3e**), and 4-fluoro (**3f**) groups underwent condensation to afford *S*-aryl benzothiazole-2-carbothioates **4c**, **4d**, **4e**, and **4f**, respectively (65−76% yields, Table 2). Moreover the reaction of para-substituted thiophenol with a nitro group did not provide any desired product under the optimized condition. Substrates **3g** and **3h** with 3-methoxy and 3-chloro substituents furnished the products **4g** and **4h** (78% and 72% yields, respectively, Table 2). It was observed that aromatic thiols with electron-donating groups served as efficient reacting partners. The presence of an electron-withdrawing group however gave slightly lower yields.

The steric factor due to ortho-substituted thiols was found to have less impact on the present protocol as with 2-methyl (**3i**), 2-chloro (**3j**), and 2-bromo (**3k**) correspondingly provided **4i**, **4j**, and **4k** in good yields. In addition, thiophenol (**3l**) and 2-naphthalenethiol (**3m**) also reacted with 2-aminothiophenol to obtain the products **4l** and **4m** (68% and 70% yields, respectively, Table 2). Benzylthiol (**3n**) and 2-chlorobenzylthiol (**3o**) reacted to give corresponding *S*-alkylbenzothiazole-2-carbothioates **4n** and **4o** (Table 2) on condensation with 2-aminothiophenol. Aliphatic thiols such as ethanethiol (**3p**), propanethiol (**3q**), and dodecanethiol (**3r**) also underwent reaction to give the corresponding *S*-alkyl benzothiazole-2-carbothioates **4p**, **4q**, and **4r** (Table 2) in good yields.

To explore the scope of the reaction, the presence of chloro or methoxy/ethyl groups at 4- or 5-position of the 2-aminothiophenol did not interfere with the formation of the product, i.e., the yields were found to be comparable. However, the presence of trifluoromethyl at the 4-position of the 2-aminothiophenol decreased the rate of reaction and eventually the product formation. Furthermore, the remaining factors for the synthesis of **4s** to **4z** and **4za** to **4zd** (Table 3) were identical as discussed above, i.e., the reactions of 2-amino-4-chlorobenzenethiol with thiophenol produced **4s** in 71% yield while substrates bearing substituted aryl rings with 4-methyl, 4-chloro, and 4-bromo functionalities produced the corresponding *S*-alkylbenzothiazole-2-carbothioates **4s−v** in 73−77% yields. Similarly, the reactions of 2-amino-4-trifluoromethylbenzenethiol with thiophenol having 4-methyl, 4-methoxy, 2-chloro, and 2-bromo substituents in the aryl ring underwent reaction to furnish **4w−z** in 56−62% yields. Likewise, the reactions of 2-amino-5-methoxybenzenethiol with substrates bearing substituted aryl rings with 4-methyl, 4-methoxy, and 4-bromo functionalities produced the corresponding *S*-alkylbenzothiazole-2-carbothioates **4za-c** in 77−80% yields. Finally, the reactions of 2-amino-5-ethylbenzenethiol with 4-methylthiophenol produced **4zd** in 76% yield.

Maximum yields were observed when both the substrates possessed electron-donating groups. Replacement with either an electron-neutral or electron-withdrawing substituent reduced yields. Also a drop in the yields was noticed when electron-withdrawing groups were present on both of the reacting substrates.

All the isolated products were confirmed on the basis of their analytical data (^{1}H NMR, ^{13}C NMR, IR, and HRMS). Additionally, the target compounds **4a** and **4o** were further determined by X-ray crystallographic analysis (Figure S1, Supporting Information).

To understand the reaction mechanism, we carried out three sets of reaction using permutation and combination of three substrates (Scheme 2). It was observed that 4-methylthiophenol (**3a**) reacts with oxalyl chloride (**2**) under the experimental conditions to give the expected product **5** in 50% yield by nucleophilic substitution reaction along with some unreacted starting material (Scheme 2, eq 1). Similarly, 4-methylthiophenol (**3a**) was reacted with 2-aminothiophenol (**1a**), and the expected products **6a** and **6b** were obtained in equal ratio (Scheme 2, eq 2). Likewise, treatment of 2-aminothiophenol with oxalyl chloride furnished **7**, but in lower yield, and major starting materials were recovered (Scheme 2, eq 3). On the basis of these results, it can be speculated that the present protocol suppresses the formation of these above byproduct during the course of reaction, thereby generating the desired product in major yields.

The formation of the *S*-alkyl benzothiazole-2-carbothioate products can be proposed, as TBAI reacts with thiol to generate thiolate anion in the reaction medium. Subsequently, the anion attacks a side of oxalyl chloride to form a thioester moiety intermediate. Finally, 2-aminobenzenethiol in the presence of TBAI can undergo condensation with the in situ-generated thioester intermediate to form the desired products (Scheme 3).

Antimicrobial Activity. The antileishmanial activity and mammalian cell toxicity of the 16 *S*-alkyl/aryl benzothiazole-2-carbothioate derivatives were investigated. The IC_{50} and IC_{90} values were calculated for each compound (Table 4). The results of statistcal analysis showed that all the compounds possessed moderate to potent activity against the promastigote forms of *L. donovani*. However, toxicity incurred on mammalian

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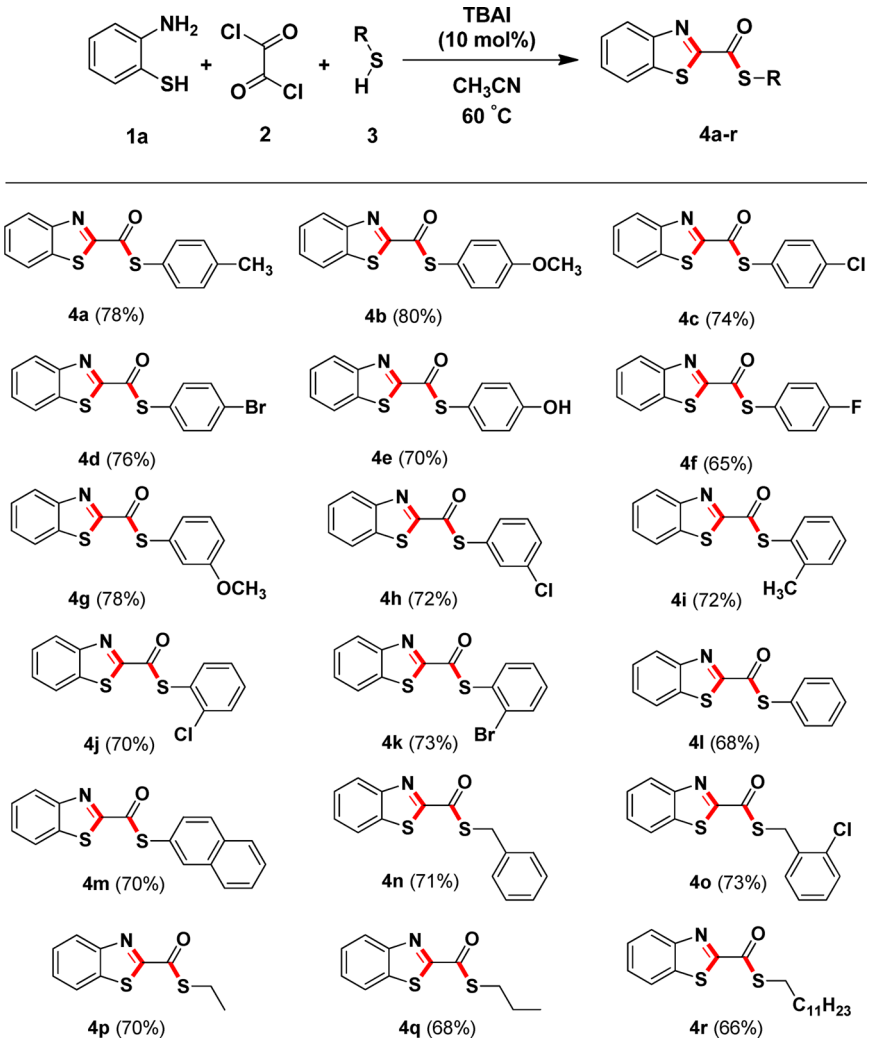
Table 2. Reaction of 2-Aminobenzenethiol (1a) with Various Thiols[a,b]



[a]Conditions: **1a** (1 mmol), **2** (1 mmol), **3** (1 mmol), CH_3CN (5.0 mL), 60 °C, 4 h. [b]Yield based on **3**.

macrophage cell line RAW 264.7 by a few of them could limit their use as antileishmanial agents. For instance, four compounds, namely **4s**, **4a**, **4i**, and **4b**, displayed toxicity toward the mammalian macrophage cells with IC_{50} values of 313.7 ± 52.28 μM, 322.9 ± 66.8 μM, 360.5 ± 37.11 μM, and 432.5 ± 82.32 μM, respectively. These IC_{50} values against macrophages are near the IC_{90} values against promastigotes. Therefore, the efficacy of these compounds is limited due to their toxicity. The compounds **4f**, **4x**, **4l**, **4h**, **4e**, **4g**, **4j**, **4m**, and **4n** with IC_{50} values of 191.1 ± 2.78 μM, 200.4 ± 4.31 μM, 202.5 ± 23.45 μM, 207.5 ± 30.89 μM, 210.6 ± 30.34 μM, 212.2 ± 28.82 μM, 215.2 ± 35.33 μM, 236.4 ± 47.09 μM, and 280.6 ± 64.79 μM, respectively, against promastigote forms could be promising antileishmanial agents, as their toxic effect toward macrophages is negligible at the doses used against the parasite (as depicted by their IC_{50} values). Herein the compounds **4y**, **4z**, and **4w** are found to be most effective against promastigotes with IC_{50} values of 190.3 ± 14.05 μM, 198.1 ± 19.65 μM, and 199.8 ± 2.370 μM, respectively.

The percent cell viability of *L. donovani* and macrophages upon treatment with increasing concentrations of these three compounds from 0.00 to 500 μM was also evaluated as shown in Figure 2 and Figure 3, respectively. The results showed a dose-dependent killing of the promastigotes of *L. donovani*. Further, at these doses of the compounds, no or insignificant killing of mammalian macrophages was observed, indicating their potential as promising antileishmanials.

Molecular Docking Study of Benzothiazole-2-carbothioate Derivatives against Trypanothione Reductase. The molecular docking of benzothiazole derivatives against trypanothione reductase (TryR) showed that most of the compounds show hydrogen bonds with Asn 340 and Arg 472. Interestingly, some of these derivatives show hydrophobic interaction with His-461′ (protonated histidine) which is a part of catalytic triad (Cys-52-His-461′-Cys-57). The His-461′ forms a π−cation interaction with the aryl group of these derivatives (~5 Å) whereas the Arg 472 is shows π−cation interaction with the benzothiazole nucleus (~3 Å) which may help in stabilizing the ligand in the cavity. The two representative examples **4u** and **4f** revealing the mode of interactions are provided in Figure 4. The G_{score} values of **4u** and **4f** are −4.15 and −3.03, respectively. Table 5 shows the molecular docking scores and E_{model} scores for the 25 compounds. The molecular docking results indicate that the binding of these designed compounds to trypanothione reductase enzyme is sufficiently strong, which may play an important role against promastigotes.

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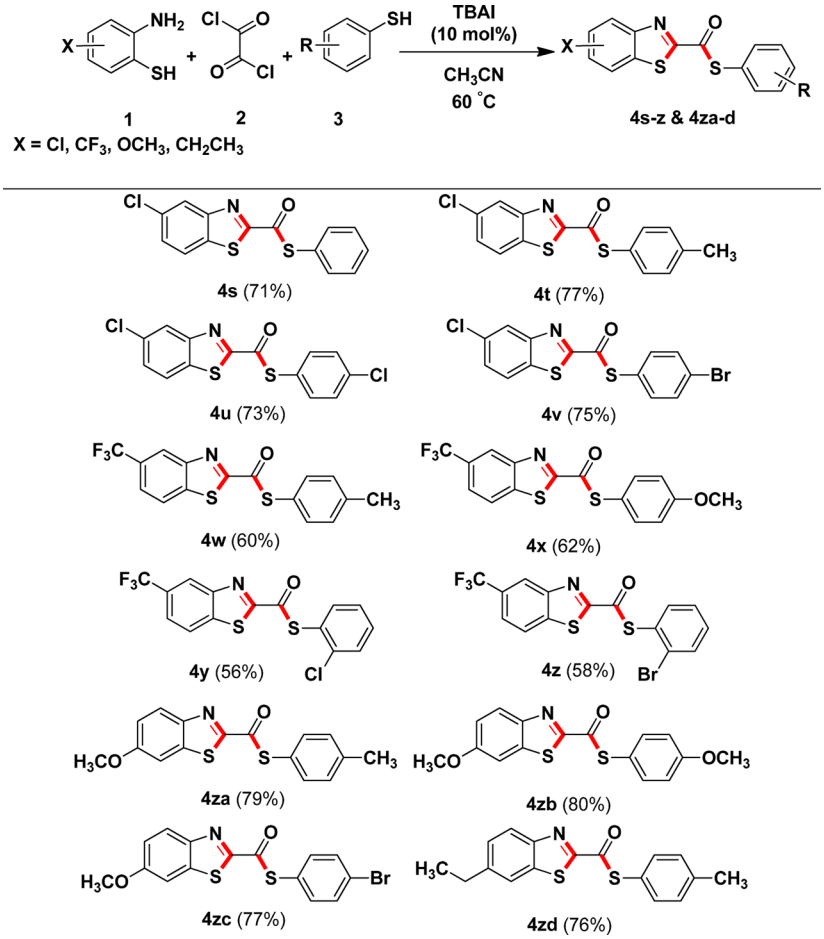
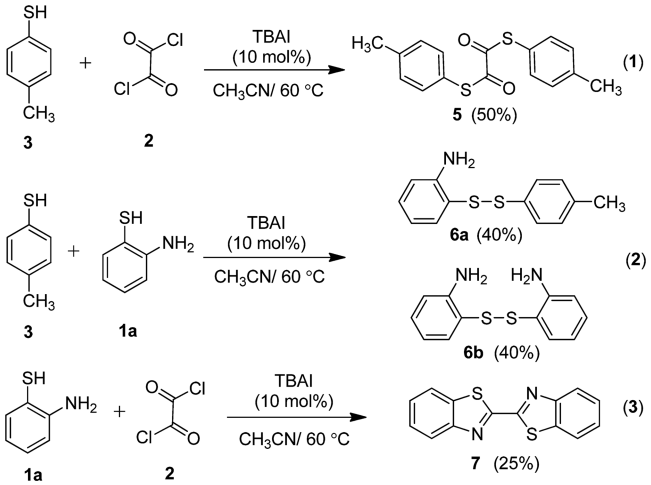
Table 3. Reaction with Substituted 2-Aminobenzenethiols with Arylthiols[a]

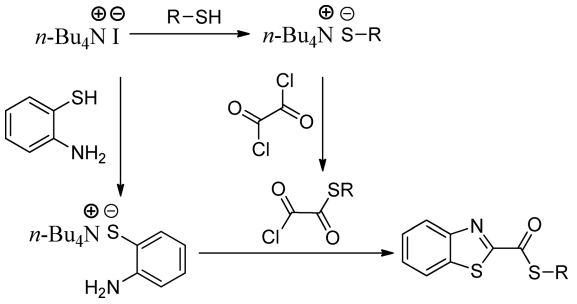


[a]Conditions: **1b/1c/1d/1e** (1 mmol), **2** (1 mmol), **3** (1 mmol), CH_3CN (5.0 mL), 60 °C, 6 h.

Scheme 2. Crossover Experiments



Scheme 3. Proposed Reaction Mechanism



Lipinsky Rule. The ligands were also checked for amenability to the Lipinsky rule of five, and the results are summarized in Table 6. The rule states that a molecule likely to be developed as an orally active drug candidate should show no more than one violation of the following four criteria: It should not have more than five hydrogen bond donors, it should not have more than 10 hydrogen bond acceptors, it should not have molecular weight greater than 500 Da, and it should not have an octanol–water partition coefficient greater than 5. Molecular properties of all ligands were calculated by Molinspiration, and it was found that all the ligands followed the Lipinsky rule with maximium ligands (except **4m**, **4w**, **4y**, and **4z**) and showed no violation of the above criteria (Table 6). Therefore, these ligands have a good potential for ensuing development as oral agents and could be potentially active drug candidates.

CONCLUSION

In summary, we have developed a one-pot three-component condensation with a variety of thiols and 2-aminothiophenols with oxalyl chloride in acetonitrile through a multicomponent reaction (MCR) strategy, under mild reaction conditions, with high efficiency, tolerance to a wide range of substrates, and easy

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Table 4. Leishmanicidal Activity of Compounds against *L. donovani* Promastigotes

	activity against *L. donovani promastigotes*		cytotoxicity to macrophages	
compounds	(IC_{50} μM ± SD)[a]	(IC_{90} μM ± SD)[a]	(IC_{50} μM ± SD)[a]	(IC_{90} μM ± SD)[a]
4a	211.6 ± 17.36	380.9 ± 31.25	322.9 ± 66.80	581.1 ± 120.30
4b	250.1 ± 29.52	450.2 ± 53.14	432.5 ± 82.32	778.4 ± 148.20
4e	210.6 ± 30.34	379 ± 54.610	6803 ± 65.45	12245 ± 117.80
4f	191.1 ± 2.78	344.1 ± 5.01	765.5 ± 31.62	1382 ± 56.94
4g	212.2 ± 28.82	381.9 ± 51.88	1775 ± 229.90	3196 ± 413.80
4h	207.5 ± 30.89	373.5 ± 55.61	935.3 ± 234.80	1683 ± 422.70
4i	208.4 ± 20.66	375.1 ± 37.18	360.5 ± 37.11	648.8 ± 66.79
4j	215.2 ± 35.33	387.3 ± 63.59	3165 ± 56.65	5697 ± 102.0
4l	202.5 ± 23.45	364.5 ± 42.21	543.4 ± 52.78	978.1 ± 95.01
4m	236.4 ± 47.09	425.5 ± 84.76	2554 ± 383.10	4597 ± 689.50
4n	280.6 ± 64.79	651.2 ± 90.07	1745 ± 171.30	3140 ± 308.40
4s	180 ± 10.42	323.9 ± 18.76	313.7 ± 52.28	564.6 ± 94.10
4w	199.8 ± 2.37	359.6 ± 4.26	2407 ± 114.50	4332 ± 145.80
4x	200.4 ± 4.317	360.8 ± 7.77	880 ± 144.80	1584 ± 260.60
4y	190.3 ± 14.05	342.6 ± 25.28	6338 ± 340.40	11409 ± 612.70
4z	198.1 ± 19.65	356.5 ± 35.37	2559 ± 330.70	4607 ± 595.30

[a] $n = 2$.

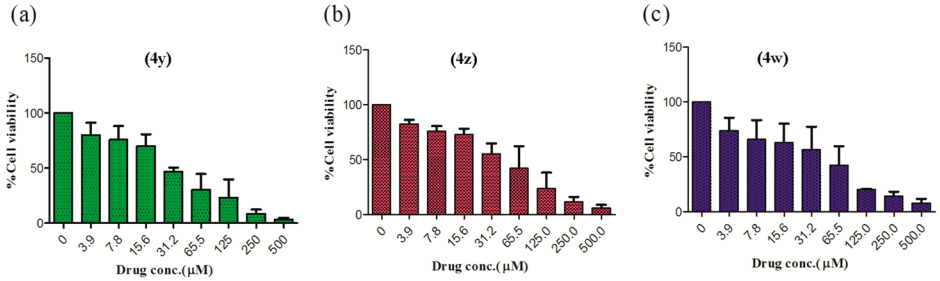

Figure 2. Leishmanicidal effect of **4y**, **4z**, and **4w** on promastigotes of *L. donovani*. *L. donovani* promastigotes were treated for 24 h with increasing concentrations of three different compounds **4y**, **4z**, and **4w**, and then cell viability was assessed using alarm blue reagent (as described in Experimental Section).

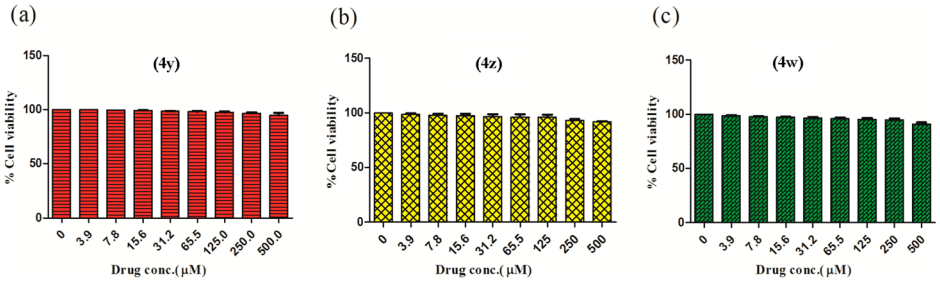

Figure 3. Toxic effect of **4y**, **4z**, and **4w** on RAW 264.7 macrophage. RAW 264.7 macrophages were treated for 24 h with increasing concentrations of **4y**, **4z**, and **4w**, and cell viability was assessed.

synthesis of *S*-alkyl/aryl benzothiazole-2-carbothioate derivatives. The *n*-tetrabutylammonium iodide (TBAI) was found to be particularly suitable and of importance for the success of this transformation. The protocol involves the formation of three new bonds, i.e., two C−S and one C═N, in a highly efficient and atom economical manner and without addition of oxidizing or reducing agents or coupling catalysts. In vitro analysis indicated compounds **4y**, **4z**, and **4w** to be most active among others. Docking studies also revealed a possible mode of binding in the binding pocket of TryR. Benzothiazole-2-carbothioate derivatives are expected to be promising lead molecules for the advancement of novel drugs against leishmania.

EXPERIMENTAL SECTION

Materials and Methods for Biological Screening. *Cell Culture and Parasite.* *L. donovani* strain AG83 (MHOM/IN/1983/AG83), originally isolated from an Indian kala-azar patient, was maintained by serial passage in hamsters. *L. donovani* amastigotes periodically recovered from the spleens of infected hamsters were transformed into promastigotes through amastigote culture in M199 supplemented with 10% FCS, 2 mM glutamine, penicillin G (100 U/mL), streptomycin sulfate (100 μg/mL) at 22 °C. Promastigotes were used at the log phase of growth, approximately 2 to 3 days after subculture. Parasites were kept in culture by weekly passaging.

In Vitro Antipromastigote Activity. Antiparasitic activity of compounds against *L. donovani* (AG83) promastigotes was determined by a quantitative colorimetric assay using Alamar blue reagent (Life Technologies). When cells are alive they maintain a reducing

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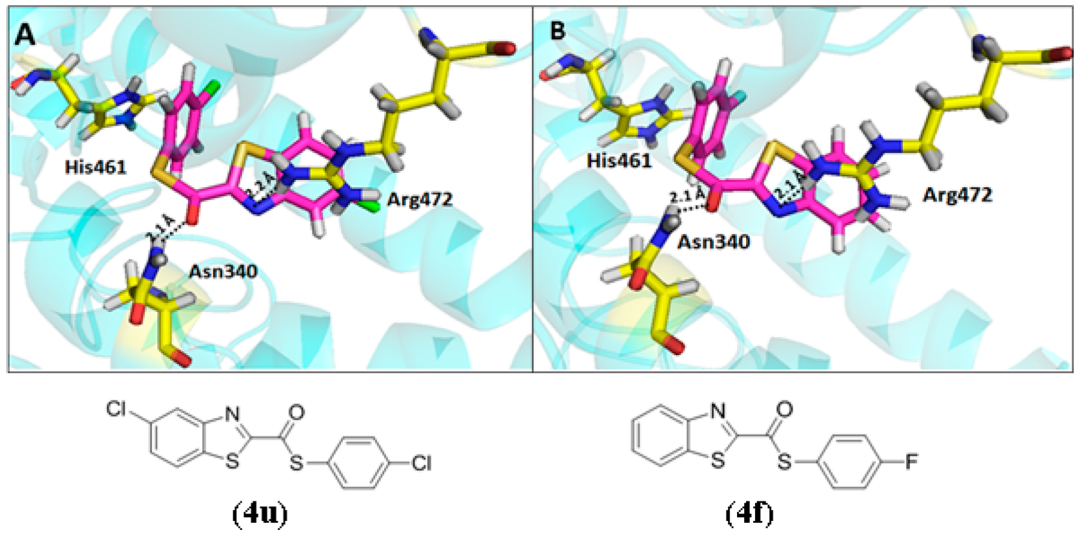

Figure 4. Binding model of ligands at the interface of the homodimer. Ligands are shown in stick models (magenta color). Hydrogen bonding interactions are shown as black dashes, and residues involved in hydrogen bonding or hydrophobic interactions (π–cation) are represented in stick models. (A) The binding mode of **4u**. (B) The binding mode of **4f**.

Table 5. G_{score} and E_{model} for the 25 Docked Compounds[a]

sample no.	compounds	G_{score}	E_{model}	sample no.	compounds	G_{score}	E_{model}
1	**4a**	−3.70	−44.12	14	**4n**	−3.54	−33.45
2	**4b**	−3.42	−31.10	15	**4o**	−3.58	−35.39
3	**4c**	−3.62	−32.90	16	**4p**	−3.84	−30.66
4	**4d**	−3.40	−33.02	17	**4q**	−3.66	−30.19
5	**4e**	−3.81	−35.44	18	**4s**	−3.58	−33.02
6	**4f**	−3.03	−35.49	19	**4t**	−4.72	−42.99
7	**4g**	−3.81	−36.36	20	**4u**	−4.15	−37.22
8	**4h**	−3.00	−31.43	21	**4v**	−3.57	−34.70
9	**4i**	−3.69	−33.45	22	**4w**	−3.70	−48.00
10	**4j**	−3.53	−30.17	23	**4x**	−3.85	−40.57
11	**4k**	−3.12	−32.33	24	**4y**	−4.87	−44.62
12	**4l**	−3.53	−43.75	25	**4z**	−3.81	−32.52
13	**4m**	−3.00	−32.02				

[a] G_{score} values are listed; for comparison, G_{score} of diarrylpyrrole[13a] is −4.27.

Table 6. Molinspiration Calculation of Properties for the Lipinsky Rule[a]

entry	nViol	natoms	miLog P	MW	nON	nOHNH	nrotb
acceptable range			<5	<500	<10	<5	
4a	0	19	4.46	285.39	2	0	3
4b	0	20	4.07	301.39	3	0	4
4e	0	19	3.53	287.37	3	1	3
4f	0	19	4.17	289.36	2	0	3
4g	0	20	4.04	301.39	3	0	4
4h	0	19	4.66	305.81	2	0	3
4i	0	19	4.41	285.39	2	0	3
4j	0	19	4.64	305.81	2	0	3
4l	0	18	4.01	271.37	2	0	3
4m	1	22	5.19	321.43	2	0	3
4n	0	19	4.07	285.39	2	0	4
4s	0	19	4.66	305.81	2	0	3
4w	1	23	5.33	353.39	2	0	4
4x	0	24	4.94	369.39	3	0	5
4y	1	23	5.51	373.81	2	0	4
4z	1	23	5.64	418.26	2	0	4

[a] nViol, no. of violations; natoms, no. of atoms; miLog P, Molinspiration predicted log *P*; MW, molecular weight; nON, no. of hydrogen bond acceptors; nOHNH, no. of hydrogen bond donors; nrotb, no. of rotatable bonds.

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environment within their cytosol. Resazurin/AlamarBlueH (7-Hydroxy-3*H*-phenoxazin-3-one 10-oxide), the active ingredient of AlamarBlue reagent, is a nontoxic, cell-permeable compound that is blue in color and virtually nonfluorescent. Upon entering cells, resazurin is reduced to resorufin, a compound that is red in color and highly fluorescent. Viable cells continuously convert resazurin to resorufin, increasing the overall fluorescence and color of the media surrounding cells. This assay has been reported to be more sensitive than MTT assay when compared for efficacy in estimating cell viability against a cancer cell line treated with more than 100 drugs.[13b] So we have used this assay for assessing the cell viability of cells treated with our compounds.

Assays were performed in sterile 96-well plates using 100 μL of log-phase promastigotes adjusted to 2×10^6 cells/mL. These cells were incubated in the absence (control) and presence of 3.9 μM, 7.8 μM, 15.6 μM, 31.2 μM, 65.5 μM, 125.0 μM, 250.0 μM, and 500.0 μM of compounds and the equivalent volume of the solvent (DMSO) for 24 h. After completion of treatment, 10 μL of the resazurin dye (0.01%) was added, and plates were incubated for a further 4 h at 37 °C. After incubation, cells were analyzed in a microplate reader at a wavelength of 570 nm, using 600 nm as a reference wavelength (normalized to the 600 nm value). Absorbance in the absence of any compound or solvent was set as the 100% control. Cell viability was evaluated based on a comparison with untreated control cells, and the inhibitory concentration of the compounds or the solvents that are necessary to reduce the growth of promastigotes by 50% (IC_{50} values) and 90% (IC_{90} values) was calculated.

Culture of RAW 264.7 Macrophage Cell Line and Cytotoxicity Measurement. The murine macrophage-like cell line RAW 264.7 was cultured in RPMI medium containing 10% FBS in tissue culture flasks. For the experiment, cells were detached in medium using a cell scraper. The cells were counted and plated overnight (5×10^4 cells/well) in a 96-well culture plate. The cytotoxic effect of compounds on RAW cells was than evaluated in the absence and presence 3.9 μM, 7.8 μM, 15.6 μM, 31.2 μM, 65.5 μM, 125.0 μM, 250.0 μM, and 500.0 μM of compounds and the equivalent volume of the solvent (DMSO) for 24 h. After completion of treatment, 10 μL of AlamarBlue reagent was employed to determine cytotoxicity as described above. The cell viability was evaluated based on a comparison with untreated control cells and the concentration of the compounds or the solvents that are necessary to reduce the viability of macrophages by 50% (IC_{50} values) and 90% (IC_{90} values) was calculated.

Molecular Docking Study. There is no crystal structure yet available for trypanothione reductase of *L. donovani* and thus we conducted our molecular docking studies (by using Glide 5.8 module in Maestro 9.3.)[13c−e] with trypanothione reductase from *L. infantum*, as there is 98% similarity between the trypanothione reductase of *L. donovani* and *L. infantum*. The molecular docking study was carried out using X-ray crystal structures of trypanothione reductase from *L. infantum* (PDB code: 2jk6, 2.95 Å).[14] Protein preparation and ligand preparation were carried out as per our previous work.[6] For the purpose of molecular docking studies, X-ray crystal structure of *L. infantum* trypanothione reductase was selected (PDB ID: 2jk6, resolution: 2.95 Å).[14] The crystal structure is in dimeric form, and it is cocrystallized with cofactor FAD. Both chains were considered for molecular docking studies because the binding site of trypanothione reductase is at the interface of the chain A and chain B. Protein preparation was performed using Maestro 9.3. Hydrogen atoms were added during protein preparation wizard. Three-dimensional structures of these compounds were then prepared using LigPrep module of Maestro implementing OPLS_2005 force field and ionic states for the ligands at pH values of 7.0 ± 2.0 were generated. Docking was performed using Glide 5.8 (grid-based ligand docking with energetics), with the standard precision (SP) mode to estimate protein−ligand binding affinities and static intermolecular interactions. The grid was defined 15 Å by considering all the key amino acids of the binding pocket. All 25 compounds were docked into the active site of TyR. A maximum of 10 docking poses per ligand were generated in each case and analyzed further for the binding mode and intermolecular interactions.

General Experimental Details. Melting points were determined on a melting point apparatus and are uncorrected. IR spectra were recorded on an IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on 400 and 600 MHz spectrometers using TMS as internal reference; chemical shifts (δ scale) are reported in parts per million (ppm). ^{1}H NMR spectra are reported in the following order: multiplicity, coupling constant (J value) in hertz (Hz) and no. of protons; signals were characterized as s (singlet), d (doublet), dd (doublet of doublets), t (triplet), and m (multiplet). Mass spectra were recorded using ESI/APCI mode (Q-TOF type mass analyzer). Column chromatographic separations were performed using silica gel (60−120 mesh). Complete crystallographic data of **4a** and **4o** for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC nos. 1430385 and 1430384, respectively. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

General Procedure for Synthesis of Compound ***4****.* To a stirred reaction mixture of thiol (**3**) (1.0 mmol), oxalyl chloride (**2**) (85 μL or 0.085 mL, 1.0 mmol), and catalyst TBAI (36.9 mg, 0.10 mmol) in acetonitrile (3 mL) at room temperature was added dropwise a solution of (**1**) 2-aminobenzenethiol or substituted 2-aminobenzenethiol (1.0 mmol) in acetonitrile (2 mL); in the case of 2-amino-4-(trifluoromethyl)benzenethiol hydrochloride, the solution is neutralized with potassium bicarbonate for 10 min before addition and subjected to heating at 60 °C until reaction completion. After completion of the reaction, the solvent was evaporated under reduced pressure and extracted with ethyl acetate (3 × 10 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield the crude product, which was purified by column chromatography on silica gel (60−120 mesh) to give the pure product (hexane:ethyl acetate).

*Spectral Data for All Products. S-p-Tolyl Benzo[d]thiazole-2-carbothioate (****4a****).* White solid; R_f = 0.73; yield 78% (223 mg); mp 137−139 °C. IR (KBr): 3055, 1919, 1810, 1690, 1659, 1616, 1593, 1548, 1482, 1455, 1421, 1399, 1376, 1318, 1281, 1240, 1203, 1180, 1157, 1127, 1104, 1063, 1038, 1018, 947, 880, 868, 853, 806, 758, 731, 700, 673, 636, 617, 540, 480 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 7.30 (d, J = 7.6 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.55 (t, J = 8.0 Hz, 1H), 7.62 (t, J = 7.2 Hz, 1H), 7.99 (d, J = 7.6 Hz, 1H), 8.27 (d, J = 8.0 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 21.6, 122.5, 122.9, 125.6, 127.4, 127.9, 130.5 (2C), 135.0 (2C), 136.9, 140.5, 153.1, 164.0, 185.6 ppm. HRMS (ESI): calcd for $C_{15}H_{11}NOS_2$ [M + H]$^+$: 286.0355; found 286.0374.

*S-(4-Methoxyphenyl) Benzo[d]thiazole-2-carbothioate (****4b****).* White solid; R_f = 0.53; yield 80% (242 mg); mp 150−152 °C. IR (KBr): 2959, 2837, 2048, 1965, 1929, 1893, 1801, 1692, 1673, 1612, 1592, 1573, 1550, 1497, 1480, 1455, 1439, 1419, 1408, 1316, 1294, 1253, 1203, 1185, 1174, 1123, 1109, 1061, 1033, 964, 948, 879, 859, 835, 808, 763, 731, 701, 674, 641, 619, 579, 545, 499 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.86 (s, 3H), 7.01 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.55 (t, J = 8.0 Hz, 1H), 7.61 (t, J = 7.6 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 8.26 (d, J = 8.4 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 55.5, 115.2 (2C), 116.8, 122.4, 125.5, 127.3, 127.8, 136.5 (2C), 136.8, 153.0, 161.2, 163.9, 185.9 ppm. HRMS (ESI): calcd for $C_{15}H_{11}NO_2S_2$ [M + H]$^+$: 302.0304; found 302.0306.

*S-(4-Chlorophenyl) Benzo[d]thiazole-2-carbothioate (****4c****).* White solid; R_f = 0.71; yield 74% (227 mg); mp 161−163 °C. IR (KBr): 3422, 3088, 2925, 2853, 1959, 1909, 1793, 1690, 1670, 1612, 1573, 1552, 1487, 1475, 1457, 1419, 1389, 1318, 1267, 1203, 1164, 1125, 1090, 1012, 941, 878, 861, 815, 758, 747, 726, 703, 669, 619, 529, 484 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (dd, J_1 = 7.6 Hz and J_2 = 8.4 Hz, 4H), 7.56 (t, J = 7.6 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 8.26 (d, J = 8.0 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 122.6, 125.1, 125.7, 127.6, 128.1, 129.9 (2C), 136.3 (2C), 136.7, 137.0, 153.1, 163.5, 184.8 ppm. HRMS (ESI): calcd for $C_{14}H_8ClNOS_2$ [M + H]$^+$: 305.9809; found 305.9810.

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*S-(4-Bromophenyl) Benzo[d]thiazole-2-carbothioate (**4d**).* White solid; R_f = 0.68; yield 76% (267 mg); mp 191−193 °C. IR (KBr): 3085, 2923, 2853, 1912, 1671, 1567, 1551, 1486, 1472, 1454, 1419, 1384, 1317, 1202, 1162, 1090, 1066, 1009, 885, 877, 844, 815, 758, 726, 703, 670, 619, 548, 477 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, J = 8.4 Hz, 2H), 7.57 (t, J = 8.0 Hz, 1H), 7.62 (d, J = 7.6 Hz, 3H), 7.80 (d, J = 7.6 Hz, 1H), 8.26 (d, J = 8.0 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 122.6, 125.0, 125.7 (2C), 127.6, 128.1, 132.8 (2C), 136.5 (2C), 137.0, 153.1, 163.5, 184.7 ppm. HRMS (ESI): calcd for $C_{14}H_8BrNOS_2$ $[M + H]^+$: 351.9282; found 351.9291.

*S-(4-Hydroxyphenyl) Benzo[d]thiazole-2-carbothioate (**4e**).* White solid; R_f = 0.14; yield 70% (202 mg); mp 191−192 °C. IR (KBr): 3452, 3059, 2923, 2848, 1650, 1624, 1597, 1581, 1550, 1497, 1480, 1455, 1429, 1417, 1337, 1317, 1269, 1201, 1168, 1098, 1062, 1010, 949, 880, 830, 816, 761, 731, 700, 671, 637, 624, 564, 509 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.34 (s, 1H, OH), 6.81 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 7.39 (t, J = 7.2 Hz, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$ + DMSO): δ 114.5, 116.7 (2C), 122.2, 125.1, 127.1, 127.6, 136.3 (2C), 136.4, 152.7, 159.2, 163.6, 185.9 ppm. HRMS (ESI): calcd for $C_{14}H_9NO_2S_2$ $[M + H]^+$: 288.0147; found 288.0149.

*S-(4-Fluorophenyl) Benzo[d]thiazole-2-carbothioate (**4f**).* White solid; R_f = 0.64; yield 65% (189 mg); mp 139−141 °C. IR (KBr): 3428, 3093, 3058, 1891, 1664, 1588, 1553, 1488, 1456, 1397, 1317, 1293, 1223, 1205, 1160, 1124, 1088, 1064, 1012, 941, 879, 860, 820, 758, 726, 696, 670, 635, 619, 542, 499 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.18 (t, J = 8.8 Hz, 2H), 7.54 (t, J = 7.6 Hz, 3H), 7.61 (t, J = 7.6 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 8.25 (d, J = 8.4 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 116.8, 117.0, 121.8, 121.8, 122.5, 125.7, 127.5, 128.1, 136.9, 137.1, 137.2, 153.1, 162.8, 163.5, 165.3, 185.3 ppm. HRMS (ESI): calcd for $C_{14}H_8FNOS_2$ $[M + H]^+$: 290.0104; found 290.0106.

*S-(3-Methoxyphenyl) Benzo[d]thiazole-2-carbothioate (**4g**).* White solid; R_f = 0.50; yield 78% (236 mg); mp 108−110 °C. IR (KBr): 3056, 3001, 2943, 2839, 1922, 1861, 1801, 1692, 1665, 1615, 1590, 1550, 1481, 1463, 1454, 1439, 1421, 1346, 1318, 1276, 1255, 1201, 1185, 1160, 1127, 1106, 1072, 1063, 1028, 991, 947, 896, 881, 872, 863, 809, 786, 758, 731, 705, 687, 675, 625, 558 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.84 (s, 3H), 7.03 (d, J = 8.0 Hz, 1H), 7.13 (s, 1H), 7.17 (d, J = 7.6 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.56 (t, J = 7.2 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 8.00 (d, J = 7.6 Hz, 1H), 8.26 (d, J = 8.0 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 55.6, 116.4, 120.0, 122.5, 125.6, 127.2, 127.4, 127.5, 128.0, 130.3, 136.9, 153.1, 160.2, 163.9, 185.1 ppm. HRMS (ESI): calcd for $C_{15}H_{11}NO_2S_2$ $[M + H]^+$: 302.0304; found 302.0313.

*S-(3-Chlorophenyl) Benzo[d]thiazole-2-carbothioate (**4h**).* White solid; R_f = 0.64; yield 72% (221 mg); mp 132−133 °C. IR (KBr): 3422, 3055, 2961, 1798, 1669, 1612, 1575, 1566, 1488, 1457, 1399, 1316, 1261, 1207, 1162, 1082, 1070, 1024, 995, 947, 881, 844, 820, 820, 776, 757, 726, 703, 678, 661, 623 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.40−7.48 (m, 3H), 7.57 (t, J = 8.0 Hz, 2H), 7.63 (t, J = 7.6 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 8.27 (d, J = 8.4 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 122.6, 125.7, 127.6, 128.2, 128.3, 130.4, 130.6, 133.2, 134.8, 135.2, 137.0, 153.0, 163.4, 184.6 ppm. HRMS (ESI): calcd for $C_{14}H_8ClNOS_2$ $[M + H]^+$: 305.9809; found 305.9827.

*S-o-Tolyl Benzo[d]thiazole-2-carbothioate (**4i**).* White solid; R_f = 0.62; yield 72% (206 mg); mp 65−67 °C. IR (KBr): 3053, 2925, 1918, 1798, 1697, 1662, 1627, 1589, 1550, 1482, 1456, 1419, 1318, 1281, 1209, 1125, 1060, 1037, 1013, 945, 879, 857, 814, 804, 755, 730, 703, 675, 669, 619, 551 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H), 7.29 (t, J = 7.2 Hz, 1H), 7.40 (t, J = 7.2 Hz, 2H), 7.56 (t, J = 8.0 Hz, 2H), 7.62 (t, J = 7.2 Hz, 1H), 8.00 (d, J = 7.6 Hz, 1H), 8.28 (d, J = 8.0 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 21.0, 122.5, 125.6, 125.9, 127.0, 127.4, 127.9, 130.8, 131.1, 136.3, 136.9, 142.9, 153.1, 164.0, 184.6 ppm. HRMS (ESI): calcd for $C_{15}H_{11}NOS_2$ $[M + H]^+$: 286.0355; found 286.0369.

*S-(2-Chlorophenyl) Benzo[d]thiazole-2-carbothioate (**4j**).* White solid; R_f = 0.64; yield 70% (215 mg); mp 144−146 °C. IR (KBr): 2924, 2850, 1957, 1921, 1692, 1673, 1612, 1573, 1551, 1485, 1450, 1433, 1419, 1382, 1319, 1249, 1208, 1115, 1064, 1034, 982, 950, 879, 852, 809, 759, 750, 725, 700, 670, 657, 617, 545, 469 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (t, J = 7.6 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.54−7.62 (m, 3H), 7.66 (d, J = 7.2 Hz, 1H), 7.99 (d, J = 7.6 Hz, 1H), 8.27 (d, J = 8.4 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 122.6, 125.7, 126.2, 127.5, 127.7, 128.1, 130.7, 131.9, 137.0, 137.6, 139.5, 153.1, 163.4, 183.5 ppm. HRMS (ESI): calcd for $C_{14}H_8ClNOS_2$ $[M + H]^+$: 305.9809; found 305.9829.

*S-(2-Bromophenyl) Benzo[d]thiazole-2-carbothioate (**4k**).* White solid; R_f = 0.63; yield 73% (256 mg); mp 167−169 °C. IR (KBr): 2926, 2856, 1740, 1691, 1672, 1610, 1485, 1457, 1447, 1429, 1415, 1384, 1319, 1258, 1208, 1109, 1064, 1018, 923, 879, 851, 808, 759, 749, 726, 697, 669, 646, 616 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (t, J = 8.0 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.57 (t, J = 8.0 Hz, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.78 (d, J = 7.6 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 8.28 (d, J = 8.0 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 122.6, 125.8, 127.6, 128.1, 128.4, 128.5, 130.2, 131.9, 134.0, 137.0, 137.6, 153.1, 163.4, 183.6 ppm. HRMS (ESI): calcd for $C_{14}H_8BrNOS_2$ $[M + H]^+$: 351.9282; found 351.9285.

*S-Phenyl Benzo[d]thiazole-2-carbothioate (**4l**).* White solid; R_f = 0.69; yield 68% (185 mg); mp 121−123 °C. IR (KBr): 3057, 2959, 2870, 1951, 1925, 1882, 1807, 1687, 1663, 1615, 1551, 1482, 1477, 1457, 1439, 1420, 1320, 1201, 1154, 1129, 1062, 1025, 948, 878, 808, 761, 749, 730, 723, 704, 686, 673, 620, 543, 457 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (s, 3H), 7.53−7.63 (m, 4H), 7.99 (d, J = 8.0 Hz, 1H), 8.26 (d, J = 8.0 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 122.4, 125.5, 126.4, 127.4, 127.9, 129.5 (2C), 130.1, 134.9 (2C), 136.8, 153.0, 163.7, 185.1 ppm. HRMS (ESI): calcd for $C_{14}H_9NOS_2$ $[M + H]^+$: 272.0198; found 272.0208.

*S-Naphthalen-2-yl Benzo[d]thiazole-2-carbothioate (**4m**).* White solid; R_f = 0.66; yield 70% (225 mg); mp 127−129 °C. IR (KBr): 3050, 2963, 1687, 1659, 1591, 1574, 1551, 1495, 1456, 1346, 1316, 1291, 1250, 1201, 1177, 1095, 1064, 1028, 943, 877, 860, 815, 758, 744, 728, 701, 671, 641, 544, 477 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.57 (t, J = 8.4 Hz, 3H), 7.63 (t, J = 8.4 Hz, 2H), 7.89 (t, J = 8.4 Hz, 2H), 7.95 (d, J = 8.0 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 8.12 (s, 1H), 8.29 (d, J = 8.4 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 122.6, 123.9, 125.7, 126.9, 127.5, 127.6, 128.0, 128.1 (2C), 128.3, 129.3, 131.1, 133.8, 135.2, 137.0, 153.2, 163.9, 185.5 ppm. HRMS (ESI): calcd for $C_{18}H_{11}NOS_2$ $[M + H]^+$: 322.0355; found 322.0354.

*S-Benzyl Benzo[d]thiazole-2-carbothioate (**4n**).* White solid; R_f = 0.68; yield 71% (203 mg); mp 102−104 °C. IR (KBr): 3418, 3059, 3031, 2924, 2856, 1946, 1656, 1631, 1551, 1496, 1482, 1454, 1420, 1384, 1318, 1210, 1070, 1020, 943, 884, 855, 820, 758, 729, 697, 675, 617, 561, 474 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.37 (s, 2H), 7.28 (d, J = 7.2 Hz, 1H), 7.33 (t, J = 7.6 Hz, 2H), 7.41 (d, J = 7.6 Hz, 2H), 7.52 (t, J = 7.6 Hz, 1H), 7.57 (t, J = 8.0 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 8.19 (d, J = 7.6 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 33.7, 122.5, 125.6, 127.4, 127.7, 127.9, 128.9 (3C), 129.3 (2C), 136.8, 153.1, 164.1, 186.3 ppm. HRMS (ESI): calcd for $C_{15}H_{11}NOS_2$ $[M + H]^+$: 286.0355; found 286.0354.

*S-2-Chlorobenzyl Benzo[d]thiazole-2-carbothioate (**4o**).* White solid; R_f = 0.62; yield 73% (234 mg); mp 131−132 °C. IR (KBr): 3447, 3056, 2925, 1656, 1634, 1552, 1491, 1471, 1439, 1420, 1404, 1316, 1279, 1246, 1209, 1160, 1123, 1068, 1050, 1035, 948, 889, 872, 856, 822, 762, 739, 729, 704, 688, 670, 584, 455 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.48 (s, 2H), 7.22 (t, J = 4.4 Hz, 2H), 7.38 (t, J = 4.4 Hz, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.57 (t, J = 8.0 Hz, 2H), 8.00 (d, J = 8.4 Hz, 1H), 8.19 (d, J = 8.0 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 31.5, 122.4, 125.5, 127.2, 127.3, 127.8, 129.2, 129.8, 131.5, 134.5, 134.7, 136.6, 153.0, 163.8, 186.1 ppm. HRMS (ESI): calcd for $C_{15}H_{10}ClNOS_2$ $[M + H]^+$: 319.9965; found 319.9981.

*S-Ethyl Benzo[d]thiazole-2-carbothioate (**4p**).* White solid; R_f = 0.76; yield 70% (157 mg); mp 91−93 °C. IR (KBr): 3050, 2967, 2933, 1948, 1912, 1708, 1657, 1636, 1551, 1484, 1455, 1422, 1410, 1373, 1317, 1270, 1211, 1165, 1125, 1059, 1011, 969, 883, 863, 850, 824,

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766, 731, 705, 682, 617 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.40 (t, J = 7.6 Hz, 3H), 3.14 (q, J = 8.0 Hz, 2H), 7.52 (t, J = 7.6 Hz, 1H), 7.58 (t, J = 8.0 Hz, 1H), 7.97 (d, J = 8.4 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 14.6, 23.8, 122.5, 125.6, 127.3, 127.8, 136.7, 153.2, 164.6, 187.0 ppm. HRMS (ESI): calcd for $C_{10}H_9NOS_2$ $[M + H]^+$: 224.0198; found 224.0203.

*S-Propyl Benzo[d]thiazole-2-carbothioate (**4q**).* Semisolid; R_f = 0.76; yield 68% (162 mg); IR (KBr): 3062, 2963, 2930, 2871, 1701, 1660, 1636, 1554, 1487, 1457, 1422, 1378, 1339, 1317, 1292, 1241, 1206, 1162, 1125, 1092, 1066, 1012, 941, 881, 854, 821, 760, 729, 703, 677, 617, 577 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.05 (t, J = 7.6 Hz, 3H), 1.74 (sext, J_1 = 7.2 Hz and J_2 = 7.6 Hz, 2H), 3.11 (t, J = 7.6 Hz, 2H), 7.51 (t, J = 8.0 Hz, 1H), 7.56 (t, J = 8.4 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H), 8.20 (d, J = 8.0 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 13.6, 22.8, 31.2, 122.5, 125.5, 127.3, 127.7, 136.7, 153.1, 164.6, 186.9 ppm. HRMS (ESI): calcd for $C_{11}H_{11}NOS_2$ $[M + H]^+$: 238.0355; found 238.0357.

*S-Dodecyl Benzo[d]thiazole-2-carbothioate (**4r**).* Gummy liquid; R_f = 0.84; yield 66% (240 mg); IR (KBr): 3449, 2952, 2915, 2850, 1659, 1633, 1486, 1471, 1383, 1317, 1209, 1069, 881, 855, 824, 757, 723, 678 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, J = 7.6 Hz, 3H), 1.23 (s, 16H), 1.45 (t, J = 7.6 Hz, 2H), 1.69−1.74 (m, 2H), 3.14 (t, J = 7.2 Hz, 2H), 7.52 (t, J = 8.4 Hz, 1H), 7.58 (t, J = 8.0 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 8.22 (d, J = 8.0 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 14.3, 22.9, 29.1, 29.3, 29.4, 29.5, 29.6, 29.7, 29.8 (2C), 29.9, 32.1, 122.5, 125.6, 127.3, 127.8, 136.7, 153.2, 164.7, 187.0 ppm. HRMS (ESI): calcd for $C_{20}H_{29}NOS_2$ $[M + H]^+$: 364.1763; found 364.1762.

*S-Phenyl 5-Chlorobenzo[d]thiazole-2-carbothioate (**4s**).* White solid; R_f = 0.69; yield 71% (218 mg); mp 148−150 °C. IR (KBr): 3419, 3058, 2924, 2852, 1902, 1749, 1680, 1642, 1585, 1570, 1538, 1487, 1477, 1438, 1308, 1204, 1176, 1092, 1068, 1060, 1023, 920, 866, 828, 808, 775, 756, 745, 735, 718, 687, 668, 648, 604 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.47−7.57 (m, 6H), 7.90 (d, J = 8.0 Hz, 1H), 8.23 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 123.3, 125.1, 126.2, 128.6, 129.7 (2C), 130.3, 133.7, 134.6, 135.0 (2C), 153.8, 165.7, 185.1 ppm. HRMS (ESI): calcd for $C_{14}H_8ClNOS_2$ $[M + H]^+$: 305.9809; found 305.9813.

*S-p-Tolyl 5-Chlorobenzo[d]thiazole-2-carbothioate (**4t**).* White solid; R_f = 0.65; yield 77% (247 mg); mp 169−171 °C. IR (KBr): 3420, 2923, 2854, 1743, 1681, 1640, 1568, 1541, 1485, 1434, 1404, 1310, 1203, 1182, 1091, 1068, 919, 867, 834, 806, 718, 669, 603, 544, 478 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 7.30 (d, J = 7.6 Hz, 2H), 7.44 (d, J = 7.6 Hz, 2H), 7.53 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 8.25 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 21.6, 122.7, 123.3, 125.2, 128.6, 130.5 (2C), 133.6, 134.9 (2C), 135.1, 140.7, 153.9, 165.8, 185.5 ppm. HRMS (ESI): calcd for $C_{15}H_{10}ClNOS_2$ $[M + H]^+$: 319.9965; found 319.9969.

*S-(4-Chlorophenyl) 5-Chlorobenzo[d]thiazole-2-carbothioate (**4u**).* White solid; R_f = 0.75; yield 73% (249 mg); mp 166−168 °C. IR (KBr): 3430, 3088, 2924, 2853, 1892, 1697, 1682, 1640, 1588, 1573, 1541, 1489, 1477, 1432, 1389, 1310, 1201, 1179, 1093, 1071, 1013, 919, 871, 833, 815, 798, 736, 718, 669, 648, 602, 532, 483 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.45−7.50 (m, 4H), 7.53 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.8 Hz, 1H), 8.24 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 123.3, 124.8, 125.2, 128.7, 129.9 (2C), 133.8, 135.1, 136.2 (2C), 136.8, 153.8, 165.2, 184.6 ppm. HRMS (ESI): calcd for $C_{14}H_7Cl_2NOS_2$ $[M + H]^+$: 339.9419; found 339.9415.

*S-(4-Bromophenyl) 5-Chlorobenzo[d]thiazole-2-carbothioate (**4v**).* White solid; R_f = 0.73; yield 75% (289 mg); mp 185−187 °C. IR (KBr): 3447, 3082, 2924, 2852, 1894, 1677, 1634, 1589, 1540, 1488, 1470, 1431, 1382, 1310, 1204, 1086, 1067, 1006, 916, 875, 836, 809, 729, 718, 669, 647, 603, 547, 480 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.91 (d, J = 8.8 Hz, 1H), 8.23 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 123.3, 125.1, 125.2, 125.4, 128.8, 132.9 (2C), 133.8, 135.1, 136.4 (2C), 153.8, 165.2, 184.5 ppm. HRMS (ESI): calcd for $C_{14}H_7BrClNOS_2$ $[M + H]^+$: 385.8891; found 385.8893.

*S-p-Tolyl 5-(Trifluoromethyl)benzo[d]thiazole-2-carbothioate (**4w**).* White solid; R_f = 0.73; yield 60% (213 mg); mp 153−155 °C. IR (KBr): 3428, 3047, 2924, 2856, 1918, 1732, 1678, 1645, 1490, 1463, 1332, 1318, 1254, 1224, 1203, 1176, 1146, 1132, 1071, 1051, 1021, 924, 895, 828, 807, 725, 667, 643 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 7.31 (d, J = 7.6 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.78 (d, J = 8.0 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 8.55 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 21.6, 122.5, 122.9 (q, $^3J_{C-F}$ = 4.5 Hz), 123.4, 124.0 (q, $^1J_{C-F}$ = 270.7 Hz), 124.1 (q, $^{3\prime}J_{C-F}$ = 3.1 Hz), 130.2 (q, $^2J_{C-F}$ = 33.6 Hz), 130.6 (2C), 134.9 (2C), 140.0, 140.8, 152.6, 166.2, 185.5 ppm. HRMS (ESI): calcd for $C_{16}H_{10}F_3NOS_2$ $[M + H]^+$: 354.0229; found 354.0224.

*S-(4-Methoxyphenyl) 5-(Trifluoromethyl)benzo[d]thiazole-2-carbothioate (**4x**).* White solid; R_f = 0.64; yield 62% (230 mg); mp 139−141 °C. IR (KBr): 3299, 3064, 2922, 2850, 2548, 2048, 1897, 1677, 1643, 1593, 1574, 1531, 1488, 1463, 1445, 1409, 1335, 1321, 1293, 1254, 1207, 1190, 1174, 1146, 1125, 1069, 1050, 1028, 925, 889, 833, 820, 800, 759, 728, 707, 666 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.86 (s, 3H), 7.02 (d, J = 7.2 Hz, 2H), 7.47 (d, J = 7.6 Hz, 2H), 7.77 (d, J = 7.6 Hz, 1H), 8.11 (d, J = 7.6 Hz, 1H), 8.54 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 55.6, 114.8, 115.4 (2C), 116.4, 122.9 (q, $^3J_{C-F}$ = 3.8 Hz), 123.4, 124.0 (q, $^1J_{C-F}$ = 271.5 Hz), 124.1 (q, $^{3\prime}J_{C-F}$ = 3.0 Hz), 130.2 (q, $^2J_{C-F}$ = 32.8 Hz), 132.8, 136.6 (2C), 140.0, 152.6, 161.4, 166.2, 185.9 ppm. HRMS (ESI): calcd for $C_{16}H_{10}F_3NO_2S_2$ $[M + H]^+$: 370.0178; found 370.0174.

*S-(2-Chlorophenyl) 5-(Trifluoromethyl)benzo[d]thiazole-2-carbothioate (**4y**).* White solid; R_f = 0.66; yield 56% (210 mg); mp 113−115 °C. IR (KBr): 3433, 3075, 2924, 2853, 1979, 1934, 1909, 1687, 1635, 1612, 1574, 1488, 1453, 1435, 1421, 1331, 1259, 1224, 1205, 1179, 1150, 1135, 1070, 1054, 1034, 923, 895, 865, 821, 756, 738, 723, 702, 666, 658, 638 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.79 (d, J = 8.8 Hz, 1H), 8.13 (d, J = 8.8 Hz, 1H), 8.56 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 123.0 (q, $^3J_{C-F}$ = 4.6 Hz), 123.5, 124.0 (q, $^1J_{C-F}$ = 270.8 Hz), 124.2 (q, $^{3\prime}J_{C-F}$ = 3.1 Hz), 125.8, 127.8, 130.3 (q, $^2J_{C-F}$ = 32.8 Hz), 130.8, 132.1, 137.5, 139.4, 140.1, 152.6, 165.6, 183.4 ppm. HRMS (ESI): calcd for $C_{15}H_7ClF_3NOS_2$ $[M + H]^+$: 373.9682; found 373.9681.

*S-(2-Bromophenyl) 5-(Trifluoromethyl)benzo[d]thiazole-2-carbothioate (**4z**).* White solid; R_f = 0.65; yield 58% (243 mg); mp 117−119 °C. IR (KBr): 3445, 3078, 2924, 2853, 1973, 1934, 1907, 1688, 1634, 1614, 1575, 1561, 1488, 1460, 1450, 1432, 1417, 1332, 1258, 1224, 1205, 1179, 1151, 1135, 1070, 1054, 1018, 923, 894, 821, 754, 730, 716, 707, 698, 665, 638 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (t, J = 8.0 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.78 (dd, J_1 = 7.6 Hz and J_2 = 8.8 Hz, 2H), 8.13 (d, J = 8.8 Hz, 1H), 8.56 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 123.0 (q, $^3J_{C-F}$ = 4.6 Hz), 123.5, 124.0 (q, $^1J_{C-F}$ = 270.8 Hz), 124.2 (q, $^{3\prime}J_{C-F}$ = 3.0 Hz), 128.0, 128.4, 130.1, 130.3 (q, $^2J_{C-F}$ = 33.6 Hz), 132.1, 134.1, 137.5, 140.1, 152.5, 165.6, 183.4 ppm. HRMS (ESI): calcd for $C_{15}H_7BrF_3NOS_2$ $[M + H]^+$: 417.9177; found 417.9174.

*S-p-Tolyl 6-Methoxybenzo[d]thiazole-2-carbothioate (**4za**).* White solid; R_f = 0.44; yield 79% (250 mg); mp 130−132 °C. IR (KBr): 3006, 2929, 2833, 1898, 1665, 1604, 1558, 1550, 1492, 1461, 1449, 1427, 1327, 1305, 1271, 1230, 1198, 1178, 1118, 1094, 1051, 1020, 907, 842, 818, 808, 798, 727, 700, 688, 668, 634, 607, 588, 515, 479 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 3.91 (s, 3H), 7.20 (dd, J_1 = 9.2 and J_2 = 9.6 Hz, 1H), 7.29 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 2.4 Hz, 1H), 7.45 (d, J = 7.6 Hz, 2H), 8.12 (d, J = 9.2 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 21.6, 56.0, 103.7, 118.1, 123.0, 126.3, 130.4 (2C), 135.0 (2C), 138.9, 140.4, 147.7, 159.9, 161.2, 185.3 ppm. HRMS (ESI): calcd for $C_{16}H_{13}NO_2S_2$ $[M + H]^+$: 316.0460; found 316.0464.

*S-(4-Methoxyphenyl) 6-Methoxybenzo[d]thiazole-2-carbothioate (**4zb**).* White solid; R_f = 0.40; yield 80% (265 mg); mp 181−183 °C. IR (KBr): 3061, 2958, 2827, 1666, 1597, 1570, 1553, 1490, 1476, 1447, 1429, 1410, 1292, 1268, 1257, 1245, 1199, 1174, 1121, 1116, 1054, 1021, 903, 842, 831, 824, 798, 735, 689, 667, 657, 611, 588, 526, 503, 438 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.82 (s, 3H), 3.84 (s, 3H), 6.97 (d, J = 8.8 Hz, 2H), 7.03 (dd, J_1 = 8.4 and J_2 =

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8.8 Hz, 1H), 7.27 (d, J = 2.4 Hz, 1H), 7.34 (d, J = 8.8 Hz, 2H), 7.81 (d, J = 8.8 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 55.5, 56.0, 104.3, 115.1, 115.4 (2C), 122.9, 126.3, 136.1 (2C), 136.7, 147.9, 157.4, 161.3, 164.5, 188.0 ppm. HRMS (ESI): calcd for $C_{16}H_{13}NO_3S_2$ $[M + H]^+$: 332.0410; found 332.0407.

*S-(4-Bromophenyl) 6-Methoxybenzo[d]thiazole-2-carbothioate (**4zc**).* White solid; R_f = 0.43; yield 77% (293 mg); mp 198−200 °C. IR (KBr): 2956, 2924, 2853, 1664, 1602, 1571, 1548, 1489, 1472, 1430, 1413, 1384, 1326, 1274, 1233, 1196, 1183, 1121, 1092, 1069, 1052, 1020, 1009, 904, 839, 822, 802, 734, 723, 665, 587, 518, 477, 437 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.92 (s, 3H), 7.21 (dd, J_1 = 9.2 and J_2 = 9.6 Hz, 1H), 7.37 (d, J = 2.4 Hz, 1H), 7.42 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 8.12 (d, J = 9.2 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 56.1, 103.8, 118.3, 124.9, 125.9, 126.4, 132.8 (2C), 136.6 (2C), 139.1, 147.7, 160.1, 160.6, 184.0 ppm. HRMS (ESI): calcd for $C_{15}H_{10}BrNO_2S_2$ $[M + H]^+$: 379.9409; found 379.9416.

*S-p-Tolyl 6-Ethylbenzo[d]thiazole-2-carbothioate (**4zd**).* White solid; R_f = 0.57; yield 76% (239 mg); mp 155−157 °C. IR (KBr): 3442, 2961, 2923, 2853, 1909, 1686, 1640, 1593, 1489, 1404, 1374, 1302, 1261, 1210, 1182, 1091, 1017, 896, 830, 809, 782, 699, 668, 624, 556, 474, 447, 421 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.31 (t, J = 8.0 Hz, 3H), 2.40 (s, 3H), 2.81 (q, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.4 Hz, 3H), 7.78 (s, 1H), 8.04 (d, J = 8.4 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 16.1, 21.6, 29.1, 120.5, 122.0, 123.4, 127.0, 128.7, 130.0, 130.6 (2C), 134.5 (2C), 140.8, 142.3, 153.2, 187.7 ppm. HRMS (ESI): calcd for $C_{17}H_{15}NOS_2$ $[M + H]^+$: 314.0668; found 314.0671.

*S,S-Di-p-tolyl Ethanebis(thioate) (**5**).* White solid; yield 50% (152 mg); mp 177−179 °C. IR (KBr): 3447, 2959, 2922, 2853, 1908, 1684, 1637, 1595, 1489, 1398, 1302, 1261, 1210, 1182, 1114, 1093, 1040, 1016, 809, 781, 698, 668, 627 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 2.41 (s, 6H), 7.28 (d, J = 7.8 Hz, 4H), 7.34 (d, J = 7.8 Hz, 4H) ppm. $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 21.6 (2C), 122.1 (2C), 130.6 (4C), 134.5 (4C), 140.8 (2C), 187.6 (2C) ppm. HRMS (ESI): calcd for $C_{16}H_{14}O_2S_2$ $[M + K]^+$: 341.0067; found 341.0056.

*2-(p-Tolyldisulfanyl)aniline (**6a**).* Gummy solid; yield 40% (99 mg); IR (KBr): 3470, 3373, 3064, 3017, 2919, 2853, 1690, 1608, 1506, 1488, 1476, 1446, 1397, 1307, 1251, 1209, 1179, 1158, 1139, 1115, 1078, 1017, 936, 806, 748, 620 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 2.35 (s, 3H), 4.38 (s, 2H, NH_2), 6.65 (t, J = 7.8 Hz, 1H), 6.75 (d, J = 7.8 Hz, 1H), 7.14 (d, J = 7.8 Hz, 2H), 7.17 (t, J = 7.8 Hz, 1H), 7.27−7.29 (m, 1H), 7.43−7.44 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 21.3, 115.8, 118.7, 119.6, 129.9 (2C), 131.3 (3C), 133.9, 135.6, 138.5, 147.8 ppm. HRMS (ESI): calcd for $C_{13}H_{13}NS_2$ $[M + H]^+$: 248.0562; found 248.0550.

2,2′-Disulfanediyldianiline[15] *(**6b**).* White solid; yield 40% (100 mg); mp 94−96 °C. IR (KBr): 3380, 3297, 3064, 1624, 1584, 1473, 1446, 1302, 1247, 1156, 1093, 1046, 1024, 963, 863, 848, 754, 696, 668 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 4.24 (s, 4H), 6.60 (t, J = 7.8 Hz, 2H), 6.72 (t, J = 7.8 Hz, 2H), 7.16 (t, J = 7.8 Hz, 4H) ppm. $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 115.4, 115.5, 118.4, 118.6, 131.8 (3C), 137.0 (3C), 148.6, 148.8 ppm. HRMS (ESI): calcd for $C_{12}H_{12}N_2S_2$ $[M + H]^+$: 249.0515; found 249.0504.

2,2′-Bibenzo[d]thiazole[16] *(**7**).* White solid; R_f = 0.35; yield 25% (68 mg); mp 239−240 °C. IR (KBr): 3056, 1691, 1660, 1596, 1550, 1484, 1457, 1423, 1402, 1378, 1320, 1205, 1182, 1159, 1128, 1105, 1065, 1019, 948, 881, 869, 855, 805 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.49 (t, J = 7.8 Hz, 2H), 7.57 (t, J = 7.2 Hz, 2H), 7.99 (d, J = 7.8 Hz, 2H), 8.17 (d, J = 8.4 Hz, 2H) ppm. $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 122.3 (2C), 124.3 (2C), 126.9 (2C), 127.1 (2C), 136.0 (2C), 153.8 (2C), 161.8 (2C) ppm. HRMS (ESI): calcd for $C_{14}H_8N_2S_2$ $[M + H]^+$: 269.0202; found 269.0198.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00113.

Complete crystallographic description, ^1H NMR and ^{13}C NMR spectra, and HRMS spectra (PDF)

Shelx 97 data for **4a** (CIF)

Shelx 97 data for **4o** (CIF)

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Notes

The authors declare no competing financial interest.

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