

Domino Reaction Protocol to Synthesize Benzothiophene-Derived Chemical Entities as Potential Therapeutic Agents

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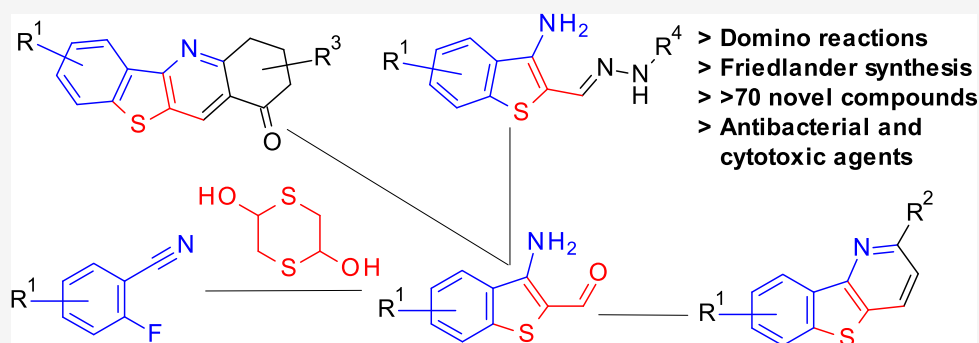
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ABSTRACT: An efficient synthesis of 3-amino-2-formyl-functionalized benzothiophenes by a domino reaction protocol and their use to synthesize a library of novel scaffolds have been reported. Reactions of ketones and 1,3-diones with these amino aldehyde derivatives formed a series of benzothieno[3,2-*b*]pyridine and 3,4-dihydro-2*H*-benzothienopheno[3,2-*b*]quinolin-1-one, respectively. A plausible mechanism for the formation of fused pyridine derivatives by the Friedlander reaction has been elucidated by density functional theory (DFT) calculations. Furthermore, hydrazones were obtained by reacting the aldehyde functional group of benzothiophenes with different hydrazine derivatives. Preliminary screening of these compounds against several bacterial strains and cancer cell lines led to the discovery of several hit molecules. Hydrazone and benzothieno[3,2-*b*]pyridine derivatives are potent cytotoxic and antibacterial agents, respectively. One of the potent compounds effected ~97% growth inhibition of the LOX IMVI cell line at 10 μ M concentration.

INTRODUCTION

Benzothiophene derivatives are known for their wide range of therapeutic properties.¹ Several drugs, such as arzoxifene² and raloxifene,³ selective estrogen receptor modulators; brexpiprazole,⁴ an antipsychotic agent; sertaconazole,⁵ an antifungal agent; and zileuton,⁶ a 5-lipoxygenase inhibitor, contain a benzothiophene core in their structures (Figure 1). Benzothiophene-derived polymers are gaining attention in the optoelectronic industry due to their π -conjugated system.⁷ Due to their useful therapeutic and material properties, a number of methodologies have been reported to synthesize benzothiophene derivatives. One of the most frequently used methodologies to synthesize benzothiophene derivatives is the 5-*endo*-dig or 5-*exo*-dig cyclization of *ortho*-thioanisole-containing arylalkynes in the presence of different electrophilic reagents such as iodine, bromine, *N*-bromosuccinimide (NBS), *p*-O₂NC₆H₄SCl, or PhSeCl.^{8–12} Perchloric and tetrafluoroboric acids have been reported as electrophiles to promote the intramolecular electrophilic cyclization of *o*-alkynyl aryl thioether.¹³ In addition, different transition metal catalysts such as PdCl₂,¹⁴ CuCl₂,¹⁵ and AuCl¹⁶ were used for the

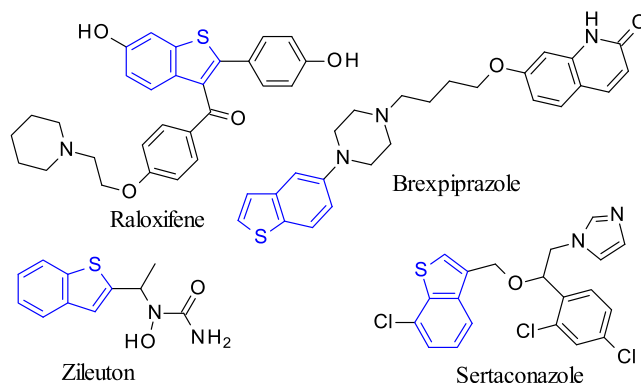


Figure 1. Available drugs containing the benzothiophene core.

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Scheme 1. Synthesis of 3-Amino-2-formyl Benzothiophene Derivatives

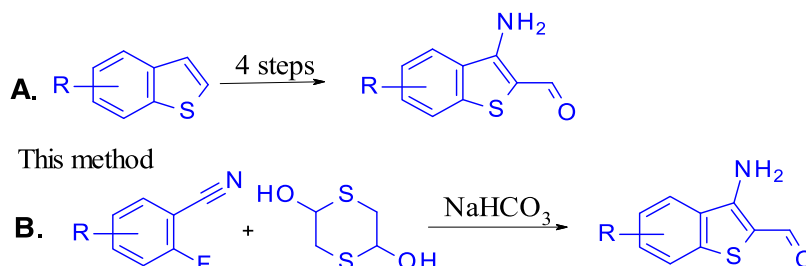
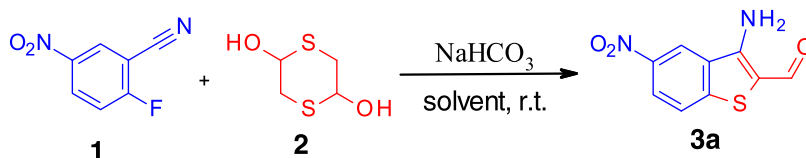
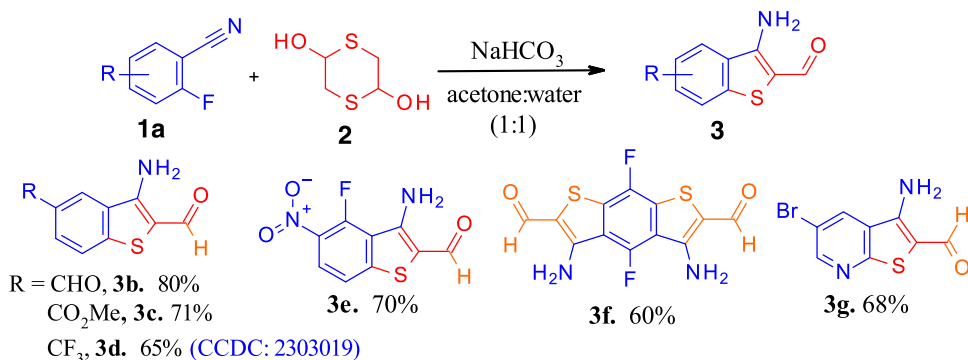


Table 1. Optimization of Reaction Conditions



entry	solvent	yield
1	water	N. R
2	methanol	75%
3	ethanol	72%
4	acetonitrile	traces
5	acetone	traces
6	THF	traces
7	DMF	traces
8	DMSO	traces
9	methanol/water (5:1)	29%
10	ethanol/water (5:1)	30%
11	acetone/water (5:1)	87%
12	acetone/water (1:1)	87%
13	THF/water (5:1)	63%

Scheme 2. Synthesis of 3-Amino-2-carbaldehyde Benzothiophene Derivatives



electrophilic cyclization of *o*-alkynyl aryl thioether to synthesize benzothiophene.¹² The reaction of *o*-bromo alkynyl benzenes with elemental chalcogens (sulfur, selenium, and tellurium) to synthesize benzo[*b*]chalcogenophenes has been reported.^{17,18} Other inorganic sulfur sources such as sodium sulfide (Na₂S·9H₂O),^{19–21} thionyl chloride,²² hydrogen sulfide,²³ thiourea,²⁴ and carbon disulfide²⁵ were reacted with *o*-halo alkynyl benzenes to synthesize benzothiophenes. 2-Halo benzonitrile derivatives were reacted with ethyl mercaptoacetate to synthesize 3-amino-2-ester-functionalized benzothiophenes.^{26–32}

However, the synthesis of 3-amino-2-aldehyde-functionalized benzothiophene is rare in the literature. 3-Amino-2-formyl-functionalized benzothiophenes have been synthesized from the corresponding benzothiophenes by a 4-step reaction process

(Scheme 1A).³³ In a continuation of developing domino methodologies to synthesize novel heterocyclic molecules,^{34–38} herein, we report the synthesis of 3-amino-2-formyl-function-alized benzothiophenes using a domino protocol (Scheme 1B).

RESULTS AND DISCUSSION

To find out the appropriate reaction conditions for the synthesis of 3-amino-2-formyl benzothiophene, initially, 2-fluoro-5-nitro benzonitrile (**1**) and 2,5-dihydroxy-1,4-dithiane (**2**) were reacted in water (Table 1, entry 1) in the presence of sodium bicarbonate at room temperature. We did not find any evidence for the product formation in this condition. Methanol and ethanol (entries 2 and 3) were found to be effective, and the reaction provided the product in 75 and 72% yields (**3a**),

respectively. In terms of polar aprotic solvents (entries 4–8), trace amounts of products were obtained. Concerning the solubility of the bicarbonate, we observed that the addition of water to the solvents facilitated the reaction. It was found that the addition of water to acetone provided the maximum yield (entries 11 and 12) of **3a**. Immediate formation of a red-colored precipitate indicated the starting of the reaction, and the reaction provided 87% yield in 8 h.

With satisfactory results, we explored the substrate scope of 2-fluorobenzonitrile derivatives. It was found that the presence of an electron-withdrawing group in the 2-fluorobenzonitrile furnished into 3-amino-2-formyl benzothiophene at room temperature or mild heating at 60 °C. The presence of an aldehyde group in the benzene ring provided the desired product (**3b**) in 80% yield under similar reaction conditions (Scheme 2). In the case of an ester and trifluoromethyl on 2-fluorobenzonitrile, mild heating at 60 °C was required, and acetonitrile with water (5%) was found as the best solvent to provide the desired products in 71% (**3c**) and 65% (**3d**) yields, respectively. Fluoro substitution on the nitro benzonitrile provided 70% (**3e**) yield at room temperature in an acetone solvent. The presence of four fluorine atoms and two nitriles made the benzene ring of tetrafluoroisophthalonitrile highly electron-deficient, and it also furnished the desired product (**3f**) in 60% yield under similar reaction conditions. We observed the feasibility of our reaction in the presence of nitrogen in the benzene ring of 2-fluorobenzonitrile. To our delight, 5-bromo-2-chloro-pyridine-3-carbonitrile furnished the reaction with the desired product in 68% (**3g**) yield under similar reaction conditions. To further utilize these products, we carried out these reactions in gram scales, and the desired compounds were obtained without compromising the yield and purity. These compounds have been characterized by ^1H , ^{13}C , and ^{19}F decoupled ^{13}C NMR spectroscopy. Furthermore, the structure of **3d** was confirmed by single-crystal X-ray diffraction (Figure S-221 and Table S1). Unsubstituted and 2-fluorobenzonitrile with electron-donating substituents did not give clean products.

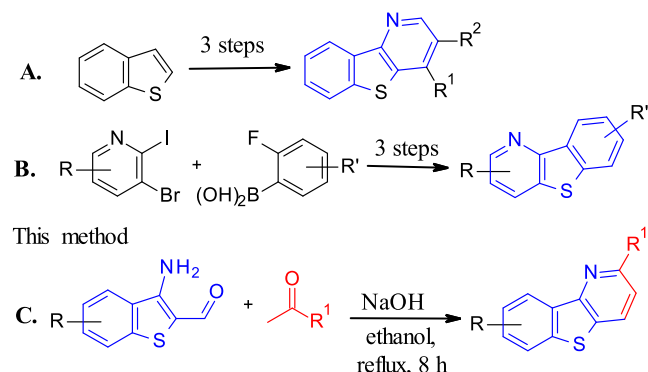
Synthesis of Benzothieno[3,2-*b*]Pyridine. To generate a library of novel compounds, we explored the reaction of 2-amino aldehyde derivatives to synthesize fused benzothieno[3,2-*b*]pyridines. Few literature reports were found describing the synthesis of these unique fused heterocycles. The synthesis of benzothieno[3,2-*b*]pyridines has been reported in three steps by using benzothiophene as a starting material (Scheme 3A).³⁹ They synthesized azido benzothiophene from benzothiophene, and in the second step, the iminotriphenylphosphorane group was produced by reacting with triphenylphosphine, followed by

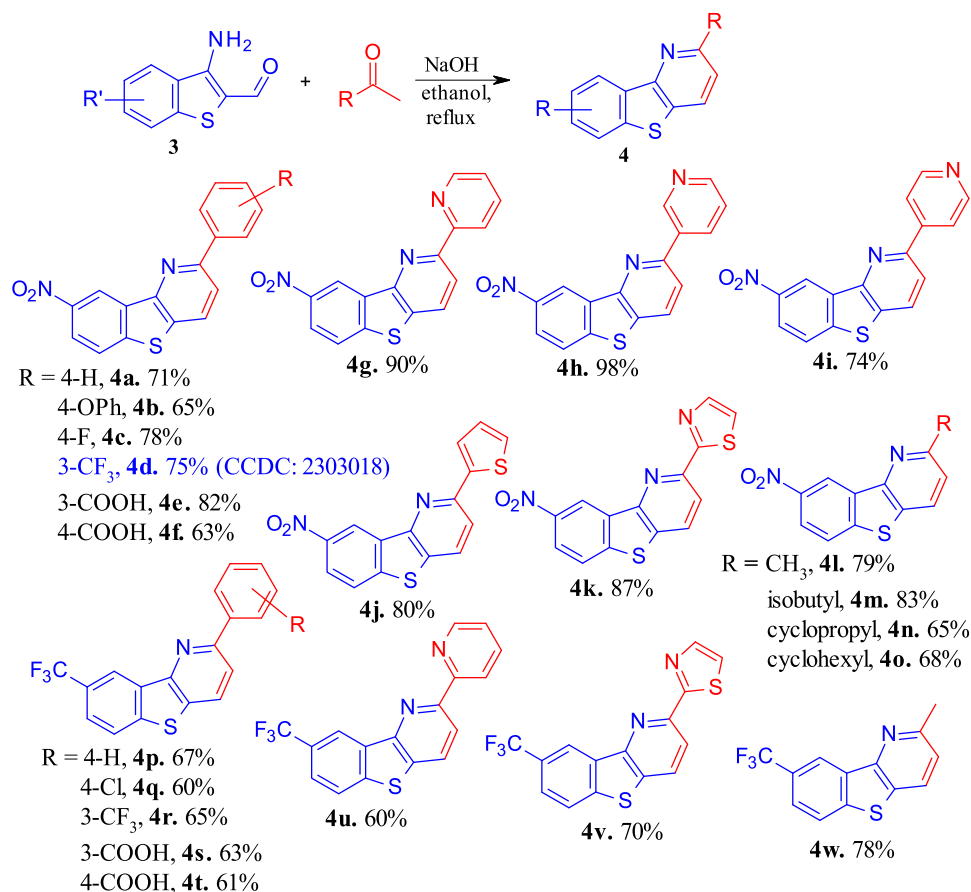
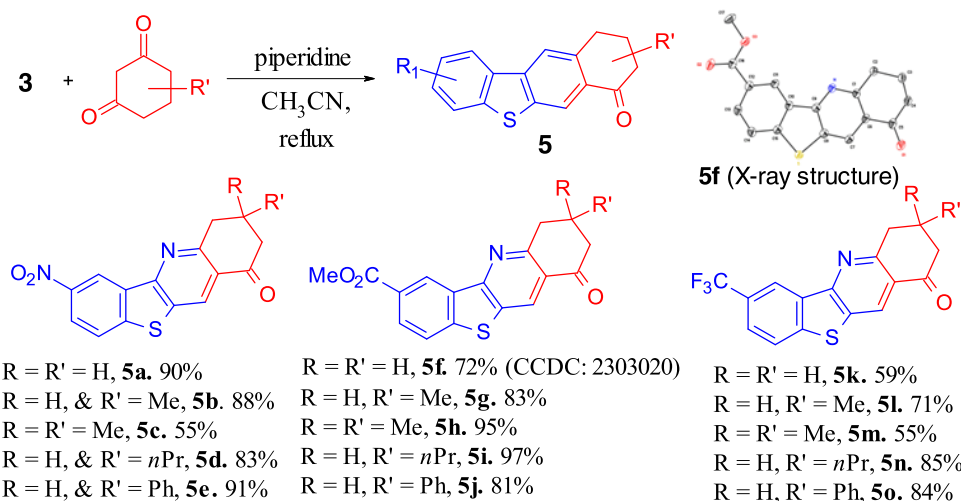
reacting with acrylaldehyde to form benzothieno[3,2-*b*]pyridines in the third step. In another report, dibenzothiophenes were synthesized in three steps, where the diphenyl type compound was obtained by Suzuki–Miyaura coupling and Pd-catalyzed C–S coupling in the next step by reacting with mercaptopropionate, and finally, benzothieno[3,2-*b*]pyridine was formed by in situ cyclization (Scheme 3B).⁴⁰ In another process, thiolate ion promoted 2,2'-bis(methylthio)–1,1'-biaryl derivatives to synthesize dibenzothiophene by cleaving two carbon–sulfur bonds and following cyclization by the concerted $\text{S}_{\text{N}}\text{Ar}$ reaction provided benzothieno[3,2-*b*]pyridine.⁴¹ We synthesized benzothieno[3,2-*b*]pyridine in an efficient and facile way by reacting 3-amino-2-formyl benzothiophene derivatives with simple ketones and active methylene-containing 1,3-diones in the presence of sodium hydroxide or piperidine and generated two libraries of benzothieno[3,2-*b*]pyridine (Scheme 3C).

We reacted **3a** with acetophenone in the ethanol solvent in the presence of sodium hydroxide (Scheme 4). The reaction provided pure fused product (**4a**) in 71% yield. Confident with the result, we explored the scope of ketones for this efficient reaction. We reacted **3a** with 4'-phenoxyacetophenone under similar reaction conditions, and it provided the product in 65% yield. We reacted electron-withdrawing groups containing acetophenone, such as 4-fluoro and 3-trifluoromethyl groups. These electron-deficient substituted ketones provided the desired product with 78% (**4c**) and (**4d**) 75% yield, respectively. The structure of this trifluoromethyl-substituted derivative (**4d**) was confirmed by a single-crystal X-ray structure (Figure S-222 and Table S1). We reacted *meta* (**4e**) and *para*-carboxyl (**4f**) groups containing acetophenones, and the expected products were formed without compromising the yields. Realizing the worth of heterocycles in medicinal chemistry, we reacted 2-, 3-, and 4-acetylpyridine with **3a**, and the reactions furnished the products in 90% (**4g**), 98% (**4h**), and 74% (**4i**) yields, respectively. The reaction with 2-acetyl thiophene and acetyl thiazole also completed the reaction in 80% (**4j**) and 87% (**4k**), respectively. It was observed that heterocycles containing ketone substrates provided better average yields when reacted with **3a** than other ketone derivatives. This may be due to the activating of the ketone by the electron-withdrawing nature of the heterocycles, which makes the carbonyl of the acetyl more reactive toward electrophilic reactions or enolate formation.

We further studied the scope of this methodology to synthesize novel molecules by reacting **3a** with aliphatic ketones. To our delight, this amino aldehyde derivative (**3a**) reacted with acetone (**4l**), methyl isobutyl ketone (**4m**), cyclopropyl methyl ketone (**4n**), and cyclohexyl methyl ketone (**4o**) under similar reaction conditions to give the products in good yields. We reacted trifluoromethyl-containing benzothiophene (**3d**) with acetophenone under similar reaction conditions, and it provided the desired product in 67% (**4p**) yield. The electron-withdrawing groups, such as 4-chloro- (**4q**), 3-trifluoromethyl- (**4r**), 3- (**4s**), and 4-carboxyl (**4t**)-containing acetophenones, also provided good yields of the products. The heterocycle-derived ketones, such as 2-acetylpyridine and acetyl thiazole, ended the reaction with 60% (**4u**) and 70% (**4v**) yields, respectively. A very good yield of the product (**4w**) was obtained when aliphatic ketone, acetone, was reacted with **3d**. In general, it was observed that the presence of the nitro group with benzothiophene provided a better yield in the formation of benzothieno[3,2-*b*]pyridine than in the presence of the trifluoromethyl group.

Scheme 3. Synthesis of Benzothieno[3,2-*b*]pyridine

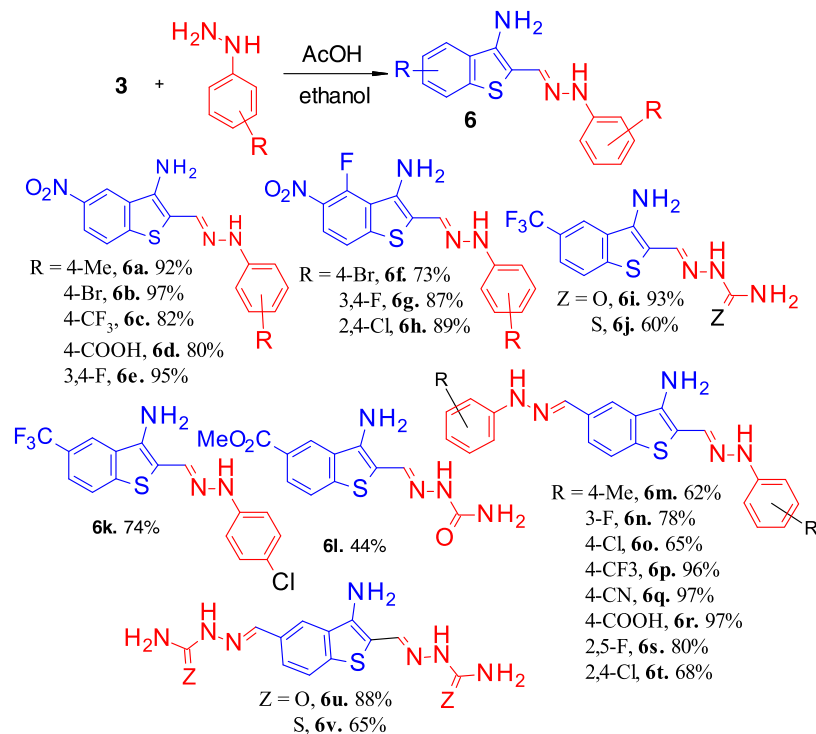


Scheme 4. Library of Benzothieno[3,2-*b*]pyridine DerivativesScheme 5. Synthesis of 3,4-Dihydro-2*H*-benzothiopheno[3,2-*b*]quinolin-1-one Derivatives

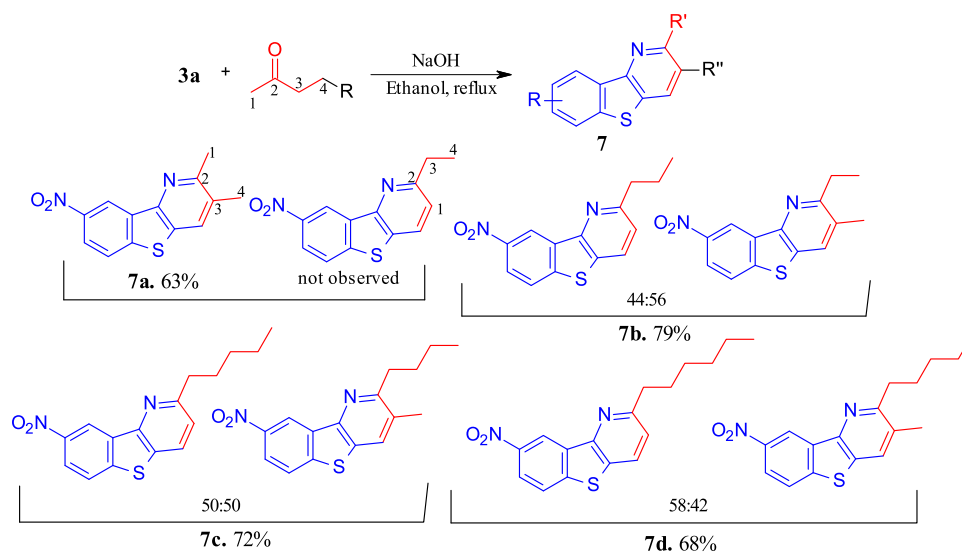
In continuation of observing the tolerability of the 3-amino-2-carbaldehyde functional group, we reacted benzothiophenes (**3a**, **3c**, **3d**) with 1,3-dione derivatives, an active methylene group containing ketones. A reaction between **3a** and 1,3-cyclohexanedione was conducted under similar reaction conditions, but no product formation was observed. However, the reaction of **3a** with 1,3-cyclohexanedione in acetonitrile and piperidine provided the desired product, 7-nitro-3,4-dihydro-2*H*-benzothiopheno[3,2-*b*]quinolin-1-one (**5a**), in 90% yield (Scheme 5). Then, we reacted other derivatives of 1,3-

cyclohexanediones with **3a** under similar reaction conditions. Some aliphatic substituents containing diones such as 5-methyl, 5,5-dimethyl, and 5-propylcyclohexane-1,3-dione provided 88% (**5b**), 55% (**5c**), and 83% (**5d**) yields, respectively. The phenyl-substituted cyclohexanedione also provided the desired product in 91% (**5e**) yield. The ester group containing benzothiophene (**3c**) reacted with different 1,3-diones under similar reaction conditions. It was observed that 1,3-cyclohexanedione provided 72% yield (**5f**), whereas the addition of aliphatic substituents increased the yields to 83% for 5-methyl (**5g**), 95% for 5,5-

Scheme 6. Library of Hydrazone with Different Substituted Benzothiophene



Scheme 7. Formation of Mixture Products with Aliphatic Ketones



dimethyl (**5h**), and 97% for 5-propylcyclohexane-1,3-diones (**5i**). In addition to ¹H and ¹³C NMR spectroscopy, the structure of **5f** has been confirmed by single-crystal X-ray diffraction (Figure S-223 and Table S1). 5-Phenyl-substituted 1,3-diones provided the desired product in 81% (**5j**) yield. We reacted trifluoromethyl-containing benzothiophene (**3d**) with different 1,3-diones under similar reaction conditions. All of the reactions provided the desired products with moderate to very good yields. 1,3-Cyclohexanedione provided the desired product in 59% (**5k**) yield. The addition of aliphatic substituents such as 5-methyl-, 5,5-dimethyl-, and 5-propyl-substituted 1,3-cyclohexanediones furnished the reaction in 71% (**5l**), 55% (**5m**), and 85% (**5n**) yields, respectively. The phenyl-substituted 1,3-dione provided a very good yield of the product (**5o**).

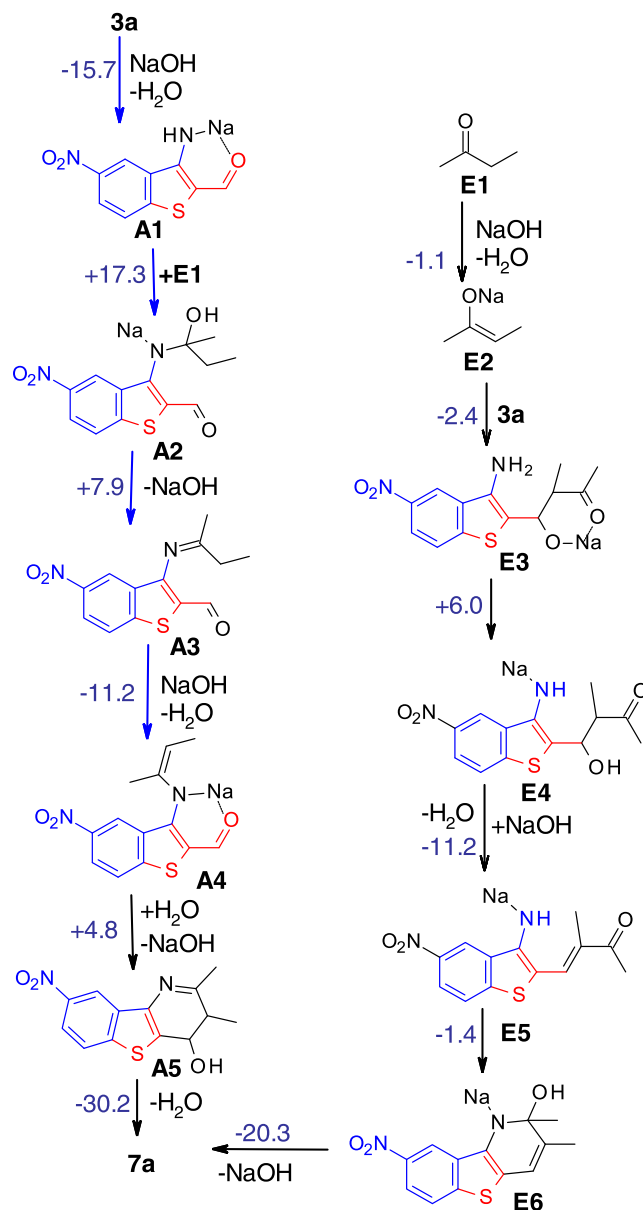
Synthesis of Hydrazones. Hydrazone derivatives are known for their wide range of therapeutic properties.⁴² We have found that pyrazole-derived hydrazones are potent antibacterial agents with selective activity against *Acinetobacter baumannii*.^{43,44} Envisioning the synthesis of hydrazones, we reacted our functionalized benzothiophenes with substituted hydrazines (Scheme 6). Initially, a reaction was conducted between nitro-substituted benzothiophene (**3a**) and 4-methylphenylhydrazine hydrochloride in an ethanol solvent and a few drops of acetic acid. The reaction provided the desired product in 92% yield (**6a**). By encouraging with the result, we reacted some electron-withdrawing group-substituted phenylhydrazines such as 4-bromo-, 4-trifluoromethyl-, 4-carboxy-, and 3,4-difluorophenyl hydrazine. These reactions provided the desired

products in 97% (**6b**), 82% (**6c**), 80% (**6d**), and 95% (**6e**) yields, respectively. Looking at the substrate scope in our benzothio-*phene* library, the 4-fluoro-5-nitro-substituted benzothio-*phene* (**3b**) also furnished the reaction with 4-bromo, 3,4-difluoro, and 2,4-dichlorophenyl hydrazine to afford hydrazone products in 73% (**6f**), 87% (**6g**), and 89% (**6h**) yields, respectively. Realizing the importance of semicarbazide, thiosemicarbazide, and trifluoromethyl in medicinal chemistry, we reacted them with 5-trifluoromethyl-substituted benzothio-*phene* (**3d**), and the reactions furnished semicarbazone and thiosemicarbazone products in 93% (**6i**) and 60% (**6j**) yields, respectively. The reaction of 4-chlorophenylhydrazine with **3d** also provided the desired product (**6k**) in 74% yield. The reaction between the ester group containing benzothio-*phene* (**3c**) and semicarbazide formed the semicarbazone (**6l**) product in 44% yield. The presence of two aldehyde functional groups in **3b** enabled us to make a library of dihydrazone-benzothio-*phene* compounds. Initially, a reaction was conducted between **3b** and 4-methylphenylhydrazine, and the reaction provided a pure product in 62% (**6m**) yield. The 3-fluoro- and 4-chloro-substituted phenylhydrazines provided the desired products in 78% (**6n**) and 65% (**6o**) yields, respectively. Other strong electron-withdrawing groups containing phenylhydrazines such as 4-trifluoromethyl, 4-cyano, and 4-carboxy likewise furnished the reactions efficiently with 96% (**6p**), 97% (**6q**), and 97% (**6r**) yields, respectively. The disubstituted phenylhydrazines such as 2,5-difluoro and 2,4-dichloro correspondingly formed the products in 80% (**6s**) and 68% (**6t**) yield, respectively. It was observed that a strong electron-withdrawing group containing phenylhydrazines provided a higher yield compared to mild electron-withdrawing group-substituted hydrazines. Finally, semicarbazide and thiosemicarbazide also provided dihydrazone-benzothio-*phene* products in 88% (**6u**) and 65% (**6v**) yields, respectively (Scheme 6).

Products of Long-Chain Aliphatic Ketones. For some aliphatic ketones, two products were formed from 2-amino aldehydes (**3**) in the Friedlander reaction (Scheme 7). In the reaction between methyl ethyl ketone and **3a**, we observed the formation of two methyl substituents in the pyridine ring (**7a**) with 63% yield. It shows that the C3 carbon of methyl ethyl ketone participated in the aldol product formation or the intramolecular reaction of the Schiff base formation in the Friedlander reaction.⁴⁵ The reaction of 2-pentanone, 2-heptanone, and 2-octanone with **3a** formed the mixture of products, **7b**, **7c**, and **7d** in 79, 72, and 68% yields, respectively. Both carbons, C1 and C3, of 2-pentanone, 2-heptanone, and 2-octanone reacted and provided the mixture of products. Due to little polarity difference between the compounds in a mixture, one single spot was observed on the TLC plate, and we were unable to separate them. The mixture of two compounds was confirmed in **7b**, **7c**, and **7d** by ¹H and ¹³C NMR spectra, while a single peak was observed in high-resolution mass spectra.

Mechanistic Analysis of the Friedlander Synthesis. Due to the lack of understanding of the mechanism of the Friedlander reaction in the literature and the complexity of fused pyridine compounds, we were motivated to investigate its feasibility by quantum chemical calculations. The mechanism of Friedlander Synthesis has been reported in literature studies by various research groups.^{45–48} Most of these studies are focused on the acid- or base-catalyzed mechanism forming aldol or imine intermediates, which eliminate water molecules to form the product. However, in the present system, we have explored both the possible mechanisms (Scheme 8) with other possible

Scheme 8. Plausible Mechanism for the Formation of Fused Pyridine derivatives by the Friedlander Reaction Computed Using M06-2X/6-31+G(d,p) + SCRF (Solvent = Ethanol), $\Delta G = \text{kcal/mol}$



intermediates (Scheme S1) of the Friedlander reaction. The Gibbs free energy (kcal/mol) for the formation of intermediate and products was calculated and is shown in Scheme 8. We first calculated the feasibility of the product formation (**7a**) via the enolate pathway (E). Based on our calculation of other possibilities, we found that E1 reacted in the presence of NaOH, simultaneously releasing a water molecule that was found to be exergonic with 1.1 kcal/mol. The reaction of enolate (E2) with the amino aldehyde to form the hydroxy ketone derivative (E3) is an exergonic reaction, with the Gibbs free energy (ΔG) of formation being -2.4 kcal/mol. The formation of E4 from E3 is endergonic with $+6$ kcal/mol. Water elimination from E4 to form E5 is highly favorable and exergonic ($\Delta G = -11$ kcal/mol), and water elimination from E5 to form E6 is also exergonic ($\Delta G = -1.4$ kcal/mol), followed by the sodium-amide derivative (E6) formation, which is also

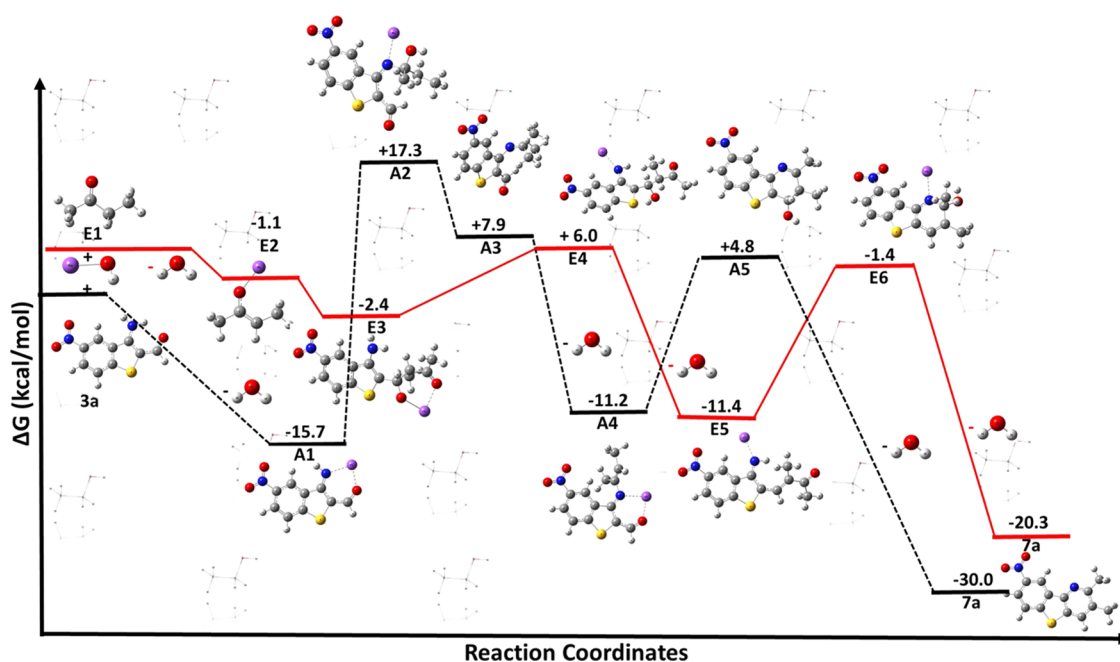


Figure 2. Probable Gibbs energy for the formation of fused pyridine derivatives by the Friedlander reaction calculated at M06-2X/6-31+G(d,p) in the presence of ethanol. The energy shown is with respect to each species.

exergonic. Intramolecular cyclization is also feasible, and the product (E6) formation is moderately exergonic. The final product (7a) formation via aromatization and removal of NaOH is highly exergonic with a ΔG value of -20.3 kcal/mol. The structure of intermediates and the energy change in each step are shown in the energy profile diagram (Figure 2).

In the imine pathway, the formation of sodium-amide derivative (A1) is highly exergonic, but the subsequent steps to react with the ketone (E1) are unfavorable due to the very high ΔG value (Scheme 8 and Figure 2). The imine (A3) formation is also endergonic, followed by an exergonic step to form the enamine derivative (A4). The intramolecular cyclization to form dihydropyridine (A5) is mildly endergonic, but the final step for the aromatization is highly exergonic. Based on the favorable energy change values, we propose a plausible mechanism for the Friedlander synthesis (7a) via an enolate pathway. We also calculated the Gibbs free energy change of other possible steps, but they were found to be unfavorable (Scheme S1).

Antibacterial and Cytotoxic Properties. In our quest to find antibacterial and antineoplastic agents,^{38,49–51} we tested these novel benzothiophene compounds against several strains of Gram-positive and Gram-negative bacterial strains. To our delight, we found several compounds with potent activity against Gram-positive bacteria and *A. baumannii*, a Gram-negative bacterium. The representative compound (4e) inhibited the bacteria with a minimum inhibitory concentration as low as 4 $\mu\text{g/mL}$ (Figure 3). This pyridine-fused benzothiophene is very effective in inhibiting the growth of *Staphylococcus aureus* and *Bacillus subtilis* strains. *S. aureus* strains included methicillin and oxacillin-resistant strains such as *S. aureus* ATCC 700699 (MRSA). The positive control, an approved antibiotic (vancomycin), inhibited the growth of MRSA with an MIC value of 2 $\mu\text{g/mL}$. These results are very important as MRSA causes the most common antibiotic-resistant bacterial infections,⁵² and finding new antibiotics with novel scaffolds is very important to address the antibiotic resistance problem.

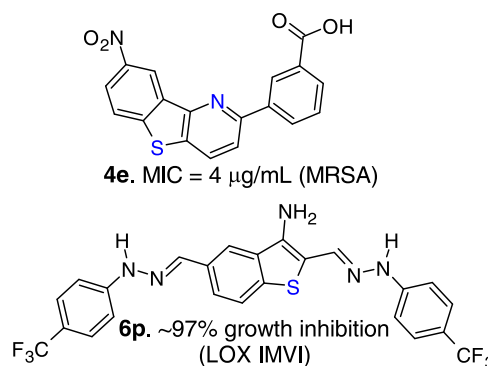


Figure 3. Structure of the hit compounds: potent antibacterial (4e) and potent cytotoxic (6p) agents.

To study the anticancer potential of these compounds, we submitted some of these novel benzothiophene derivatives to the National Cancer Institute's Developmental Therapeutics Program (DTP) (<https://dctd.cancer.gov/>). We found that the hydrazone class of compounds (Scheme 6) is very active against the NCI-60 cell lines. NCI-60 data for one of these potent compounds are shown in Figure 4. The preliminary cytotoxicity data is very promising. This potent compound (6p) inhibited the growth of the melanoma cell line very effectively as ~97% growth inhibition was observed against the LOX IMVI cell line at the 10 μM treatment of the compound. The growth of MALME-3 M and SK-MEL-5 was inhibited very significantly. This compound consistently inhibited the growth of the colon cancer cell line panel, with the maximum effect seen against the HCT-15 cell line. These results are very significant as melanoma is the most lethal form of skin cancer and colon cancer is the third most deadly and fourth most commonly diagnosed cancer in the world.^{53,54} Moderate inhibition was seen for other cell lines such as non-small cell lung cancer, ovarian cancer, and breast cancer. This compound is least effective against cell lines of the leukemia panel. Thus, this compound is not generally

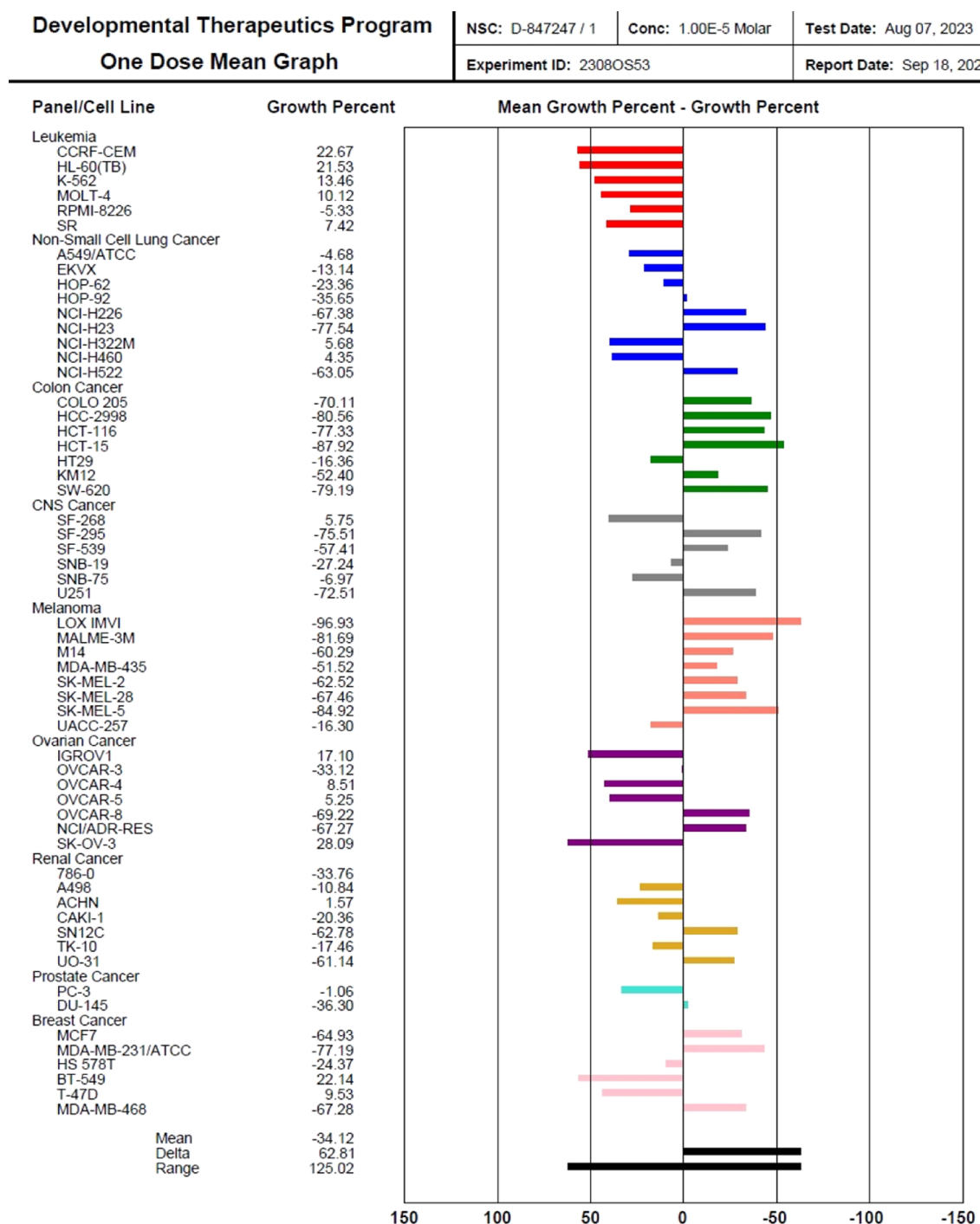


Figure 4. Cytotoxicity data of compound **6p** against NCI-60 cancer cell lines.

cytotoxic (poison) against human cell lines. Rather, it works on selective cell lines, most likely by inhibiting a particular protein or cell signaling pathway. Furthermore, this compound did not show any antibacterial activity at 32 $\mu\text{g/mL}$ concentration, which further confirms the selectivity toward some cancer cell lines.

CONCLUSIONS

We have developed an efficient methodology to synthesize 3-amino-2-formyl-functionalized benzothienophenes on a gram scale by using benign reaction conditions. The use of these amino aldehyde compounds has been shown by synthesizing

different classes of novel molecular entities. The reaction of 2-ketones and 1,3-diones with amino aldehydes has formed simple pyridine-fused and ketone-bearing pyridine-fused derivatives of benzothienophenes, respectively. The aldehyde group of 3-amino-2-formyl-functionalized benzothienophenes has been functionalized to hydrazones. Antibacterial and cytotoxic studies of these compounds led to the discovery of several hit compounds with the selective activity of benzothieno[3,2-*b*]pyridine and hydrazone derivatives as potent antineoplastic and antibacterial agents, respectively. These will be the foundation to further synthesize a library of compounds based on the structure of hit molecules to study the structure–activity relationship (SAR)

and further in vitro and in vivo studies to find novel therapeutic agents.

EXPERIMENTAL SECTION

General Information. All reactions were carried out in the standard air atmosphere in round-bottom flasks. All reacting materials, reagents, and solvents were bought from Fischer Scientific (Hanover Park, IL) and Oakwood Chemical (Estill, SC). No chemicals were further purified. Proton (^1H), Fluorine (^{19}F), Carbon (^{13}C), and ^{19}F decoupled ^{13}C spectra were recorded on JEOL with 400 MHz for ^1H , 101 MHz for ^{13}C , 100 MHz for ^{19}F decoupled ^{13}C , and 376 MHz for ^{19}F in $\text{DMSO}-d_6$, CDCl_3 and $\text{TFA}-d$ solvents. ^1H NMR spectra are described in chemical shift (δ , ppm), and multiplicity are designated as follows: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublets of doublet, ddd = doublets of doublets of doublet, td = triplets of doublet, and m = multiplet. The Shimadzu IT-TPF mass spectrometer was used to obtain high-resolution mass spectroscopy (HRMS). The crystal structures of the compounds were obtained by a Rigaku XtaLAB Synergy-S diffractometer.

General Procedure for the Synthesis of Compounds 3a–3g.

A mixture of 2-fluoro nitrile derivative (1 mmol), 2,5-dihydroxy-1,4-dithiane (0.55 mmol, 0.55 equiv), and sodium bicarbonate (1.1 mmol, 1.1 equiv) were taken in a 50 mL round-bottom flask. An equal ratio of acetone and water (10 mL) solvent was added, and the reaction mixture was stirred at room temperature for 8 h. The reaction formed solid products. The solid products were filtered, washed thoroughly with distilled water, and vacuum-dried to get the desired products. In the case of products 3c and 3d, the reactions were conducted in acetonitrile (10 mL) and water (0.5 mL) as solvents. Acetonitrile was used for recrystallization of compounds 3c, 3e, 3f, and 3g. Toluene was used to recrystallize compound 3d.

General Procedure for the Synthesis of Compounds 4a–4w.

These compounds were synthesized by following the Friedlander reaction protocol⁴⁵ with some modifications. A mixture of 3-amino-2-formyl benzothiophene (0.5 mmol), ketone (0.7 mmol, 1.4 equiv), 10 mL of ethanol, and 0.5 mL of aqueous NaOH (7 M) was added to a 50 mL round-bottom flask sequentially. The reaction mixture was refluxed for 12 h. Then, 10% HCl (5 mL) was added to quench the reaction mixture. The obtained precipitates were filtered and washed thoroughly with distilled water. Vacuum drying provided the desired products. In the case of impurity, acetonitrile or methanol solvent was used for recrystallization.

General Procedure for the Synthesis of Compounds 5a–5o.

These compounds were synthesized by following the Friedlander reaction protocol⁴⁵ with some modifications. A mixture of 3-amino-2-formyl benzothiophene (0.5 mmol), 1,3-dione (0.55 mmol, 1.1 equiv), 10 mL of acetonitrile, and 0.5 mL of piperidine was added to a 50 mL round-bottom flask sequentially. The reaction mixture was refluxed for 12 h. Distilled water was added to quench the reaction mixture. The obtained precipitates were filtered and washed thoroughly with distilled water. Vacuum drying provided the desired products. In the case of impurities, acetonitrile or methanol solvent was used for recrystallization.

General Procedure for the Synthesis of Compounds 6a–6w.

A mixture of 3-amino-2-formyl benzothiophene (0.5 mmol), hydrazine derivative (0.55 mmol, 1.1 equiv), 10 mL ethanol, and ~5 drops of acetic acid was added to a 50 mL round-bottom flask. The reaction mixture was refluxed for 12 h in an oil bath. Then, distilled water was added to make the precipitates. The precipitates were filtered, washed thoroughly with water, and vacuum-dried to get pure hydrazone products.

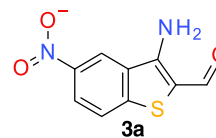
Procedure for DFT Calculations. The optimized geometries of reactants, intermediates, and products were computed using hybrid-density functional theory, i.e., M06-2X⁵⁵ with Pople 6-31+G(d,p) in ethanol solvent medium. M06-2X is a frequently used preeminent functional to investigate the reaction mechanism for investigating chemical systems that encounter nonbonding interaction. In our previous studies, we used a similar level of theory to predict the reaction mechanism, and the results were consistent with the experimental

analysis.^{36,38} To account for the van der Waals interaction, Grimme empirical dispersion “GD3” was used.⁵⁶ The normal modes of vibrational frequency were performed at M06-2X/6-31+G(d,p) to account for zero point corrections (ZPE) for the reactants, intermediate, and products. The positive vibrational frequencies indicate that all of the optimized structures have minimal energy. All of the DFT calculations were carried out using the Gaussian 16 suite of programs.⁵⁷

EXPERIMENTAL DATA

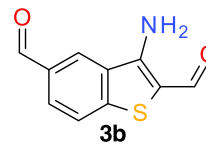
3-Amino-5-nitro-1-benzothiophene-2-carbaldehyde (3a).

Red solid (193 mg, 87%); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.00 (s, 1H), 9.14 (s, 1H), 8.22 (d, J = 8.6 Hz, 1H), 8.03–7.95 (m, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, $\text{DMSO}-d_6$) δ 182.4, 151.7, 147.5, 145.2, 132.6, 125.4, 123.5, 120.4, 111.6; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_9\text{H}_7\text{N}_2\text{O}_3\text{S}$ 223.0172; found 223.0166.



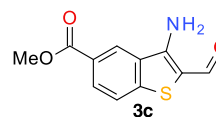
3-Amino-1-benzothiophene-2,5-dicarbaldehyde (3b).

Yellowish solid (164 mg, 80%); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.03–9.99 (m, 2H), 8.73 (s, 1H), 8.02–7.88 (m, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, $\text{DMSO}-d_6$) δ 192.5, 182.3, 152.0, 147.2, 133.2, 132.9, 129.1, 126.9, 125.0, 110.6; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{10}\text{H}_8\text{N}_2\text{O}_2\text{S}$ 206.0270; found 206.0265.



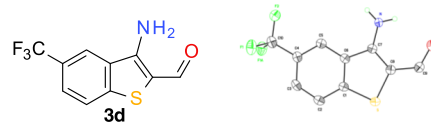
Methyl 3-Amino-2-formyl-1-benzothiophene-5-carboxylate (3c).

Yellowish solid (167 mg, 71%); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.01 (s, 1H), 8.84 (s, 1H), 8.00 (dd, J = 8.5, 1.0 Hz, 1H), 7.94–7.87 (m, 3H), 3.86 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, $\text{DMSO}-d_6$) δ 182.1, 166.5, 152.0, 146.0, 132.6, 130.0, 129.5, 126.2, 126.0, 124.5, 52.8; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}_5\text{S}$ 236.0376; found 236.0371.



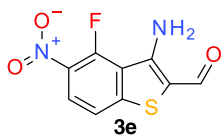
3-Amino-5-(trifluoromethyl)-1-benzothiophene-2-carbaldehyde (3d).

Gray solid (159 mg, 65%); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.03 (s, 1H), 8.62 (s, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.83–7.76 (m, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, $\text{DMSO}-d_6$) δ 151.4, 145.0, 132.5, 126.0, 125.6 (q, $^3J_{\text{C}-\text{CF}_3}$ = 3.4 Hz), 125.5 (q, $^2J_{\text{C}-\text{CF}_3}$ = 32.3 Hz), 125.4, 125.1, 125.0 (q, $^1J_{\text{C}-\text{CF}_3}$ = 272.1 Hz), 121.7 (q, $^3J_{\text{C}-\text{CF}_3}$ = 4.33 Hz), 110.9; ^{19}F decoupled ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ 182.4, 151.4, 145.0, 132.5, 125.6, 125.5, 125.5, 125.0, 121.7, 49.1; ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ –60.0; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{10}\text{H}_7\text{F}_3\text{NOS}$ 246.0195; found 246.0189.

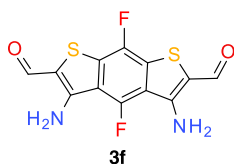


3-Amino-4-fluoro-5-nitro-1-benzothiophene-2-carbaldehyde (3e).

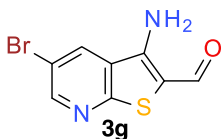
Dark red solid (168 mg, 70%); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.03 (s, 1H), 8.57 (dd, J = 8.8, 4.2 Hz, 1H), 7.55–7.41 (m, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, $\text{DMSO}-d_6$) δ 183.3, 163.6 (d, $^2J_{\text{C}-\text{F}}$ = 265.9 Hz), 149.1, 139.2, 139.1, 129.7 (d, $^3J_{\text{C}-\text{F}}$ = 11.1 Hz), 122.8 (d, $^3J_{\text{C}-\text{F}}$ = 14.4 Hz), 112.3 (d, $^2J_{\text{C}-\text{F}}$ = 23.1 Hz), 112.0; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_9\text{H}_6\text{FN}_2\text{O}_3\text{S}$ 241.0078; found 241.0068.



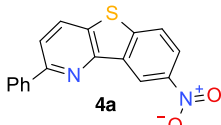
3-Amino-4,5,6-trifluoro-2-formyl-1-benzothiophene-7-carbonitrile (3f). Light yellow solid (153 mg, 60%); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.94–10.10 (1H), 7.60–7.86 (2H); ^{19}F decoupled $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, $\text{DMSO}-d_6$) δ 182.5, 153.5, 149.5, 147.7, 128.6, 119.7, 110.0; ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ 124.61 (d, $^1J_{\text{F}-\text{C}} = 22.9$ Hz), 125.19 (d, $^1J_{\text{F}-\text{C}} = 22.9$ Hz); HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{12}\text{H}_7\text{F}_3\text{N}_2\text{O}_2\text{S}_2$ 312.9911; found 312.9909.



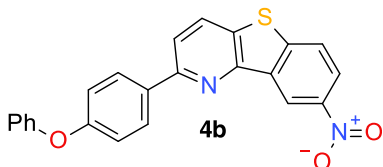
3-Amino-5-bromo-thieno[2,3-b]pyridine-2-carbaldehyde (3g). Yellowish solid (174.8 mg, 68%); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.03 (s, 1H), 8.82 (d, $J = 2.1$ Hz, 1H), 8.76 (d, $J = 2.2$ Hz, 1H), 7.81 (s, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, $\text{DMSO}-d_6$) δ 204.5, 182.5, 160.3, 152.3, 148.8, 134.8, 128.4, 116.0; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_8\text{H}_6\text{BrN}_2\text{O}_2\text{S}$ 256.9379; found 256.9383.



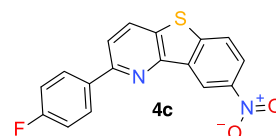
8-Nitro-2-phenyl[1]benzothieno[3,2-b]pyridine (4a). Gray solid (217 mg, 71%); ^1H NMR (400 MHz, $\text{TFA}-d$) δ 9.75 (d, $J = 1.8$ Hz, 1H), 9.12 (d, $J = 8.7$ Hz, 1H), 8.68 (dd, $J = 9.1, 1.5$ Hz, 1H), 8.35–8.30 (m, 2H), 7.94 (d, $J = 7.8$ Hz, 2H), 7.79–7.75 (m, 1H), 7.72–7.68 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, $\text{TFA}-d$) δ 153.0, 148.6, 146.2, 141.7, 141.7, 138.2, 133.6, 130.0, 129.7, 128.0, 126.7, 125.6, 124.9, 123.0, 119.7; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{11}\text{N}_2\text{O}_2\text{S}$ 307.0536; found 307.0535.



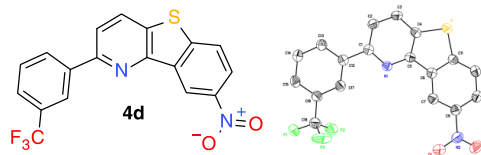
8-Nitro-2-(4-phenoxyphenyl)[1]benzothieno[3,2-b]pyridine (4b). Gray solid (258 mg, 65%); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.96 (d, $J = 4.9$ Hz, 1H), 8.53 (t, $J = 7.5$ Hz, 1H), 8.32–8.22 (m, 4H), 8.05 (t, $J = 7.5$ Hz, 1H), 7.44–7.39 (m, 2H), 7.20–7.15 (m, 1H), 7.09–7.08 (m, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, $\text{DMSO}-d_6$) δ 158.6, 156.6, 154.2, 150.4, 146.8, 145.8, 134.9, 133.5, 133.4, 133.2, 130.7, 129.2, 125.3, 124.5, 123.0, 119.7, 119.0, 117.7; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{15}\text{N}_2\text{O}_3\text{S}$ 399.0798; found 399.0795.



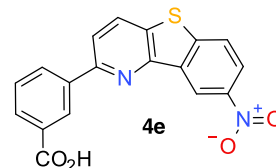
2-(4-Fluorophenyl)-8-nitro[1]benzothieno[3,2-b]pyridine (4c). Gray solid (253 mg, 78%); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.10 (d, $J = 5.8$ Hz, 1H), 8.65–8.61 (m, 1H), 8.41–8.33 (m, 4H), 8.18–8.14 (m, 1H), 7.38–7.32 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, $\text{DMSO}-d_6$) δ 163.7 (d, $^1J_{\text{C}-\text{F}} = 246.6$ Hz), 153.8, 150.5, 146.9, 145.9, 135.0, 134.9, 133.8, 133.5, 129.7 (d, $^3J_{\text{C}-\text{F}} = 8.1$ Hz), 125.4, 123.2, 119.9, 117.8, 116.3 (d, $^2J_{\text{C}-\text{F}} = 21.2$ Hz); HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{10}\text{FN}_2\text{O}_2\text{S}$ 325.0442; found 325.0438.



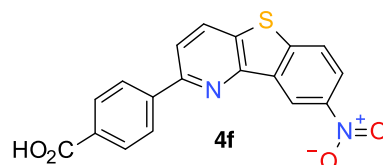
8-Nitro-2-[3-(trifluoromethyl)phenyl][1]benzothieno[3,2-b]pyridine (4d). Gray solid (280 mg, 75%); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.05 (d, $J = 2.8$ Hz, 1H), 8.67 (dd, $J = 8.4, 3.8$ Hz, 1H), 8.55 (s, 2H), 8.36–8.32 (m, 2H), 8.29–8.26 (m, 1H), 7.82–7.75 (m, 2H); ^{19}F decoupled $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 154.0, 151.4, 146.4, 146.0, 139.4, 135.3, 133.9, 131.8, 131.5, 130.5, 129.6, 126.1, 124.2, 124.0, 123.7, 123.0, 119.4, 119.0; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{10}\text{F}_3\text{N}_2\text{O}_2\text{S}$ 375.0409; found 375.0409.



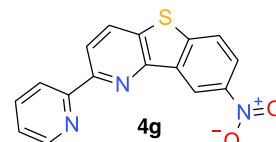
3-(8-Nitro[1]benzothieno[3,2-b]pyridin-2-yl)benzoic Acid (4e). Dark gray solid (287 mg, 82%); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.00 (d, $J = 2.2$ Hz, 1H), 8.76 (s, 1H), 8.64–8.61 (m, 1H), 8.48–8.46 (m, 1H), 8.37–8.30 (m, 2H), 8.18 (dd, $J = 8.5, 4.6$ Hz, 1H), 8.03–8.01 (m, 1H), 7.64 (td, $J = 7.7, 4.7$ Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, $\text{DMSO}-d_6$) δ 167.7, 153.7, 150.6, 146.9, 145.8, 138.8, 134.8, 134.3, 133.6, 132.0, 131.7, 130.7, 129.9, 128.0, 125.4, 123.2, 120.2, 117.7; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{11}\text{N}_2\text{O}_4\text{S}$ 351.0434; found 351.0430.



4-(8-Nitrobenzothienopheno[3,2-b]pyridin-2-yl)benzoic acid (4f). Gray solid (220 mg, 63%); ^1H NMR (400 MHz, $\text{TFA}-d$) δ 9.95 (s, 1H), 9.35 (d, $J = 8.6$ Hz, 1H), 8.87 (d, $J = 9.1$ Hz, 1H), 8.63–8.61 (m, 2H), 8.55–8.47 (m, 2H), 8.27–8.26 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, $\text{TFA}-d$) δ 171.0, 151.1, 148.9, 146.4, 142.5, 142.2, 139.5, 135.1, 132.7, 131.7, 128.8, 126.7, 126.1, 125.1, 123.4, 120.2; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{11}\text{N}_2\text{O}_4\text{S}$ 351.0434; found 351.0430.

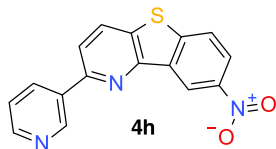


8-Nitro-2-(pyridin-2-yl)[1]benzothieno[3,2-b]pyridine (4g). Gray solid (276 mg, 90%); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.52 (s, 1H), 9.01–8.96 (m, 2H), 8.89 (d, $J = 8.6$ Hz, 1H), 8.73–8.65 (m, 2H), 8.48–8.39 (m, 2H), 8.08 (t, $J = 6.4$ Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, $\text{DMSO}-d_6$, $\text{TFA}-d$, CDCl_3) δ 151.2, 147.8, 147.7, 146.9, 146.3, 144.2, 142.9, 138.4, 134.0, 134.0, 127.4, 124.8, 124.7, 124.0, 120.7, 119.0; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{10}\text{N}_3\text{O}_2\text{S}$ 308.0488; found 308.0492.

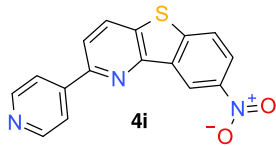


8-Nitro-2-(pyridin-3-yl)[1]benzothieno[3,2-b]pyridine (4h). Gray solid powder (301 mg, 98%); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.68 (s, 1H), 9.33 (d, $J = 8.3$ Hz, 1H), 8.99–8.98 (m, 1H), 8.92–8.90 (m, 1H), 8.53 (d, $J = 8.4$ Hz, 1H), 8.24–8.20 (m, 2H), 8.14–8.07 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, $\text{DMSO}-d_6$, $\text{TFA}-d$) δ 150.8, 148.1, 146.7, 145.8, 143.7, 141.8, 140.4, 137.6, 136.1, 134.2, 133.4, 127.7,

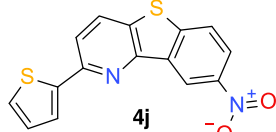
124.7, 123.2, 120.0, 117.9; HRMS (ESI-TOF) m/z : $[M + H]^+$ calcd for $C_{16}H_{10}N_3O_2S$ 308.0488; found 308.0492.



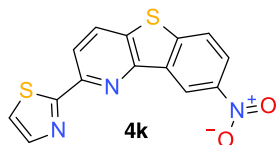
8-Nitro-2-(pyridin-4-yl)[1]benzothiopheno[3,2-b]pyridine (4i). Gray solid (227 mg, 74%); 1H NMR (400 MHz, DMSO- d_6) δ 9.06 (s, 1H), 8.72–8.67 (m, 3H), 8.35–8.34 (m, 2H), 8.27 (dd, J = 8.2, 5.1 Hz, 1H), 8.21 (s, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO- d_6) δ 152.1, 151.0, 150.8, 147.0, 146.0, 145.4, 135.7, 134.7, 133.8, 125.5, 123.5, 121.5, 120.5, 117.9; HRMS (ESI-TOF) m/z : $[M + H]^+$ calcd for $C_{16}H_{10}N_3O_2S$ 308.0488; found 308.0484.



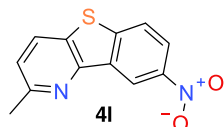
8-Nitro-2-(2-thienyl)benzothiopheno[3,2-b]pyridine (4j). Gray powder (249 mg, 80%); 1H NMR (400 MHz, DMSO- d_6) δ 8.98 (s, 1H), 8.59 (d, J = 8.5 Hz, 1H), 8.41–8.34 (m, 2H), 8.13 (d, J = 8.6 Hz, 1H), 7.94 (d, J = 3.6 Hz, 1H), 7.69 (d, J = 4.5 Hz, 1H), 7.19 (dd, J = 4.9, 3.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO- d_6) δ 150.9, 150.2, 146.9, 145.9, 144.3, 134.5, 133.4, 133.4, 129.6, 129.2, 127.1, 125.5, 123.3, 118.9, 117.7; HRMS (ESI-TOF) m/z : $[M + H]^+$ calcd for $C_{15}H_9N_2O_2S_2$ 313.0110; found 313.0113.



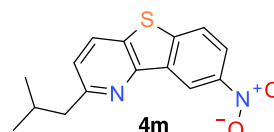
8-Nitro-2-thiazol-2-yl-benzothiopheno[3,2-b]pyridine (4k). Light greenish solid (272 mg, 87%); 1H NMR (400 MHz, TFA- d) δ 9.60 (d, J = 6.6 Hz, 1H), 8.73–8.66 (m, 2H), 8.41–8.38 (m, 2H), 8.25–8.23 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, TFA- d) δ 170.5, 152.0, 148.2, 145.8, 140.9, 140.0, 133.8, 133.4, 133.3, 124.3, 124.1, 124.1, 120.1, 119.1; HRMS (ESI-TOF) m/z : $[M + H]^+$ calcd for $C_{14}H_8N_3O_2S_2$ 314.0052; found 314.0058.



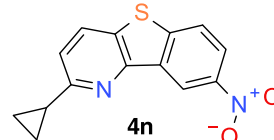
2-Methyl-8-nitrodibenzo[b,d]thiophene (4l). Gray solid (192 mg, 79%); 1H NMR (400 MHz, DMSO- d_6) δ 8.95 (s, 1H), 8.41 (d, J = 8.4 Hz, 1H), 8.34–8.27 (m, 2H), 7.45 (d, J = 8.4 Hz, 1H), 2.67 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO- d_6) δ 157.3, 150.2, 146.5, 146.0, 135.0, 132.4, 132.3, 125.2, 123.3, 122.7, 117.5, 24.6; HRMS (ESI-TOF) m/z : $[M + H]^+$ calcd for $C_{12}H_9N_2O_2S$ 245.0379; found 245.0373.



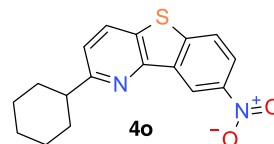
2-Isobutyl-8-nitro-benzothiopheno[3,2-b]pyridine (4m). Light brick red powder (237 mg, 83%); 1H NMR (400 MHz, DMSO- d_6) δ 8.99 (s, 1H), 8.50 (d, J = 8.3 Hz, 1H), 8.39–8.33 (m, 2H), 7.48 (d, J = 8.1 Hz, 1H), 2.81–2.79 (m, 2H), 2.19–2.16 (m, 1H), 0.91 (d, J = 6.3 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO- d_6) δ 160.3, 150.2, 146.6, 145.9, 135.0, 132.6, 132.5, 125.4, 123.6, 122.9, 117.6, 47.0, 29.4, 22.8; HRMS (ESI-TOF) m/z : $[M + H]^+$ calcd for $C_{15}H_{15}N_2O_2S$ 287.0849; found 287.0844.



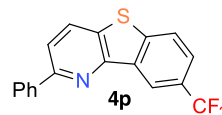
2-Cyclopropyl-8-nitro-benzothiopheno[3,2-b]pyridine (4n). Gray powder (175 mg, 65%); 1H NMR (400 MHz, DMSO- d_6) δ 8.91 (s, 1H), 8.43–8.30 (m, 3H), 7.51 (d, J = 8.3 Hz, 1H), 2.30–2.29 (m, 1H), 1.10–1.05 (m, 4H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO- d_6) δ 161.8, 150.2, 146.7, 145.8, 134.8, 132.3, 131.9, 125.4, 122.9, 121.8, 117.5, 17.3, 11.2; HRMS (ESI-TOF) m/z : $[M + H]^+$ calcd for $C_{14}H_{11}N_2O_2S$ 271.0536; found 271.0532.



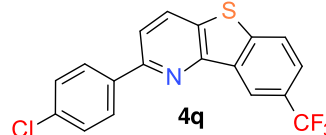
2-Cyclohexyl-8-nitro-benzothiopheno[3,2-b]pyridine (4o). Gray solid (212 mg, 68%); 1H NMR (400 MHz, DMSO- d_6) δ 8.97 (s, 1H), 8.48 (d, J = 8.5 Hz, 1H), 8.37–8.31 (m, 2H), 7.50 (d, J = 8.5 Hz, 1H), 2.90–2.84 (m, 1H), 1.94–1.58 (m, 7H), 1.45–1.26 (m, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO- d_6) δ 165.1, 149.9, 146.6, 145.8, 135.0, 132.8, 132.7, 125.4, 122.9, 121.6, 117.5, 46.1, 33.1, 26.6, 26.1; HRMS (ESI-TOF) m/z : $[M + H]^+$ calcd for $C_{17}H_{17}N_2O_2S$ 313.1005; found 313.1007.



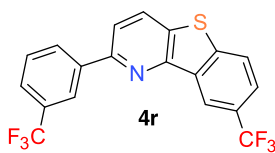
2-Phenyl-8-(trifluoromethyl)benzothiopheno[3,2-b]pyridine (4p). Light yellowish solid (220 mg, 67%); 1H NMR (400 MHz, DMSO- d_6) δ 8.71 (d, J = 4.4 Hz, 1H), 8.66–8.62 (m, 1H), 8.37–8.33 (m, 1H), 8.30–8.27 (m, 2H), 8.19–8.15 (m, 1H), 7.93 (t, J = 6.3 Hz, 1H), 7.55–7.45 (m, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO- d_6) δ 154.6, 150.7, 144.4, 138.6, 134.8, 133.4, 133.2, 129.9, 129.5, 127.4, 127.4, 126.6 ($^2J_{C-CF_3}$ = 32.3 Hz), 125.5, 125.3 ($^3J_{C-CF_3}$ = 3.8 Hz), 119.8, 119.6 ($^3J_{C-CF_3}$ = 3.8 Hz); HRMS (ESI-TOF) m/z : $[M + H]^+$ calcd for $C_{18}H_{11}F_3NS$ 330.0559; found 330.0563.



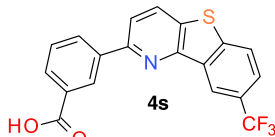
2-(4-Chlorophenyl)-8-(trifluoromethyl)benzothiopheno[3,2-b]pyridine (4q). Brick red (217 mg, 60%); 1H NMR (400 MHz, DMSO- d_6) δ 8.68 (s, 1H), 8.62 (d, J = 8.5 Hz, 1H), 8.34–8.29 (m, 3H), 8.16 (d, J = 8.5 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.56–7.54 (m, 2H); ^{19}F decoupled $^{13}C\{^1H\}$ NMR (101 MHz, DMSO- d_6) δ 153.2, 150.7, 144.4, 137.4, 134.8, 134.6, 133.6, 133.3, 130.6, 129.4, 129.1, 126.6, 125.5, 125.4, 125.0, 119.6; HRMS (ESI-TOF) m/z : $[M + H]^+$ calcd for $C_{18}H_{10}ClF_3NS$ 364.0169; found 364.0178.



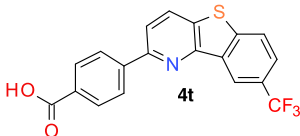
8-(Trifluoromethyl)-2-[3-(trifluoromethyl)phenyl]-benzothiopheno[3,2-b]pyridine (4r). White powder (258 mg, 65%); 1H NMR (400 MHz, DMSO- d_6) δ 8.73–8.70 (m, 2H), 8.63–8.59 (m, 2H), 8.37 (d, J = 8.5 Hz, 1H), 8.32 (d, J = 8.5 Hz, 1H), 7.96 (dd, J = 8.4, 1.3 Hz, 1H), 7.84–7.75 (m, 2H); ^{19}F decoupled $^{13}C\{^1H\}$ NMR (101 MHz, DMSO- d_6) δ 152.8, 150.8, 144.5, 139.7, 134.6, 134.2, 133.6, 131.5, 130.7, 130.2, 126.4, 126.3, 125.6, 125.5, 123.8, 123.7, 120.1, 119.8, 119.7; HRMS (ESI-TOF) m/z : $[M + H]^+$ calcd for $C_{19}H_{10}F_6NS$ 398.0433; found 398.0437.



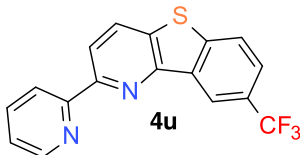
3-[8-(Trifluoromethyl)benzothiopheno[3,2-*b*]pyridin-2-yl]-benzoic acid (4s). White solid (235 mg, 63%); ^1H NMR (400 MHz, DMSO- d_6) δ 8.76 (s, 1H), 8.65 (s, 2H), 8.51 (d, J = 6.5 Hz, 1H), 8.34 (d, J = 7.8 Hz, 1H), 8.20 (d, J = 7.9 Hz, 1H), 8.03–7.92 (m, 2H), 7.67–6.65 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6) δ 167.7, 153.6, 150.7, 144.4, 139.0, 134.6, 133.8, 133.3, 132.0, 131.7, 130.6, 129.8, 128.0, 126.6 (q, $^2J_{\text{C}-\text{CF}_3}$ = 32.3 Hz), 125.5, 125.4 (q, $^3J_{\text{C}-\text{CF}_3}$ = 2.9 Hz), 125.0 (q, $^1J_{\text{C}-\text{CF}_3}$ = 271.7 Hz), 119.9, 119.5 (q, $^3J_{\text{C}-\text{CF}_3}$ = 3.8 Hz); HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{11}\text{F}_3\text{NO}_2\text{S}$ 374.0457; found 374.0462.



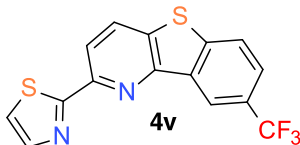
4-[8-(Trifluoromethyl)benzothiopheno[3,2-*b*]pyridin-2-yl]-benzoic acid (4t). Light Greenish solid (227 mg, 61%); ^1H NMR (400 MHz, DMSO- d_6) δ 8.72–8.68 (m, 2H), 8.43–8.41 (m, 2H), 8.36 (d, J = 8.5 Hz, 1H), 8.25 (d, J = 8.7 Hz, 1H), 8.08–8.06 (m, 2H), 7.95 (dd, J = 8.5, 1.5 Hz, 1H); ^{19}F decoupled $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6) δ 167.6, 153.3, 150.9, 144.5, 142.5, 134.6, 134.2, 133.4, 131.8, 130.4, 127.5, 126.7, 125.6, 125.5, 125.0, 120.2, 119.7; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{11}\text{F}_3\text{NO}_2\text{S}$ 374.0457; found 374.0464.



2-(2-Pyridyl)-8-(trifluoromethyl)benzothiopheno[3,2-*b*]pyridine (4u). Light brick red powder (198 mg, 60%); ^1H NMR (400 MHz, DMSO- d_6) δ 8.76–8.67 (m, 4H), 8.56 (d, J = 8.6 Hz, 1H), 8.36 (d, J = 8.4 Hz, 1H), 8.01–7.94 (m, 2H), 7.47 (dd, J = 7.0, 5.4 Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6) δ 155.4, 153.8, 150.5, 149.9, 144.4, 138.0, 135.0, 134.6, 133.2, 126.7 (q, $^2J_{\text{C}-\text{CF}_3}$ = 31.8 Hz), 125.6, 125.4 (q, $^3J_{\text{C}-\text{CF}_3}$ = 2.9 Hz), 125.1 (q, $^1J_{\text{C}-\text{CF}_3}$ = 272.1 Hz), 125.0, 121.4, 119.7; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{10}\text{F}_3\text{N}_2\text{S}$ 331.0511; found 331.0514.

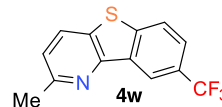


2-Thiazol-2-yl-8-(trifluoromethyl)benzothiopheno[3,2-*b*]pyridine (4v). Yellowish solid (235 mg, 70%); ^1H NMR (400 MHz, DMSO- d_6) δ 8.73 (dd, J = 8.4, 1.6 Hz, 1H), 8.60 (s, 1H), 8.40 (d, J = 8.6 Hz, 1H), 8.31 (dd, J = 8.5, 1.7 Hz, 1H), 8.02–7.92 (m, 3H); ^{19}F decoupled $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6) δ 168.5, 150.5, 149.3, 145.0, 144.6, 135.8, 133.9, 133.8, 125.8, 123.6, 119.5, 119.4, 118.6; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{15}\text{H}_8\text{F}_3\text{N}_2\text{S}_2$ 337.0075; found 337.0085.

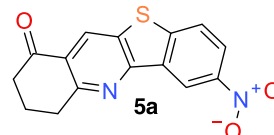


2-Methyl-8-(trifluoromethyl)[1]benzothieno[3,2-*b*]pyridine (4w). Dark red (208 mg, 78%); ^1H NMR (400 MHz, DMSO- d_6) δ 8.52 (s, 1H), 8.44 (d, J = 8.4 Hz, 1H), 8.31 (d, J = 8.5 Hz, 1H), 7.89 (d, J = 8.5 Hz, 1H), 7.45 (d, J = 8.4 Hz, 1H), 2.65 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101

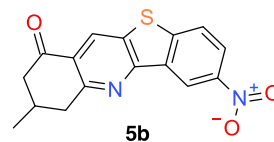
MHz, DMSO- d_6) δ 156.9, 150.2, 144.0, 134.6, 132.4, 131.8, 126.4 (q, $^2J_{\text{C}-\text{CF}_3}$ = 32.3 Hz), 125.4, 125.0 (q, $^1J_{\text{C}-\text{CF}_3}$ = 272.1 Hz), 124.9 (q, $^3J_{\text{C}-\text{CF}_3}$ = 3.4 Hz), 123.1, 119.2 (q, $^3J_{\text{C}-\text{CF}_3}$ = 4.3 Hz), 24.6; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{13}\text{H}_9\text{F}_3\text{NS}$ 268.0402; found 268.0400.



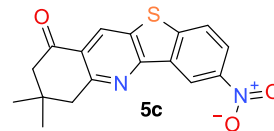
7-Nitro-3,4-dihydro-2H-benzothiopheno[3,2-*b*]quinolin-1-one (5a). White powder (268 mg, 90%); ^1H NMR (400 MHz, CDCl_3) δ 9.36 (d, J = 2.3 Hz, 1H), 8.82 (s, 1H), 8.44 (dd, J = 8.8, 2.2 Hz, 1H), 7.99 (d, J = 8.8 Hz, 1H), 3.39–3.35 (m, 2H), 2.82–2.79 (m, 2H), 2.32–2.28 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 197.3, 161.8, 153.9, 147.9, 146.1, 134.4, 133.2, 130.5, 126.8, 123.8, 119.8, 38.8, 32.9, 22.0; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{11}\text{N}_2\text{O}_3\text{S}$ 299.0484; found 299.0489.



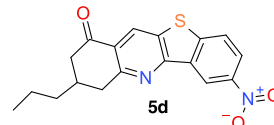
3-Methyl-7-nitro-3,4-dihydro-2H-benzothiopheno[3,2-*b*]quinolin-1-one (5b). White solid (288.6 mg, 88%); white solid (274 mg, 88%); ^1H NMR (400 MHz, CDCl_3) δ 9.36 (d, J = 2.3 Hz, 1H), 8.80 (s, 1H), 8.44 (dd, J = 8.8, 2.3 Hz, 1H), 7.99 (d, J = 8.8 Hz, 1H), 3.45 (dd, J = 16.8, 3.7 Hz, 1H), 3.03 (dd, J = 17.0, 10.7 Hz, 1H), 2.88 (dd, J = 13.0, 1.7 Hz, 1H), 2.50–2.47 (m, 2H), 1.25 (d, J = 6.2 Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 197.3, 161.2, 154.1, 147.9, 146.1, 134.4, 133.2, 130.3, 126.3, 123.8, 119.7, 46.8, 41.1, 29.4, 21.3; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{13}\text{N}_2\text{O}_3\text{S}$ 313.0641; found 313.0649.



3,3-Dimethyl-7-nitro-2,4-dihydrobenzothiopheno[3,2-*b*]quinolin-1-one (5c). White solid (179.3 mg, 55%); ^1H NMR (400 MHz, DMSO- d_6) δ 9.02–8.98 (m, 2H), 8.42–8.39 (m, 2H), 3.19 (s, 2H), 2.64 (s, 2H), 1.06 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6) δ 197.5, 160.8, 153.6, 148.6, 146.0, 133.9, 133.7, 131.3, 126.1, 125.7, 124.1, 118.6, 51.9, 46.3, 33.2, 28.3; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{15}\text{N}_2\text{O}_3\text{S}$ 327.0799; found 327.0805.

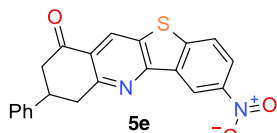


7-Nitro-3-propyl-3,4-dihydro-2H-benzothiopheno[3,2-*b*]quinolin-1-one (5d). White solid (282 mg, 83%); ^1H NMR (400 MHz, CDCl_3) δ 9.32 (d, J = 1.8 Hz, 1H), 8.77 (s, 1H), 8.41 (dd, J = 8.8, 2.1 Hz, 1H), 7.97 (d, J = 8.7 Hz, 1H), 3.46 (dd, J = 16.7, 2.4 Hz, 1H), 3.02 (dd, J = 17.0, 10.4 Hz, 1H), 2.90 (d, J = 16.2 Hz, 1H), 2.47 (dd, J = 16.4, 11.8 Hz, 1H), 2.39–2.36 (m, 1H), 1.56–1.45 (m, 4H), 0.98–0.94 (m, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 197.4, 161.3, 154.0, 147.8, 146.0, 134.4, 133.1, 130.2, 126.5, 123.8, 119.7, 45.2, 39.3, 37.9, 34.0, 19.8, 14.2; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{17}\text{N}_2\text{O}_3\text{S}$ 341.0954; found 341.0958.

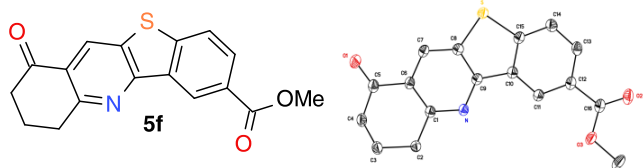


7-Nitro-3-phenyl-3,4-dihydro-2H-benzothiopheno[3,2-*b*]quinolin-1-one (5e). Light yellowish powder (340 mg, 91%); ^1H NMR (400 MHz, DMSO- d_6) δ 9.06 (s, 1H), 8.94 (d, J = 1.9 Hz, 1H), 8.43–8.36 (m, 2H), 7.42–7.40 (m, 2H), 7.36–7.33 (m, 2H), 7.26–

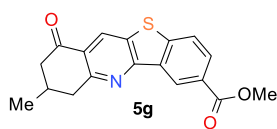
7.22 (m, 1H), 3.69–3.62 (m, 1H), 3.57 (dd, $J = 15.9, 11.1$ Hz, 1H), 3.47–3.42 (m, 1H), 3.14 (dd, $J = 16.6, 12.0$ Hz, 1H), 2.89 (dd, $J = 16.4, 1.8$ Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6) δ 196.8, 161.1, 153.3, 148.6, 145.8, 143.8, 133.7, 131.5, 129.2, 127.5, 127.3, 126.5, 125.6, 124.1, 118.5, 45.5, 39.1; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{15}\text{N}_2\text{O}_3\text{S}$ 375.0798; found 375.0801.



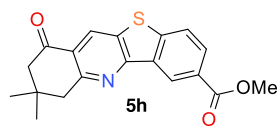
Methyl 1-oxo-3,4-Dihydro-2H-benzothiopheno[3,2-b]quinoline-7-carboxylate (5f). Light yellowish powder (224 mg, 72%); ^1H NMR (400 MHz, CDCl_3) δ 9.18 (s, 1H), 8.78 (d, $J = 1.4$ Hz, 1H), 8.26 (d, $J = 8.5$ Hz, 1H), 7.91 (dd, $J = 8.4, 1.1$ Hz, 1H), 3.99 (s, 3H), 3.37–3.34 (m, 2H), 2.80–2.77 (m, 2H), 2.31–2.27 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 197.6, 166.8, 161.3, 154.7, 146.6, 133.9, 132.6, 130.3, 130.2, 127.6, 126.2, 125.8, 123.2, 52.5, 38.9, 33.0, 22.1; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{14}\text{NO}_3\text{S}$ 312.0689; found 312.0691.



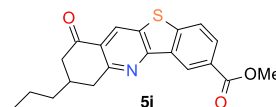
Methyl 3-Methyl-1-oxo-3,4-dihydro-2H-benzothiopheno[3,2-b]quinoline-7-carboxylate (5g). Yellowish powder (270 mg, 83%); ^1H NMR (400 MHz, CDCl_3) δ 9.18 (d, $J = 1.6$ Hz, 1H), 8.77 (s, 1H), 8.26 (dd, $J = 8.4, 1.7$ Hz, 1H), 7.91 (d, $J = 8.5$ Hz, 1H), 3.99 (s, 3H), 3.43 (dd, $J = 16.8, 3.7$ Hz, 1H), 3.02 (dd, $J = 16.8, 10.4$ Hz, 1H), 2.86 (dd, $J = 13.0, 1.7$ Hz, 1H), 2.48–2.45 (m, 2H), 1.24 (d, $J = 6.1$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6) δ 197.4, 166.4, 161.2, 153.8, 146.9, 133.6, 132.8, 130.9, 130.0, 127.2, 126.0, 124.7, 124.6, 53.0, 46.5, 29.2, 21.4; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{16}\text{NO}_3\text{S}$ 326.0845; found 326.0840.



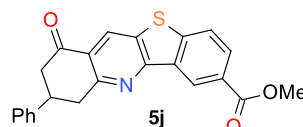
Methyl 3,3-Dimethyl-1-oxo-2,4-dihydrobenzothiopheno[3,2-b]quinoline-7-carboxylate (5h). Light yellowish powder (322 mg, 95%); ^1H NMR (400 MHz, DMSO- d_6) δ 8.97–8.96 (m, 1H), 8.88 (s, 1H), 8.26 (d, $J = 8.4$ Hz, 1H), 8.17–8.15 (m, 1H), 3.91 (s, 3H), 3.18 (s, 2H), 2.63 (s, 2H), 1.05 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6) δ 197.6, 166.4, 160.5, 154.2, 146.9, 133.7, 132.8, 130.9, 130.1, 127.3, 125.7, 124.8, 124.7, 53.0, 51.9, 46.3, 33.3, 28.3; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{18}\text{NO}_3\text{S}$ 340.1002; found 340.1003.



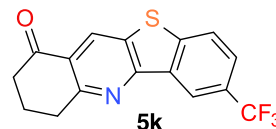
Methyl 1-oxo-3-Propyl-3,4-dihydro-2H-benzothiopheno[3,2-b]quinoline-7-carboxylate (5i). White powder (342 mg, 97%); ^1H NMR (400 MHz, DMSO- d_6) δ 8.95–8.89 (m, 2H), 8.26 (d, $J = 8.4$ Hz, 1H), 8.17 (d, $J = 8.6$ Hz, 1H), 3.91 (s, 3H), 3.01 (dd, $J = 16.8, 10.6$ Hz, 1H), 2.75 (d, $J = 13.9$ Hz, 1H), 2.56–2.52 (m, 1H), 2.29 (s, 1H), 1.40 (s, 4H), 0.88 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6) δ 197.5, 166.4, 161.3, 153.9, 147.0, 133.7, 132.9, 131.0, 130.1, 127.3, 126.4, 124.8, 124.7, 53.0, 44.9, 38.9, 37.7, 33.7, 19.7, 14.6; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{20}\text{NO}_3\text{S}$ 354.1158; found 354.1150.



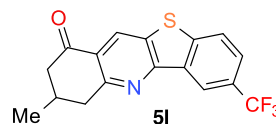
Methyl 1-oxo-3-Phenyl-3,4-dihydro-2H-benzothiopheno[3,2-b]quinoline-7-carboxylate (5j). White powder (313 mg, 81%); ^1H NMR (400 MHz, CDCl_3) δ 9.19 (d, $J = 1.6$ Hz, 1H), 8.83 (s, 1H), 8.28 (dd, $J = 8.5, 1.6$ Hz, 1H), 7.94 (d, $J = 8.5$ Hz, 1H), 7.41–7.28 (m, 5H), 3.99 (s, 3H), 3.70–3.53 (m, 3H), 3.14–3.08 (m, 1H), 2.99 (dd, $J = 16.8, 12.2$ Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 196.8, 166.8, 160.2, 155.1, 146.7, 142.7, 133.9, 132.9, 130.4, 130.2, 129.0, 127.7, 127.3, 126.8, 125.9, 125.7, 123.2, 52.5, 45.8, 40.6, 39.9; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{18}\text{NO}_3\text{S}$ 388.1002; found 388.1003.



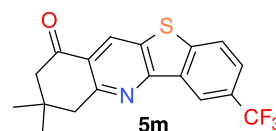
7-(Trifluoromethyl)-3,4-dihydro-2H-benzothiopheno[3,2-b]quinolin-1-one (5k). Gray solid (189 mg, 59%); ^1H NMR (400 MHz, DMSO- d_6) δ 8.98 (s, 1H), 8.56 (s, 1H), 8.37 (d, $J = 8.5$ Hz, 1H), 7.97 (dd, $J = 8.5, 1.4$ Hz, 1H), 3.24 (t, $J = 6.0$ Hz, 2H), 2.73–2.70 (m, 2H), 2.18–2.12 (m, 2H); ^{19}F decoupled $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6) δ 197.5, 161.9, 153.2, 146.2, 133.6, 133.0, 131.3, 126.8, 126.7, 126.3, 125.7, 124.9, 120.3, 38.7, 32.8, 21.9; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{11}\text{F}_3\text{NOS}$ 322.0508; found 322.0505.



3-Methyl-7-(trifluoromethyl)-3,4-dihydro-2H-benzothiopheno[3,2-b]quinolin-1-one (5l). Light yellowish powder (237 mg, 71%); ^1H NMR (400 MHz, DMSO- d_6) δ 8.64 (s, 1H), 8.23 (s, 1H), 8.03 (d, $J = 8.4$ Hz, 1H), 7.63 (d, $J = 8.4$ Hz, 1H), 2.92–2.88 (m, 1H), 2.65 (dd, $J = 16.7, 10.3$ Hz, 1H), 2.40–2.36 (m, 1H), 2.20–2.13 (m, 1H), 2.07–2.05 (m, 1H), 0.77 (d, $J = 6.3$ Hz, 3H); ^{19}F decoupled $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6) δ 197.4, 161.3, 153.4, 146.2, 133.7, 133.1, 131.2, 126.7, 126.3, 125.8, 124.9, 120.3, 69.8, 46.5, 40.7, 29.2, 21.4; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{13}\text{F}_3\text{NOS}$ 336.0664; found 336.0659.

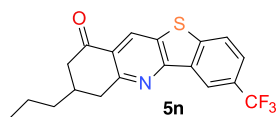


3,3-Dimethyl-7-(trifluoromethyl)-2,4-dihydrobenzothiopheno[3,2-b]quinolin-1-one (5m). Light pink powder (191 mg, 55%); ^1H NMR (400 MHz, DMSO- d_6) δ 9.01 (s, 1H), 8.58 (s, 1H), 8.39 (d, $J = 8.5$ Hz, 1H), 7.99 (d, $J = 8.5$ Hz, 1H), 3.18 (s, 2H), 2.63 (s, 2H), 1.05 (s, 6H); ^{19}F decoupled $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6) δ 197.6, 160.5, 153.7, 146.1, 133.6, 133.1, 131.0, 126.7, 126.3, 125.8, 125.8, 124.9, 120.4, 51.9, 46.3, 33.3, 28.3; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{15}\text{F}_3\text{NOS}$ 350.0820; found 350.0815.

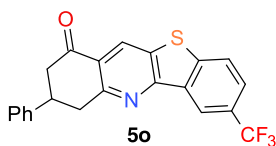


3-Propyl-7-(trifluoromethyl)-3,4-dihydro-2H-benzothiopheno[3,2-b]quinolin-1-one (5n). Light pink solid (308 mg, 85%); ^1H NMR (400 MHz, DMSO- d_6) δ 8.98 (s, 1H), 8.59 (s, 1H), 8.38 (d, $J = 8.5$ Hz, 1H), 7.98 (dd, $J = 8.5, 1.5$ Hz, 1H), 3.29–3.28 (m, 1H), 3.00 (dd, $J = 16.7, 10.5$ Hz, 1H), 2.75 (dd, $J = 16.6, 2.3$ Hz, 1H), 2.52 (dd, $J = 16.6, 11.5$ Hz, 1H), 2.31–2.28 (m, 1H), 1.43–1.36 (m, 4H), 0.87 (t, $J = 6.9$ Hz, 3H); ^{19}F decoupled $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 197.6, 160.8, 154.3, 145.2, 133.9, 132.8, 130.1, 128.0,

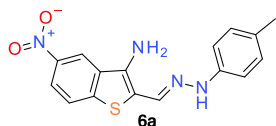
126.2, 126.0, 124.3, 123.8, 121.4, 45.2, 39.3, 37.9, 34.1, 19.8, 14.2; HRMS (ESI-TOF) m/z : $[M + H]^+$ calcd for $C_{19}H_{17}F_3NOS$ 364.0977; found 364.0979.



3-Phenyl-7-(trifluoromethyl)-3,4-dihydro-2H-benzothiopheno[3,2-b]quinolin-1-one (5n). Light yellow solid (346 mg, 84%); 1H NMR (400 MHz, DMSO- d_6) δ 9.07 (s, 1H), 8.60 (s, 1H), 8.40 (d, J = 8.5 Hz, 1H), 8.00 (dd, J = 8.6, 1.6 Hz, 1H), 7.41–7.40 (m, 2H), 7.36–7.32 (m, 2H), 7.25–7.21 (m, 1H), 3.67–3.63 (m, 1H), 3.61–3.55 (m, 1H), 3.47–3.43 (m, 1H), 3.15 (dd, J = 16.6, 11.9 Hz, 1H), 2.89 (dd, J = 16.6, 1.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO- d_6) δ 196.9, 160.9, 153.6, 146.3, 143.8, 133.6, 133.3, 131.3, 129.2, 127.5, 127.3, 126.8 (q, $^2J_{C-CF_3}$ = 32.8 Hz), 126.4, 126.3, 125.8, 124.9 (q, $^1J_{C-CF_3}$ = 272.1 Hz), 120.4 (q, $^3J_{C-CF_3}$ = 3.9 Hz), 45.5, 40.5, 39.2; HRMS (ESI-TOF) m/z : $[M + H]^+$ calcd for $C_{22}H_{15}F_3NOS$ 398.0821; found 398.0820.



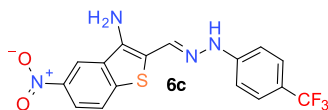
2-((E)-[2-(4-Methylphenyl)hydrazinylidene]methyl)-5-nitro-1-benzothiophen-3-amine (6a). Dark red solid (299 mg, 92%); 1H NMR (400 MHz, DMSO- d_6) δ 10.15 (s, 1H), 8.86 (d, J = 1.9 Hz, 1H), 8.12 (s, 1H), 8.05 (dd, J = 8.8, 2.1 Hz, 1H), 7.96–7.93 (m, 1H), 6.98 (d, J = 8.3 Hz, 2H), 6.88 (d, J = 8.3 Hz, 2H), 6.31 (s, 2H), 2.16 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO- d_6) δ 145.1, 144.3, 143.5, 139.3, 134.4, 131.5, 130.0, 127.6, 124.0, 119.5, 117.2, 112.4, 112.0, 20.8; HRMS (ESI-TOF) m/z : $[M + H]^+$ calcd for $C_{16}H_{15}N_4O_2S$ 327.0910; found 327.0902.



2-((E)-[2-(4-Bromophenyl)hydrazinylidene]methyl)-5-nitro-1-benzothiophen-3-amine (6b). Dark gray solid (379 mg, 97%); 1H NMR (400 MHz, DMSO- d_6) δ 10.39 (s, 1H), 8.88 (s, 1H), 8.18 (s, 1H), 8.07 (d, J = 8.8 Hz, 1H), 7.96–7.94 (m, 1H), 7.32 (d, J = 6.9 Hz, 2H), 6.92 (d, J = 8.1 Hz, 2H), 6.39 (s, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO- d_6) δ 145.1, 145.1, 144.5, 140.2, 134.2, 133.1, 132.2, 124.1, 119.8, 117.4, 114.3, 111.3, 109.8; HRMS (ESI-TOF) m/z : $[M + H]^+$ calcd for $C_{15}H_{12}BrN_4O_2S$ 390.9859; found 390.9861.

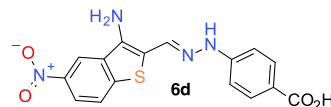


5-Nitro-2-((E)-[2-(4-(trifluoromethyl)phenyl)hydrazinylidene]methyl)-1-benzothiophen-3-amine (6c). Dark red solid (311 mg, 82%); 1H NMR (400 MHz, DMSO- d_6) δ 10.67 (s, 1H), 8.90 (s, 1H), 8.26 (s, 1H), 8.08 (d, J = 8.5 Hz, 1H), 7.96 (d, J = 8.6 Hz, 1H), 7.49 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H), 6.47 (s, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO- d_6) δ 148.7, 145.1, 144.6, 140.9, 134.6, 134.1, 127.0, 126.9, 124.1, 120.0, 118.6 (q, $^2J_{C-CF_3}$ = 32.3 Hz), 117.6, 111.9, 110.7; HRMS (ESI-TOF) m/z : $[M + H]^+$ calcd for $C_{16}H_{12}F_3N_4O_2S$ 381.0627; found 381.0625.

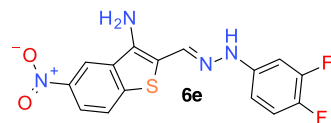


4-((2E)-2-[(3-Amino-5-nitro-1-benzothiophen-2-yl)methylidene]hydrazinyl)benzoic acid (6d). Dark red powder (284 mg, 80%); 1H NMR (400 MHz, DMSO- d_6) δ 10.78 (s, 1H), 8.90 (s, 1H), 8.31 (s, 1H), 8.09 (d, J = 8.8 Hz, 1H), 7.98 (d, J = 8.8 Hz, 1H),

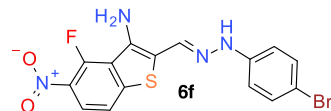
7.77 (d, J = 7.5 Hz, 2H), 6.98 (d, J = 7.6 Hz, 2H), 6.48 (s, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO- d_6) δ 168.3, 148.8, 145.1, 144.6, 140.8, 134.3, 134.1, 131.6, 124.2, 121.9, 119.9, 117.5, 111.4, 110.9; HRMS (ESI-TOF) m/z : $[M + H]^+$ calcd for $C_{16}H_{13}N_4O_4S$ 357.0652; found 357.0644.



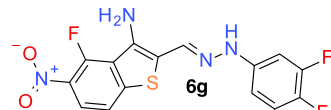
2-((E)-[2-(3,4-Difluorophenyl)hydrazinylidene]methyl)-5-nitro-1-benzothiophen-3-amine (6e). Gray solid (330 mg, 95%); 1H NMR (400 MHz, DMSO- d_6) δ 10.39 (s, 1H), 8.88 (d, J = 2.2 Hz, 1H), 8.19 (s, 1H), 8.08 (dd, J = 8.8, 2.2 Hz, 1H), 7.96 (d, J = 8.8 Hz, 1H), 7.23 (dd, J = 19.7, 9.1 Hz, 1H), 6.88 (ddd, J = 13.2, 7.1, 2.6 Hz, 1H), 6.70 (dd, J = 5.2, 3.8 Hz, 1H), 6.42 (s, 2H); ^{19}F decoupled $^{13}C\{^1H\}$ NMR (101 MHz, DMSO- d_6) δ 150.6, 145.1, 144.5, 143.3, 143.1, 140.4, 134.2, 133.4, 124.1, 119.9, 118.4, 117.5, 111.0, 107.9, 100.5; HRMS (ESI-TOF) m/z : $[M + H]^+$ calcd for $C_{15}H_{11}F_2N_4O_2S$ 349.0565; found 349.0556.



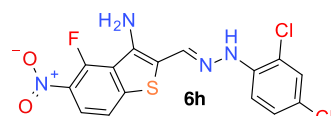
2-((E)-[2-(4-Bromophenyl)hydrazinylidene]methyl)-4-fluoro-5-nitro-1-benzothiophen-3-amine (6f). Black powder (298 mg, 73%); 1H NMR (400 MHz, DMSO- d_6) δ 10.41 (d, J = 2.6 Hz, 1H), 8.36–8.32 (m, 1H), 8.17 (d, J = 3.9 Hz, 1H), 7.35–7.31 (m, 3H), 6.94–6.92 (m, 2H), 6.00 (s, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO- d_6) δ 161. Six (d, $^1J_{C-F}$ = 262.0 Hz), 144.9, 138.8, 137.8, 136.2, 132.9, 132.3, 125.5 (d, $^3J_{C-F}$ = 10.6 Hz), 124.2 (d, $^3J_{C-F}$ = 14.9 Hz), 114.3, 112.1 (d, $^2J_{C-F}$ = 24.1 Hz), 112.0, 110.0; HRMS (ESI-TOF) m/z : $[M + H]^+$ calcd for $C_{15}H_{11}BrFN_4O_2S$ 408.9764; found 408.9762.



2-((E)-[2-(3,4-Difluorophenyl)hydrazinylidene]methyl)-4-fluoro-5-nitro-1-benzothiophen-3-amine (6g). Black solid (318 mg, 87%); 1H NMR (400 MHz, DMSO- d_6) δ 10.41 (s, 1H), 8.34 (dd, J = 8.7, 2.5 Hz, 1H), 8.17 (s, 1H), 7.37–7.32 (m, 1H), 7.24 (q, J = 9.4 Hz, 1H), 6.88 (dd, J = 13.0, 7.0 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 6.03 (s, 2H); ^{19}F decoupled $^{13}C\{^1H\}$ NMR (101 MHz, DMSO- d_6) δ 161.6, 150.6, 143.2, 143.1, 138.8, 138.0, 136.2, 133.3, 125.5, 124.2, 118.4, 112.0, 111.8, 108.0, 100.6; HRMS (ESI-TOF) m/z : $[M + H]^+$ calcd for $C_{15}H_{10}F_3N_4O_2S$ 367.0471; found 367.0473.

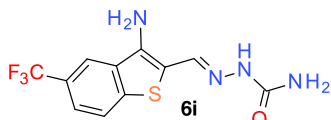


2-((E)-[2-(2,4-Dichlorophenyl)hydrazinylidene]methyl)-4-fluoro-5-nitro-1-benzothiophen-3-amine (6h). Gray solid (355 mg, 89%); 1H NMR (400 MHz, DMSO- d_6) δ 9.84 (s, 1H), 8.54 (s, 1H), 8.38 (dd, J = 8.9, 4.2 Hz, 1H), 7.42–7.30 (m, 4H), 6.04 (s, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO- d_6) δ 161.8 (d, $^1J_{C-F}$ = 262.8 Hz), 140.9, 139.0 (d, $^4J_{C-F}$ = 3.8 Hz), 138.9, 137.0, 136.4 (d, $^3J_{C-F}$ = 8.2 Hz), 129.1, 128.7, 125.9 (d, $^3J_{C-F}$ = 10.6 Hz), 124.1 (d, $^2J_{C-F}$ = 14.9 Hz), 122.6, 117.2, 115.0, 112.1 (d, $^2J_{C-F}$ = 23.6 Hz), 111.2; HRMS (ESI-TOF) m/z : $[M + H]^+$ calcd for $C_{15}H_{10}Cl_2FN_4O_2S$ 398.9880; found 398.9879.

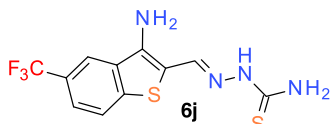


[(E)-[3-Amino-5-(trifluoromethyl)benzothiophen-2-yl]-methylethylurea (6i). White powder (280 mg, 93%); 1H NMR (400 MHz, DMSO- d_6) δ 10.04 (s, 1H), 8.41 (s, 1H), 8.08 (s, 1H), 7.95

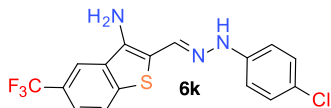
(d, $J = 8.3$ Hz, 1H), 7.58 (d, $J = 8.4$ Hz, 1H), 6.44 (s, 2H), 6.29 (s, 2H); ^{19}F decoupled $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6) δ 157.0, 141.9, 141.3, 136.0, 133.7, 125.3, 125.2, 124.3, 122.1, 119.5, 107.7; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{11}\text{H}_{10}\text{F}_3\text{N}_4\text{OS}$ 303.0522; found 303.0527.



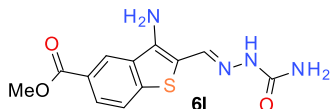
[(E)-[3-Amino-5-(trifluoromethyl)benzothiophen-2-yl]-methylethylthiourea (6j)]. Yellow powder (190 mg, 60%); ^1H NMR (400 MHz, DMSO- d_6) δ 11.22 (s, 1H), 8.48 (s, 1H), 8.24 (s, 1H), 8.06–7.97 (m, 2H), 7.67–7.61 (m, 2H), 6.72 (s, 2H); ^{19}F decoupled $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6) δ 177.0, 142.9, 142.4, 139.5, 133.2, 125.3, 125.3, 124.5, 122.6, 119.9, 105.9; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{11}\text{H}_{10}\text{F}_3\text{N}_4\text{S}_2$ 319.0293; found 319.0295.



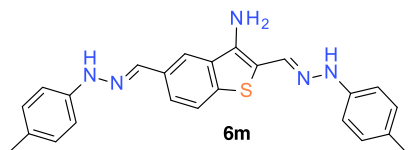
2-[(E)-[(4-Chlorophenyl)hydrazono]methyl]-5-(trifluoromethyl)benzothiophen-3-amine (6k). Gray solid (273 mg, 74%); ^1H NMR (400 MHz, DMSO- d_6) δ 10.31 (d, $J = 5.6$ Hz, 1H), 8.30 (d, $J = 5.4$ Hz, 1H), 8.17 (d, $J = 6.5$ Hz, 1H), 7.95–7.91 (m, 1H), 7.57–7.54 (m, 1H), 7.22–7.18 (m, 2H), 6.97–6.94 (m, 2H), 6.25 (s, 2H); ^{19}F decoupled $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6) δ 144.8, 141.7, 139.8, 134.1, 133.3, 129.4, 124.1, 122.0, 121.7, 121.7, 118.9, 118.8, 113.7, 110.4; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{12}\text{ClF}_3\text{N}_3\text{S}$ 370.0387; found 370.0378.



Methyl 3-Amino-2-[(E)-(carbamoylhydrazono) methyl]-benzothiophene-5-carboxylate (6l). Yellow powder (128 mg, 44%); ^1H NMR (400 MHz, DMSO- d_6) δ 9.98 (s, 1H), 8.62 (s, 1H), 8.06 (s, 1H), 7.84 (s, 2H), 6.46 (s, 2H), 6.27 (s, 2H), 3.85 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6) δ 167.0, 157.0, 143.0, 141.8, 136.2, 133.9, 126.3, 125.9, 123.8, 123.5, 106.9, 52.7; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{13}\text{N}_4\text{O}_3\text{S}$ 293.0703; found 293.0709.

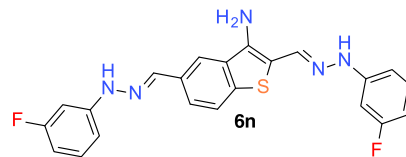


2,5-Bis[(E)-(p-tolylhydrazono)methyl]benzothiophen-3-amine (6m). Gray solid (256 mg, 62%); ^1H NMR (400 MHz, DMSO- d_6) δ 10.20 (s, 1H), 9.94 (s, 1H), 8.11 (s, 1H), 8.00 (s, 1H), 7.86 (s, 1H), 7.69–7.60 (m, 2H), 6.99–6.97 (m, 6H), 6.87–6.85 (m, 2H), 6.10 (s, 2H), 2.18–2.17 (m, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6) δ 143.8, 143.6, 139.5, 137.2, 136.5, 134.7, 132.8, 132.5, 130.1, 130.0, 127.6, 127.2, 123.2, 123.0, 119.0, 112.5, 112.3, 109.2, 20.8; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{24}\text{N}_5\text{S}$ 414.1747; found 414.1745.

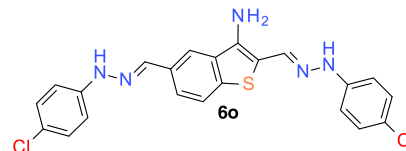


2,5-Bis[(E)-[(3-fluorophenyl)hydrazono]methyl]-benzothiophen-3-amine (6n). Gray solid (328 mg, 78%); ^1H NMR (400 MHz, DMSO- d_6) δ 10.54 (s, 1H), 10.30 (s, 1H), 8.19 (s, 1H), 8.10 (s, 1H), 7.92 (s, 1H), 7.72–7.64 (m, 2H), 7.22–7.14 (m, 2H), 6.94–6.70 (m, 4H), 6.51–6.42 (m, 2H), 6.22 (s, 2H); ^{19}F decoupled $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6) δ 164.0, 163.9, 148.0, 147.9,

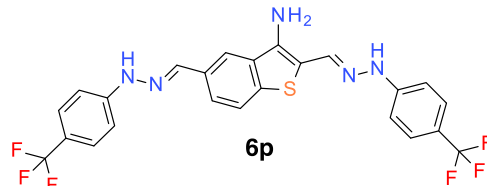
140.6, 138.4, 138.0, 134.6, 134.4, 132.0, 131.2, 131.1, 123.8, 123.3, 119.4, 108.7, 108.6, 108.4, 105.2, 104.7, 99.0, 98.5; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{22}\text{H}_{18}\text{F}_2\text{N}_5\text{S}$ 422.1245; found 422.1243.



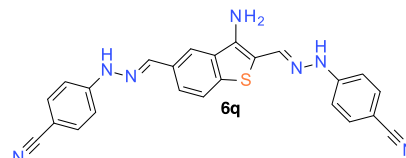
2,5-Bis[(E)-[(4-chlorophenyl)hydrazono]methyl]-benzothiophen-3-amine (6o). Gray solid (295 mg, 65%); ^1H NMR (400 MHz, DMSO- d_6) δ 10.46 (s, 1H), 10.21 (s, 1H), 8.17 (d, $J = 2.6$ Hz, 1H), 8.06 (s, 1H), 7.90 (s, 1H), 7.71–7.63 (m, 2H), 7.23–7.19 (m, 4H), 7.10–7.08 (m, 2H), 6.96–6.94 (m, 2H), 6.17 (s, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6) δ 144.9, 144.8, 140.3, 138.0, 137.8, 134.6, 134.1, 132.1, 129.4, 129.4, 123.4, 123.3, 122.3, 121.8, 119.4, 113.9, 113.6, 108.8; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{22}\text{H}_{18}\text{Cl}_2\text{N}_5\text{S}$ 454.0654; found 454.0661.



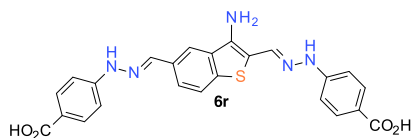
2,5-Bis[(E)-[(4-(trifluoromethyl)phenyl)hydrazono]methyl]-benzothiophen-3-amine (6p). Yellowish solid (500 mg, 96%); ^1H NMR (400 MHz, DMSO- d_6) δ 10.79 (s, 1H), 10.56 (s, 1H), 8.26 (s, 1H), 8.12 (s, 1H), 7.98 (s, 1H), 7.75–7.68 (m, 2H), 7.50 (t, $J = 9.3$ Hz, 4H), 7.21 (d, $J = 8.5$ Hz, 2H), 7.07 (d, $J = 8.5$ Hz, 2H), 6.28 (s, 2H); ^{19}F decoupled $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6) δ 148.8, 141.1, 139.6, 138.4, 135.5, 134.5, 131.8, 127.0, 125.7, 125.6, 123.8, 123.4, 119.9, 118.8, 118.2, 112.2, 111.8, 108.3; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{18}\text{F}_6\text{N}_5\text{S}$ 522.1182; found 522.1189.



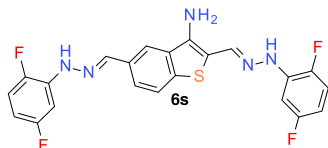
4-[(2E)-2-[[3-Amino-2-[(E)-[(4-cyanophenyl)hydrazono]methyl]benzothiophen-5-yl]methylene]hydrazino]benzonitrile (6q). Gray solid (421 mg, 97%); ^1H NMR (400 MHz, DMSO- d_6) δ 10.96 (s, 1H), 10.75 (s, 1H), 8.28 (s, 1H), 8.15 (s, 1H), 8.00 (s, 1H), 7.75–7.68 (m, 2H), 7.61–7.55 (m, 4H), 7.17 (d, $J = 8.3$ Hz, 2H), 7.02 (d, $J = 8.4$ Hz, 2H), 6.35 (s, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6) δ 149.1, 149.1, 141.7, 140.7, 138.7, 136.5, 134.4, 134.2, 134.1, 131.6, 124.2, 123.5, 120.9, 120.7, 120.1, 112.6, 112.2, 108.0, 99.7, 98.8; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{18}\text{N}_7\text{S}$ 436.1339; found 436.1347.



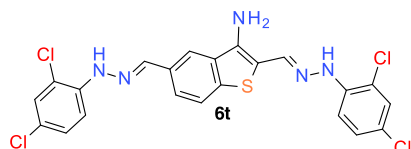
4-[(2E)-2-[[3-Amino-2-[(E)-[(4-carboxyphenyl)hydrazono]methyl]benzothiophen-5-yl]methylene]hydrazino]benzoic acid (6r). Black solid (458 mg, 97%); ^1H NMR (400 MHz, DMSO- d_6) δ 12.11–12.46 (2H), 10.82 (s, 1H), 10.60 (s, 1H), 8.26 (s, 1H), 8.13 (s, 1H), 7.99 (s, 1H), 7.81–7.73 (m, 6H), 7.14–7.11 (m, 2H), 6.99–6.97 (m, 2H), 6.30 (s, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6) δ 167.9, 149.4, 141.1, 139.6, 138.4, 135.6, 134.5, 131.9, 131.7, 123.8, 123.4, 120.7, 120.0, 119.8, 111.7, 111.3, 108.4; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{20}\text{N}_5\text{O}_4\text{S}$ 474.1230; found 474.1233.



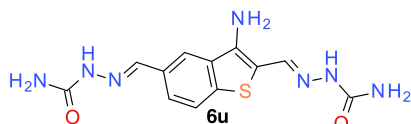
2,5-Bis[(E)-[(2,5-difluorophenyl)hydrazono]methyl]-benzothiophen-3-amine (6s). Gray solid (365 mg, 80%); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.49 (s, 1H), 10.21 (s, 1H), 8.41 (s, 1H), 8.20–8.17 (m, 2H), 7.75–7.67 (m, 2H), 7.36–7.32 (m, 1H), 7.17–7.08 (m, 2H), 7.00 (td, J = 6.9, 3.2 Hz, 1H), 6.52–6.43 (m, 2H), 6.30 (s, 2H); ^{19}F decoupled $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, $\text{DMSO}-d_6$) δ 159.9, 159.8, 145.8, 141.4, 141.1, 138.6, 137.5, 135.6, 135.5, 134.4, 131.8, 124.2, 123.5, 119.9, 116.5, 116.3, 108.0, 104.2, 103.6, 101.0, 100.2; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{22}\text{H}_{16}\text{F}_4\text{N}_3\text{S}$ 458.1057; found 458.1060.



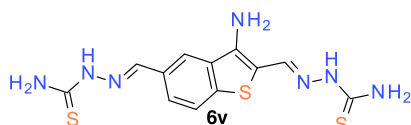
2,5-Bis[(E)-[(2,4-dichlorophenyl)hydrazono]methyl]-benzothiophen-3-amine (6t). Light greenish solid (355 mg, 68%); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.07 (d, J = 5.3 Hz, 1H), 9.66 (d, J = 5.8 Hz, 1H), 8.54 (d, J = 6.5 Hz, 1H), 8.34 (d, J = 6.2 Hz, 1H), 8.13 (d, J = 5.7 Hz, 1H), 7.76–7.62 (m, 3H), 7.44–7.26 (m, 5H), 6.28 (s, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, $\text{DMSO}-d_6$) δ 141.6, 141.2, 138.6, 138.2, 134.3, 131.9, 129.1, 129.0, 128.6, 128.5, 123.9, 123.5, 122.6, 122.0, 120.2, 117.0, 117.0, 115.7, 114.8, 108.0; ^{13}C APT NMR (101 MHz, $\text{DMSO}-d_6$) δ 141.6, 141.6, 141.2, 138.6, 138.2, 134.4, 131.9, 129.1, 129.0, 128.6, 128.5, 123.9, 123.5, 122.6, 122.0, 120.2, 117.1, 117.0, 115.7, 114.8, 108.0; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{22}\text{H}_{16}\text{Cl}_4\text{N}_3\text{S}$ 521.9875; found 521.9864.



[(E)-[3-Amino-2-[(E)-(carbamothioyl)hydrazono]methyl]-benzothiophen-5-yl]methyleneamino]thiourea (6u). Gray solid (280 mg, 88%); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.52 (s, 1H), 11.16 (s, 1H), 8.28 (d, J = 15.5 Hz, 2H), 8.21 (s, 1H), 8.08 (s, 1H), 8.01 (s, 1H), 7.92 (d, J = 9.2 Hz, 2H), 7.75 (d, J = 8.5 Hz, 1H), 7.62 (s, 1H), 6.57 (s, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, $\text{DMSO}-d_6$) δ 178.3, 176.7, 143.1, 142.4, 140.1, 139.8, 133.6, 130.9, 125.0, 123.6, 122.2, 104.7; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{14}\text{N}_7\text{S}_3$ 352.0467; found 352.0464.

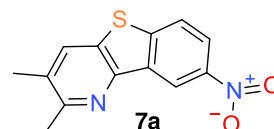


[(E)-[3-Amino-2-[(E)-(carbamoyl)hydrazono]methyl]-benzothiophen-5-yl]methyleneamino]urea (6v). Gray solid (228 mg, 65%); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.30 (s, 1H), 9.95 (s, 1H), 8.21 (s, 1H), 8.04 (s, 1H), 7.86 (s, 1H), 7.74–7.69 (m, 2H), 6.52 (s, 2H), 6.27–6.25 (m, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, $\text{DMSO}-d_6$) δ 157.4, 157.1, 141.5, 139.5, 138.7, 136.4, 134.1, 131.4, 124.4, 123.3, 120.4, 106.4; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{14}\text{N}_7\text{S}_3$ 320.0924; found 320.0923.

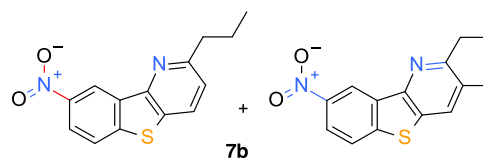


2,3-Dimethyl-8-nitro-benzothiopheno[3,2-b]pyridine (7a). Gray solid (177 mg, 63%); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.94 (s, 1H), 8.32–8.29 (m, 3H), 2.60 (s, 3H), 2.39 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR

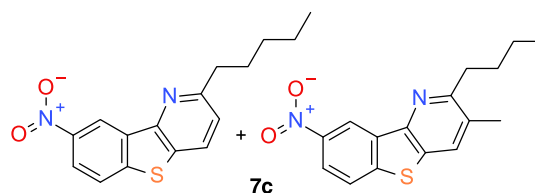
(101 MHz, $\text{DMSO}-d_6$) δ 156.7, 147.8, 146.0, 145.8, 135.0, 132.9, 132.4, 132.2, 125.3, 122.4, 117.2, 23.2, 19.9; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{11}\text{N}_2\text{O}_2\text{S}$ 259.0536; found 259.0534.



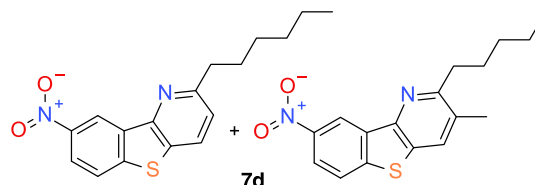
8-Nitro-2-propyl-benzothiopheno[3,2-b]pyridine and 2-Ethyl-3-methyl-8-nitro-benzothiopheno[3,2-b]pyridine (7b). Light yellow solid (215 mg, 79%); ^1H NMR (400 MHz, CDCl_3) δ 9.35 (d, J = 2.3 Hz, 1H), 9.30 (d, J = 2.2 Hz, 1H), 8.39–8.33 (m, 2H), 8.10 (d, J = 8.3 Hz, 1H), 7.96–7.92 (m, 4H), 7.33 (d, J = 8.3 Hz, 1H), 2.97 (t, J = 7.7 Hz, 2H), 2.84–2.77 (m, 3H), 2.73 (s, 4H), 1.89 (q, J = 7.5 Hz, 2H), 1.33 (t, J = 7.5 Hz, 4H), 1.03 (t, J = 7.4 Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 161.1, 155.9, 150.8, 148.4, 146.1, 145.9, 145.7, 137.2, 135.6, 135.5, 132.8, 132.0, 130.9, 129.4, 123.5, 123.4, 122.4, 122.1, 122.0, 118.8, 118.3, 40.4, 26.3, 23.4, 22.6, 14.0, 13.9; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{13}\text{N}_2\text{O}_2\text{S}$ 273.0692; found 273.0686.



8-Nitro-2-pentyl-benzothiopheno[3,2-b]pyridine and 2-Butyl-3-methyl-8-nitro-benzothiopheno[3,2-b]pyridine (7c). White powder (216 mg, 72%); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.98 (d, J = 1.4 Hz, 1H), 8.93 (d, J = 1.4 Hz, 1H), 8.49 (d, J = 8.4 Hz, 1H), 8.39–8.30 (m, 5H), 7.50 (d, J = 8.5 Hz, 1H), 2.91 (t, J = 7.7 Hz, 2H), 2.73 (t, J = 7.8 Hz, 2H), 2.65 (s, 3H), 1.76 (t, J = 7.5 Hz, 2H), 1.61–1.55 (m, 2H), 1.40–1.30 (m, 6H), 0.92 (t, J = 7.3 Hz, 3H), 0.86–0.83 (m, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, $\text{DMSO}-d_6$) δ 161.2, 156.0, 150.1, 147.8, 146.6, 146.3, 145.8, 136.4, 135.0, 133.0, 132.7, 132.6, 131.6, 125.4, 125.3, 123.0, 122.9, 122.5, 117.6, 117.2, 56.9, 40.6, 40.4, 40.2, 40.0, 39.8, 39.6, 39.4, 37.9, 32.5, 31.8, 31.5, 29.7, 22.9, 22.6, 22.5, 14.5, 14.4; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{17}\text{N}_2\text{O}_2\text{S}$ 301.1005; found 301.1008.



2-Hexyl-8-nitro-benzothiopheno[3,2-b]pyridine and 3-Methyl-8-nitro-2-pentyl-benzothiopheno[3,2-b]pyridine (7d). Gray solid (213 mg, 68%); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.92 (d, J = 1.7 Hz, 1H), 8.86 (d, J = 1.7 Hz, 1H), 8.45 (d, J = 8.4 Hz, 1H), 8.35–8.25 (m, 4H), 7.46 (d, J = 8.4 Hz, 1H), 2.89 (t, J = 7.7 Hz, 2H), 2.69–2.65 (m, 1H), 2.60 (s, 2H), 1.77–1.70 (m, 2H), 1.60–1.56 (m, 1H), 1.32–1.22 (m, 9H), 0.87–0.80 (m, 5H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, $\text{DMSO}-d_6$) δ 161.1, 156.0, 150.1, 147.8, 146.6, 146.2, 145.8, 136.4, 134.9, 133.0, 132.6, 132.5, 131.4, 125.4, 125.3, 122.9, 122.8, 122.4, 117.5, 117.1, 37.9, 32.8, 31.7, 29.9, 29.8, 29.3, 29.0, 22.8, 22.6, 22.5, 14.5, 14.5; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{19}\text{N}_2\text{O}_2\text{S}$ 315.1162; found 315.1167.



Antibacterial Studies. Bacterial Cultures. The bacterial strains (*S. aureus* ATCC 700699, *B. subtilis* ATCC 6623, *A. baumannii* ATCC 19606) were purchased from ATCC. Overnight cultures of bacteria

were prepared with a single colony and routinely cultured in cation-adjusted Muller Hinton Broth (Ca-MHB).

Antimicrobial Compounds. Vancomycin and colistin were commercially available from Sigma-Aldrich. The benzothiophene derivatives are chemically synthesized. All of the test compounds were dissolved in dimethyl sulfoxide (DMSO) and diluted in the media for the assay, resulting in a standard starting concentration.

Determination of Minimum Inhibitory Concentration (MIC). The minimum inhibitory concentration (MIC) was determined by the standard broth microdilution method as recommended by Clinical and Laboratory Standards Institute (CLSI) guidelines with slight modifications as reported by us previously.^{43,56} Briefly, bacterial strains were cultured overnight in Ca-MHB. A standard concentration of benzothiophene derivatives was dissolved in media and serially diluted 2-fold down the 96-well plate column. The plates were then incubated at 37 °C for 20 h. MIC values were then determined as the lowest concentration of the compound at which no visible growth of bacteria was observed. All of the MIC assays were performed in triplicates. Vancomycin and 1% DMSO were used as positive and negative controls, respectively.

Cytotoxicity Studies. We submitted the compounds to NCI DTP (developmental therapeutics program) (<https://dctd.cancer.gov/>) program for their antineoplastic screening. Initially, the selected compounds were studied at 10 μ M concentration for their cytotoxic properties. Several compounds (e.g., **6p**) showed potent activity at this concentration and are selected for further studies to determine their 50% growth inhibition (GI_{50}), total growth inhibition (TGI), and lethal concentration 50 (LC_{50}) values.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its [Supporting Information](#).

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.joc.3c02646>.

Supporting Information is available free of charge at Copies of 1H , ^{13}C , ^{19}F , and Mass spectra, X-ray crystal structures and data, and z-coordinates of theoretical calculations ([PDF](#))

Accession Codes

CCDC 2303018–2303020 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

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