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Dual Roles of β-Oxodithioesters in the Copper-Catalyzed Synthesis of Benzo[e]pyrazolo[1,5-c][1,3]thiazine Derivatives

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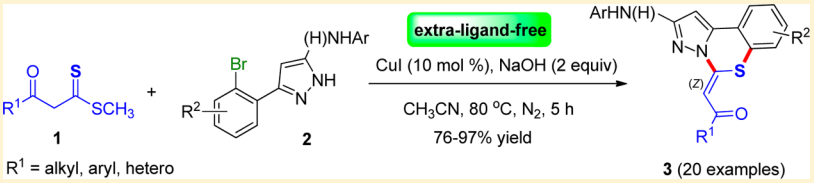
Supporting Information



ABSTRACT: A facile and efficient method for the chemoselective synthesis of benzo[e]pyrazolo[1,5-c][1,3]thiazine derivatives has been developed by tandem Ullmann coupling reactions of β-oxodithioesters (ODEs) with 3-(2-bromoaryl)-1H-pyrazoles in C−S bond formation manner, in which ODEs play dual roles as both a substrate and a ligand. A series of benzo[e]pyrazolo[1,5-c][1,3]thiazine derivatives were provided in good to excellent yields with CuI as the copper source in the presence of NaOH in CH_3CN at 80 °C under a N_2 atmosphere.

INTRODUCTION

The 1,3-benzothiazine skeleton is a key structural element that appears in the core structures of pharmaceutically relevant compounds. For example, PD 404182 (Figure 1, **A**) has been

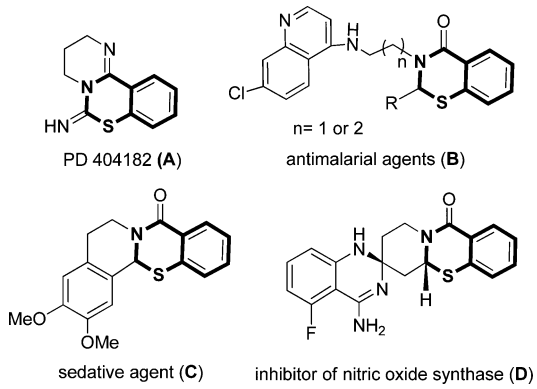


Figure 1. Examples of bioactive 1,3-benzothiazines.

reported as an antimicrobial agent that inhibits 3-deoxy-D-*manno*-octulosonic acid 8-phosphate synthase[1] and phosphopantetheinyl transferase,[2] and could be used as an antiretroviral agent with submicromolar inhibitory activity against human immunodeficiency virus-1 (HIV-1) and HIV-2 infection.[3] Compounds **B** have demonstrated anntimalarial activity against *Plasmodium falciparum* in vitro and *Plasmodium yoelii* in vivo.[4] Compound **C** can be used as sedatives.[5] Compound **D** has been studied as a promising inhibitor of nitric oxide synthase in the treatment of inflammatory disease and pain.[6] Other interesting 1,3-benzothiazine derivatives have also been investigated as antibacterials,[7] cell growth inhibitors,[8] and HIV-RT inhibitory activity.[9] Although 1,3-benzothiazine derivatives play important roles in biological and medicinal areas, few approaches to these compounds have been developed to date.[10] These methods may suffer from tedious procedures, poor precursor scopes, or low efficiency. So, there are still opportunities for the development of novel procedures for the synthesis of new and interesting 1,3-benzothiazine derivatives.

The recent advances in cross-coupling reactions using transition-metal catalysis have led to the development of effective methods for the construction of carbon−sulfur bonds.[11] For example, palladium,[12] iron,[13] and copper[14] salts have emerged as appealing catalysts for these reactions. Among the various employed metals, copper is one of the most favorable metals for C−S bond forming reactions due to its low cost and low toxicity.[15] Most of these copper-catalyzed reactions involve specially designed ligands or well-defined catalysts/reagents, which may increase the cost and limit the scope of applications in some cases.

β-Oxodithioesters (ODEs)[16] have been employed to construct various important bioactive frameworks, such as thiophene,[17] pyrrole,[18] 4H-thiopyran,[19] thiazole,[20] 1,3-oxathiole,[21] pyrazole,[22] 1,3,4-thiadiazole,[23] dihydropyrimidinone,[24] and chromene- 2-thione.[25] However, all of the above protocols did not involve the thiocarbonyl-based Ullmann coupling reactions catalyzed by copper. In continuation of our ongoing research interest in the synthesis of heterocycles,[26] we herein report a first example of a concise copper-catalyzed tandem reaction of β-oxodithioesters (**1**) with 3-(2-bromoaryl)-1H-pyrazoles (**2**) for the synthesis of benzo[e]pyrazolo[1,5-

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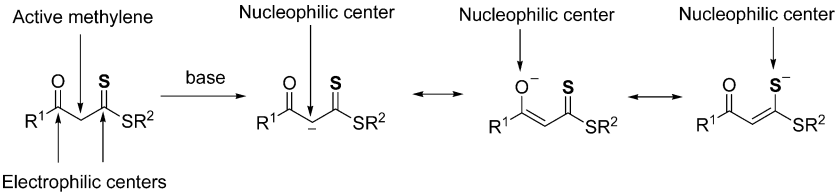


Figure 2. Reactive sites of β-oxodithioesters.

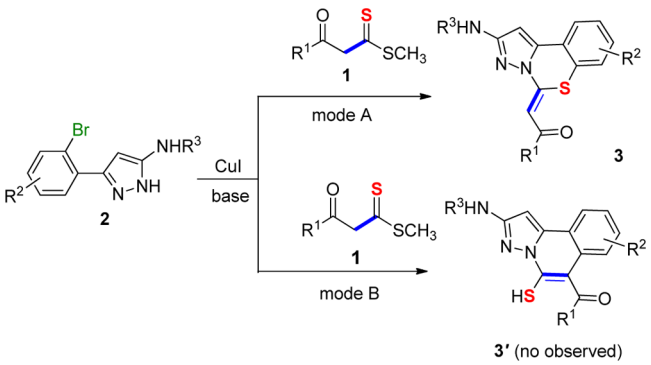
c][1,3]thiazines (**3**), in which ODEs (**1**) play dual roles as both a substrate and a ligand.

RESULTS AND DISCUSSION

The chemical properties of β-oxodithioester (**1**) can be featured by the presence of two electrophilic and three nucleophilic (one potential) centers as shown in Figure 2.

Due to the presence of these active centers, the reactions of ODEs (**1**) with various difunctional group reagents may lead to the formation of various heterocyclic systems, where the sulfur atom is present in the ring system or as an external substituent. There are two possible coupling modes when ODEs (**1**) react with 3-(2-bromoaryl)-1*H*-pyrazoles (**2**) under Cu catalysis (Scheme 1). In mode A, the S atom of the thiocarbonyl group

Scheme 1. Two Possible Copper-Catalyzed Coupling Modes Involving β-Oxodithioesters

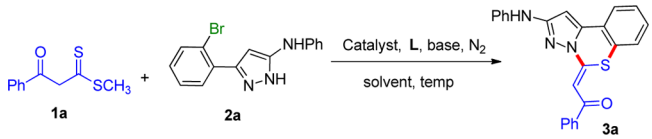


in ODEs (**1**) participates in an Ullmann coupling reaction with 3-(2-bromoaryl)-1*H*-pyrazoles (**2**) providing benzo[*e*]pyrazolo-[1,5-*c*][1,3] thiazines (**3**). In mode B, the coupling reactions occur in the methylene of ODEs (**1**), providing pyrazolo[5,1-*a*]isoquinolines (**3′**) through a Hurtley coupling reaction.[26c] Under our reaction conditions only **3** were obtained exclusively, and **3′** were not observed, which suggested that our protocol shows high chemoselectivity.

Optimization of the reaction conditions was carried out with methyl 3-oxo-3-phenylpropanedithioate (**1a**) and 5-(2-bromophenyl)-*N*-phenyl-1*H*- pyrazol-3-amine (**2a**) as model substrates under a N_2 atmosphere, and the results are shown in Table 1.

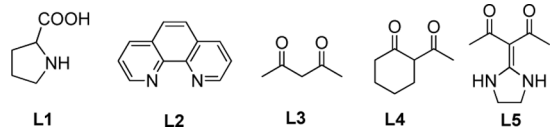
As shown in Table 1, in the absence of catalyst, no reaction was observed at room temperature in the presence of NaOH in CH_3CN under a N_2 atmosphere for 5 h (Table 1, entry 1). But after addition of CuI (0.1 equiv), the product **3a** was obtained in a yield of 25% (Table 1, entry 2). The yield of **3a** was greatly improved with increasing the reaction temperature (Table 1, entries 3 and 4), and the yield of **3a** reached 91% at reflux temperature. Then other solvents such as EtOH, dioxane, toluene, DMSO, and DMF were also investigated at reflux temperature (Table 1, entries 5−9), and the results revealed

Table 1. Reaction Condition Optimization[a]



entry	base	Cu salt (equiv)	L[b] (equiv)	solvent	T/°C	yield[c]/%
1	NaOH			CH_3CN	rt	NR[d]
2	NaOH	CuI (0.1)		CH_3CN	rt	25
3	NaOH	CuI (0.1)		CH_3CN	60	75
4	NaOH	CuI (0.1)		CH_3CN	80	91
5	NaOH	CuI (0.1)		EtOH	reflux	56
6	NaOH	CuI (0.1)		dioxane	reflux	85
7	NaOH	CuI (0.1)		toluene	reflux	78
8	NaOH	CuI (0.1)		DMSO	reflux	73
9	NaOH	CuI (0.1)		DMF	reflux	67
10	Na_2CO_3	CuI (0.1)		CH_3CN	80	53
11	Cs_2CO_3	CuI (0.1)		CH_3CN	80	78
12	Et_3N	CuI (0.1)		CH_3CN	80	30
13	DABCO	CuI (0.1)		CH_3CN	80	46
14	NaOH	CuI (0.1)	**L1** (0.2)	CH_3CN	80	88
15	NaOH	CuI (0.1)	**L2** (0.2)	CH_3CN	80	90
16	NaOH	CuI (0.1)	**L3** (0.2)	CH_3CN	80	55
17	NaOH	CuI (0.1)	**L4** (0.2)	CH_3CN	80	76
18	NaOH	CuI (0.1)	**L5** (0.2)	CH_3CN	80	88
19	NaOH	CuI (0.1)		CH_3CN	80	83[e]
20	NaOH	CuI (0.1)		CH_3CN	80	90[f]
21	NaOH	CuBr (0.1)		CH_3CN	80	78
22	NaOH	CuCl (0.1)		CH_3CN	80	64
23	NaOH	Cu_2O (0.1)		CH_3CN	80	20
24	NaOH	$CuSO_4$ (0.1)		CH_3CN	80	35
25	NaOH	CuI (0.05)		CH_3CN	80	70
26	NaOH	CuI (0.2)		CH_3CN	80	87
27	NaOH (1.0)	CuI (0.1)		CH_3CN	80	42
28	NaOH (3.0)	CuI (0.1)		CH_3CN	80	89

[a]Reaction conditions: **1a** (0.6 mmol), **2a** (0.5 mmol), base (1.0 mmol), solvent (2 mL), N_2, 5 h. [b]The structures of the ligands are as follows:



[c]Isolated yield. [d]No reaction. [e]**1a** (0.55 mmol) was used. [f]**1a** (0.65 mmol) was used.

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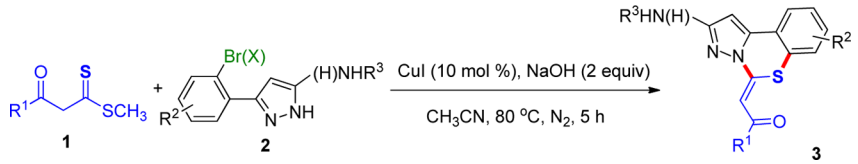
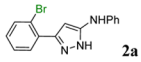
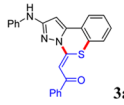
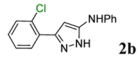
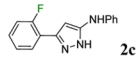
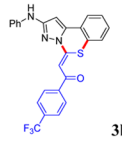
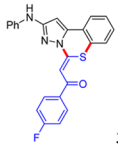
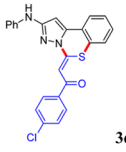
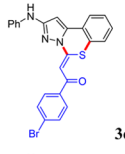
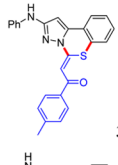
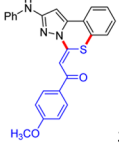
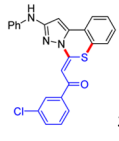
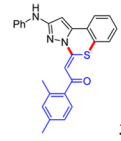
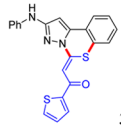
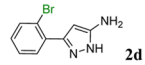
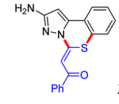
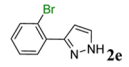
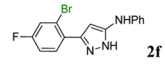
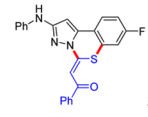
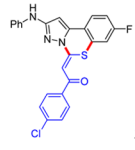
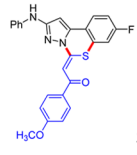
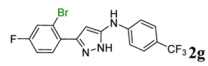
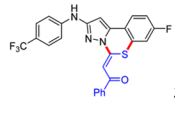
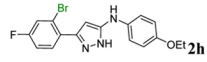
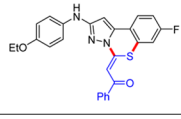
Table 2. Investigation on the Substrate Scope[a]



Entry	R^1	2	3	Yield (%)[b]
1	C_6H_5	 **2a**	 **3a**	91
2	C_6H_5	 **2b**	**3a**	72
3	C_6H_5	 **2c**	**3a**	6
4	4-$CF_3C_6H_4$	**2a**	 **3b**	97
5	4-FC_6H_4	**2a**	 **3c**	95
6	4-ClC_6H_4	**2a**	 **3d**	92
7	4-BrC_6H_4	**2a**	 **3e**	94
8	4-$CH_3C_6H_4$	**2a**	 **3f**	87
9	4-$OCH_3C_6H_4$	**2a**	 **3g**	83
10	2-ClC_6H_4	**2a**	 **3h**	90
11	3-ClC_6H_4	**2a**	 **3i**	91
12	2,4-diClC_6H_3	**2a**	 **3j**	97
13	2,4-di$CH_3C_6H_3$	**2a**	 **3k**	84
14	CH_3	**2a**	 **3l**	76
15	2-thienyl	**2a**	 **3m**	88
16	C_6H_5	 **2d**	 **3n**	84
17	C_6H_5	 **2e**	 **3o**	76
18	C_6H_5	 **2f**	 **3p**	93
19	4-ClC_6H_4	**2f**	 **3q**	94
20	4-$OCH_3C_6H_4$	**2f**	 **3r**	89
21	C_6H_5	 **2g**	 **3s**	94
22	C_6H_5	 **2h**	 **3t**	92

[a]Reaction conditions: **1** (0.6 mmol), **2** (0.5 mmol), NaOH (1.0 mmol), CuI (0.05 mmol), CH_3CN (2.0 mL), N_2, 5 h. [b]Isolated yields were based on **2**.

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that CH_3CN was most suitable. Next, various bases such as Na_2CO_3, Cs_2CO_3, Et_3N, and DABCO were tested (Table 1, entries 10−13), but they gave lower yields than NaOH.

With regard to most copper-catalyzed reactions generally involving the use of ligands, the model reaction was performed in CH_3CN with different ligands such as **L1**−**L5** (Table 1, entries 14−18). Unfortunately, these ligands did not further improve the yield of **3a**. This observation prompted us to investigate the amount of **1a**. The results revealed that when 10% excess of **1a** was used, the yield of **3a** decreased (Table 1, entry 19), while 30% excess of **1a** did not further improve the yield of **3a** (Table 1, entry 20), which suggested that 20% excess of **1a** might act as a ligand for this copper-catalyzed coupling reaction. Other copper sources such as CuBr, CuCl, Cu_2O, and $CuSO_4$ were also screened (Table 1, entries 21−24), and the results showed that CuI was most efficient for this coupling reaction. Increasing or decreasing the amount of CuI did not improve the yield of **3a** (Table 1, entries 25 and 26). Finally, the amount of NaOH was also examined (Table 1, entries 27 and 28), and the results showed that 2 equiv of NaOH is most suitable for the transformation. Therefore, the optimized conditions for this coupling reaction are as follows: 0.1 equiv of CuI as the copper source, 2.0 equiv of NaOH as the base, and CH_3CN as the solvent at 80 °C under a N_2 atmosphere.

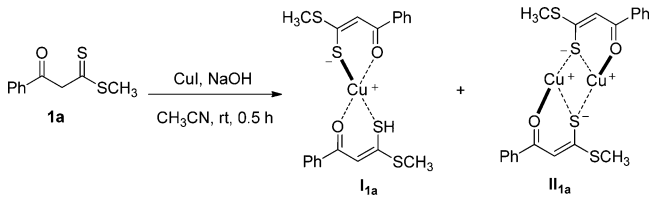
With the above optimized reaction conditions in hand, we commenced to explore the substrate scope, and the results are summarized in Table 2. As expected, other halides such as chloride (**2b**) and fluoride (**2c**) provided lower yields (Table 2, entries 2 and 3).

As can be seen from Table 2, all of the tandem reactions proceeded smoothly to give corresponding products **3** in good to excellent yields. For substrates **1**, a wide range of aromatic *β*-oxodithioesters bearing electron-withdrawing or electron-donating groups (Table 2, entries 1−13), even aliphatic *β*-oxodithioester (Table 2, entry 14) and heterocyclic *β*-oxodithioester (Table 2, entry 15), could be well tolerated. For substrates **2**, the substituents at the 5-position on the pyrazole ring have evident influence on the reaction yields. For example, arylamino substituents bearing either electron-withdrawing or electron-donating groups gave excellent yields of 89−94% (Table 2, entries 1, 20−22); a primary amino substituent provided the relatively low yield of 84% (Table 2, entry 16); while 5-unsubstituted 3-(2-bromophenyl)-1*H*-pyrazole (**2e**) could lead to the even lower yield of 76% (Table 2, entry 17), and the introduction of a fluorine atom to the phenyl ring linked directly to pyrazole could improve slightly the reaction yields (**3a** vs **3p**, **3d** vs **3q**, and **3g** vs **3r**).

The structural characterization of products **3** was achieved by spectroscopic data (^1H and ^{13}C NMR, IR, and HRMS) and unequivocally established by the X-ray single crystal diffraction analysis of compound **3k** (Figure S1 in the Supporting Information). Moreover, X-ray analysis of **3k** reveals that the obtained products take the *Z* configuration.

In order to explore the role as a ligand of ODEs (**1**) in this coupling reaction, an attempt to obtain the copper(I)−ODE complex was made. Mass spectrometric (MS-ESI-TOF, $[M + H]^+$) studies of the reaction system of CuI and **1a** in CH_3CN in the presence of NaOH at room temperature for 0.5 h exhibited the two ion peaks at *m*/*z* 482.94 and 544.84 (Figure S2 in the Supporting Information), which could be due to the mononuclear copper(I) complex $\mathbf{I}_{1a}$ (calcd 482.96) and the dinuclear copper(I) complex $\mathbf{II}_{1a}$ (calcd 544.88), respectively (Scheme 2). This observation is in accordance with the report in literature.[27] Moreover, the MS analysis suggested that, in the

Scheme 2. Coordination Mode Exploration of CuI with 1a

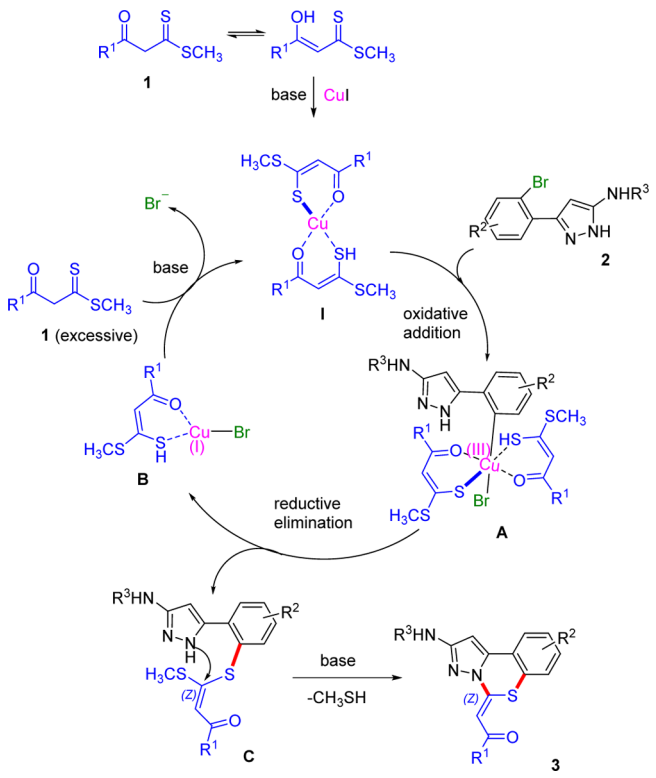


mononuclear copper(I)−ODE complex ($\mathbf{I}_{1a}$), the two molecules of **1a** play different roles: one acts as a dative ligand, and another as an anionic ligand that would be the nucleophilile in the coupling reaction.[28]

In order to investigate the mechanism of this tandem reaction, a control experiment was carried out. We utilized 3-benzylpyrazole without *o*-Br group (**2′**) and 3-(*o*-bromobenzyl)pyrazole (**2a**) to react with *β*-oxodithioester **1a** under the standard conditions, respectively. As indicated by TLC, the reaction of **2a** with **1a** provided the target product **3a** within 10 min, while the reaction of **2′** with **1a** did not occur after 30 min; even after 10 h only small amounts of **2′** and **1a** were consumed. These results reveal that the C−Br bond of 3-(*o*-bromobenzyl)pyrazole (**2a**) is easy to be activated by the present copper catalyst to lead to *S*-arylation with **1a**.

On the basis of the experimental results obtained above, a proposed mechanism for the tandem reactions is outlined in Scheme 3. Initially a reaction between substrate *β*-oxodithioesters **1** and CuI would occur to give complex **I**, which undergoes an oxidative addition reaction with **2** to yield Cu(III) intermediate **A**. The subsequent reductive elimination releases

Scheme 3. Proposed Reaction Mechanism



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intermediate **C** with the concomitant regeneration of the Cu(I) species **B**, and in **C** the dithioester segment still keeps a *Z* configuration. Finally, **C** undergoes an intramolecular nucleophilic substitution reaction (S_Ni) to give the final *Z*-configured products **3**.

CONCLUSION

In summary, we have developed a method for the synthesis of benzo[*e*]pyrazolo [1,5-*c*][1,3]thiazine derivatives from substituted 3-(2-bromoaryl)-1*H*-pyrazoles and *β*-oxodithioesters by a copper-catalyzed intermolecular C−S cross-coupling reaction and an intramolecular nucleophilic substitution reaction in cascade mode. It is the first report on employing *β*-oxodithioesters as both a substrate and a ligand to construct a pyrazolo[1,5-*c*][1,3]thiazine motif under copper-catalyzed conditions. The advantages of this strategy are high yields, mild reaction conditions, easy purification, and availability of CuI/extra-ligand-free catalyst.

EXPERIMENTAL SECTION

General Experimental Methods. All reagents and solvents were obtained from commercial suppliers and used without further purification. All reagents were weighed and handled in air at room temperature. Melting points were recorded on a microscopic melting apparatus and uncorrected. ^{1}H NMR, ^{19}F NMR, and ^{13}C NMR spectra were recorded at 500, 376, and 125 MHz in DMSO-d_6, respectively. Chemical shifts are reported in δ (ppm) relative to TMS or $CFCl_3$. IR spectra were recorded on a FT-IR spectrometer, and only major peaks are reported in cm^{-1}. HRMS spectra were performed on a spectrometer with an ESI source. The X-ray single-crystal diffraction was performed on a CCD area detector. The substrate 5-(2-fluorophenyl)-*N*-phenyl-1*H*-pyrazol-3-amine (**2c**) was prepared according to a reported procedure.[29] 3-(2-Bromophenyl)-1*H*-pyrazole (**2e**) was prepared by a reported procedure.[30]

General Procedure for the Synthesis of Products 3 (3a for Example). Under a nitrogen atmosphere, a mixture of methyl 3-oxo-3-phenylpropanedithioate (**1a**) (126.2 mg, 0.6 mmol), 3-(2-bromophenyl)-*N*-phenyl-1*H*-pyrazol-5-amine (**2a**) (157.1 mg, 0.5 mmol), and NaOH (40 mg, 1.0 mmol) was heated in the presence of CuI (9.5 mg, 0.05 mmol) in CH_3CN (2 mL) at 80 °C. After completion of the reaction as indicated by TLC, the solid product was filtered, washed with CH_3CN (3 × 5 mL), and subsequently dried to give the pure product **3a**.

*5-(2-Fluorophenyl)-N-phenyl-1H-pyrazol-3-amine (**2c**):* white solid; mp 93−94 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.49 (1H, s), 7.62 (1H, q, *J* = 7.79 Hz, *J* = 1.58 Hz), 7.31−7.27 (1H, m), 7.25−7.24 (2H, m), 7.17−7.16 (1H, m), 7.13 (3H, d, *J* = 8.45 Hz), 6.88 (1H, t, *J* = 7.30 Hz), 6.42 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3 (d, $^1J_{C-F}$ = 248.1 Hz), 151.6, 143.1, 139.0, 129.7 (d, $^3J_{C-F}$ = 6.7 Hz), 129.2, 127.8, 124.7, 120.1, 117.3 (d, $^3J_{C-F}$ = 11.0 Hz), 116.3 (d, $^2J_{C-F}$ = 22.2 Hz), 115.9, 93.4; ^{19}F NMR (376 MHz, DMSO-d_6) δ −115.8; IR (KBr, cm^{-1}) ν 3387, 3266, 3156, 3061 1602, 1589, 1576, 1552, 1505, 1469, 1454; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{15}H_{13}N_3F$ 254.1094, found 254.1098.

*(Z)-1-Phenyl-2-(2-(phenylamino)-5H-benzo[e]pyrazolo[1,5-c]-[1,3]thiazin-5-ylidene)ethan-1-one (**3a**):* isolated yield 180 mg (91%); yellowish green solid; mp 267−269 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.53 (1H, s), 8.19 (1H, d, *J* = 7.25 Hz), 7.98 (2H, d, *J* = 6.70 Hz), 7.75 (1H, d, *J* = 7.55 Hz), 7.64−7.60 (5H, m), 7.57−7.51 (2H, m), 7.37 (2H, t, *J* = 7.00 Hz), 7.04 (1H, s), 6.94 (1H, t, *J* = 6.75 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 187.2, 154.9, 147.2, 141.9, 139.2, 138.8, 132.6, 130.5, 129.5, 129.4, 128.2, 127.6, 127.1, 126.5, 126.1, 120.8, 120.7, 117.2, 98.5, 95.8; IR (KBr, cm^{-1}) ν 3342, 3048, 1610, 1602, 1576, 1560, 1498, 1485, 1439; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{24}H_{18}N_3OS$ 396.1171, found 396.1162.

*(Z)-2-(2-(Phenylamino)-5H-benzo[e]pyrazolo[1,5-c][1,3]thiazin-5-ylidene)-1-(4-(trifluoromethyl)phenyl)ethan-1-one (**3b**):* isolated yield 225 mg (97%); yellowish green solid; mp >300 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.60 (1H, s), 8.21 (2H, d, *J* = 7.55 Hz), 8.16 (2H, d, *J* = 8.00 Hz), 7.98 (2H, d, *J* = 8.05 Hz), 7.93 (1H, s), 7.78 (1H, d, *J* = 7.80 Hz), 7.65 (2H, d, *J* = 8.05 Hz), 7.58−7.51 (2H, m), 7.38 (2H, t, *J* = 7.70 Hz), 7.07 (1H, s), 6.94 (1H, t, *J* = 7.20 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 185.9, 155.2, 148.5, 142.6, 141.9, 138.9, 130.6, 129.6, 128.5, 126.9, 126.6, 126.5, 126.2, 120.9, 120.8, 117.3, 98.2, 96.3; ^{19}F NMR (376 MHz, DMSO-d_6) δ −61.3; IR (KBr, cm^{-1}) ν 3319, 1615, 1599, 1573, 1557, 1517, 1482, 1441, 1324; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{25}H_{17}N_3OSF_3$ 464.1044, found 464.1049.

*(Z)-1-(4-Fluorophenyl)-2-(2-(phenylamino)-5H-benzo[e]pyrazolo-[1,5-c][1,3]thiazin-5-ylidene)ethan-1-one (**3c**):* isolated yield 196 mg (95%); yellowish green solid; mp 255−256 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.53 (1H, s), 8.18 (1H, s), 8.04 (1H, s), 7.90 (2H, d, *J* = 7.90 Hz), 7.73 (1H, m), 7.63 (2H, d, *J* = 7.20 Hz), 7.54−7.50 (2H, m), 7.44−7.38 (4H, m), 7.03 (1H, s), 6.94 (1H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ 185.9, 155.1, 147.4, 144.5, 142.1, 139.0, 130.6, 129.6, 128.2, 127.3, 126.7, 126.0, 120.7, 117.5, 116.3 (d, $^2J_{C-F}$ = 21.75 Hz), 98.5, 98.4, 95.9, 95.7; ^{19}F NMR (376 MHz, DMSO-d_6) δ −107.8; IR (KBr, cm^{-1}) ν 3312, 1598, 1558, 1476, 1439, 1498; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{24}H_{17}N_3OFS$ 414.1076, found 414.1086.

*(Z)-1-(4-Chlorophenyl)-2-(2-(phenylamino)-5H-benzo[e]-pyrazolo[1,5-c][1,3]thiazin-5-ylidene)ethan-1-one (**3d**):* isolated yield 198 mg (92%); yellowish green solid; mp 262−263 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.54 (1H, s), 8.18 (1H, s), 7.98 (1H, s), 7.88 (1H, s), 7.74−7.65 (5H, m), 7.55−7.51 (2H, m), 7.38 (2H, s), 7.05 (1H, s), 6.95 (1H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ 185.9, 155.0, 147.8, 141.9, 138.8, 137.9, 137.4, 130.5, 129.5, 128.2, 127.0, 126.5, 126.1, 120.8, 120.7, 117.2, 98.1, 96.0; IR (KBr, cm^{-1}) ν 3314, 1609, 1598, 1589, 1570, 1557, 1496, 1478, 1440; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{24}H_{17}N_3OSCl$ 430.0781, found 430.0775.

*(Z)-1-(4-Bromophenyl)-2-(2-(phenylamino)-5H-benzo[e]-pyrazolo[1,5-c][1,3]thiazin-5-ylidene)ethan-1-one (**3e**):* isolated yield 223 mg (94%); yellowish green solid; mp 276−278 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.53 (1H, s), 8.17 (1H, d, *J* = 7.65 Hz), 7.89 (1H, s), 7.87 (2H, d, *J* = 4.15 Hz), 7.79 (2H, d, *J* = 8.35 Hz), 7.73 (1H, d, *J* = 7.80 Hz), 7.62 (2H, d, *J* = 8.05 Hz), 7.55−7.48 (2H, m), 7.36 (2H, t, *J* = 7.75 Hz), 7.03 (1H, s), 6.93 (1H, t, *J* = 7.28 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 186.3, 154.9, 147.8, 141.9, 138.9, 138.3, 132.4, 130.5, 129.6, 129.5, 128.2, 127.0, 126.5, 126.4, 126.1, 120.8, 120.7, 117.3, 98.1, 96.0; IR (KBr, cm^{-1}) ν 3306, 1601, 1587, 1569, 1558, 1491, 1474, 1438; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{24}H_{17}N_3OSBr$ 474.0276, found 474.0285.

*(Z)-2-(2-(Phenylamino)-5H-benzo[e]pyrazolo[1,5-c][1,3]thiazin-5-ylidene)-1-(p-tolyl)ethan-1-one (**3f**):* isolated yield 178 mg (87%); yellowish green solid; mp 251−253 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.51 (1H, s), 8.18 (1H, d, *J* = 7.25 Hz), 7.93 (1H, s), 7.88 (2H, d, *J* = 7.20 Hz), 7.73 (1H, d, *J* = 7.25 Hz), 7.63 (2H, d, *J* = 7.35 Hz), 7.54−7.49 (2H, m), 7.40−7.39 (4H, m), 7.03 (1H, s), 6.94 (1H, s), 2.40 (3H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ 187.0, 154.9, 146.8, 143.0, 142.2, 138.8, 136.7, 130.5, 129.9, 129.6, 128.1, 127.7, 127.2, 126.5, 126.0, 120.8, 117.1, 98.4, 95.6, 21.4; IR (KBr, cm^{-1}) ν 3319, 1598, 1568, 1553, 1519, 1482, 1438, 1405; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{25}H_{20}N_3OS$ 410.1327, found 410.1336.

*(Z)-1-(4-Methoxyphenyl)-2-(2-(phenylamino)-5H-benzo[e]-pyrazolo[1,5-c][1,3]thiazin-5-ylidene)ethan-1-one (**3g**):* isolated yield 177 mg (83%); yellowish green solid; mp 246−247 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.50 (1H, s), 8.16 (1H, d, *J* = 7.30 Hz), 7.96 (2H, d, *J* = 8.05 Hz), 7.91 (1H, s), 7.70 (1H, d, *J* = 7.55 Hz), 7.64 (2H, d, *J* = 7.50 Hz), 7.54−7.48 (2H, m), 7.38 (2H, t, *J* = 7.10 Hz), 7.13 (2H, d, *J* = 8.00 Hz), 7.00 (1H, s), 6.94 (1H, t, *J* = 6.70 Hz), 3.86 (3H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ 186.0, 162.9, 154.8, 146.3, 142.0, 138.7, 131.9, 130.4, 129.8, 129.5, 128.0, 127.4, 126.4, 126.0, 120.7, 117.2, 114.6, 98.5, 95.6, 56.0; IR (KBr, cm^{-1}) ν 3318, 1601, 1573, 1568, 1482, 1440, 1414 ; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{25}H_{20}N_3O_2S$ 426.1276, found 426.1285.

*(Z)-1-(2-Chlorophenyl)-2-(2-(phenylamino)-5H-benzo[e]-pyrazolo[1,5-c][1,3]thiazin-5-ylidene)ethan-1-one (**3h**):* isolated yield 194 mg (90%); yellowish green solid; mp 244−245 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.48 (1H, s), 8.18 (1H, d, *J* = 7.50

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Hz), 7.76 (1H, d, J = 7.70 Hz), 7.66 (1H, d, J = 6.35 Hz), 7.63 (1H, s), 7.60−7.57 (3H, m), 7.55−7.47 (4H, m), 7.29 (2H, t, J = 7.70 Hz), 7.01 (1H, s), 6.90 (1H, t, J = 7.23 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 188.1, 155.0, 147.0, 141.8, 140.4, 138.8, 132.2, 130.8, 130.3, 130.5, 130.1, 129.4, 128.3, 128.0, 126.7, 126.6, 126.1, 120.9, 120.7, 117.1, 102.0, 96.1; IR (KBr, cm^{-1}) ν 3360, 1605, 1570, 1560, 1519, 1485, 1473, 1442, 1408; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{24}H_{17}N_3OSCl$ 430.0781, found 430.0776.

(Z)-1-(3-Chlorophenyl)-2-(2-(phenylamino)-5H-benzo[e]pyrazolo[1,5-c][1,3]thiazin-5-ylidene)ethan-1-one (**3i**)*:* isolated yield 196 mg (91%); yellowish green solid; mp 270−272 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.60 (1H, s), 8.15 (1H, s), 7.90 (2H, s), 7.86 (1H, s), 7.66 (5H, s), 7.50 (2H, s), 7.35 (2H, s), 7.04 (1H, s), 6.94 (1H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ 185.4, 155.1, 148.0, 141.9, 141.1, 138.8, 134.3, 132.2, 131.4, 130.5, 129.5, 128.3, 127.4, 126.9, 126.6, 126.1, 120.9, 120.7, 117.4, 98.0, 96.1; IR (KBr, cm^{-1}) ν 3323, 1598, 1569, 1557, 1516, 1491, 1472, 1440; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{24}H_{17}N_3OSCl$ 430.0781, found 430.0785.

(Z)-1-(2,4-Dichlorophenyl)-2-(2-(phenylamino)-5H-benzo[e]pyrazolo[1,5-c][1,3]thiazin-5-ylidene)ethan-1-one (**3j**)*:* isolated yield 225 mg (97%); yellowish green solid; mp 263−264 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.63 (1H, s), 8.17 (1H, d, J = 7.45 Hz), 7.75 (2H, s), 7.69 (1H, d, J = 8.25 Hz), 7.62−7.60 (3H, m), 7.58−7.50 (3H, m), 7.29 (2H, t, J = 7.50 Hz), 7.04 (1H, s), 6.90 (1H, t, J = 7.08 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 186.8, 155.2, 147.5, 141.9, 139.1, 138.8, 135.9, 131.5, 130.5, 130.3, 129.3, 128.4, 128.3, 126.6, 126.5, 126.1, 120.8, 120.7, 117.2, 101.6, 96.3; IR (KBr, cm^{-1}) ν 3341, 1604, 1561, 1517, 1468, 1438, 1405; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{24}H_{16}N_3OSCl_2$ 464.0391, found 464.0385.

(Z)-1-(2,4-Dimethylphenyl)-2-(2-(phenylamino)-5H-benzo[e]pyrazolo[1,5-c][1,3]thiazin-5-ylidene)ethan-1-one (**3k**)*:* isolated yield 178 mg (84%); yellowish green solid; mp 265−267 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.48 (1H, s), 8.15 (1H, d, J = 7.75 Hz), 7.72 (2H, d, J = 7.80 Hz), 7.60−7.58 (3H, m), 7.55−7.47 (3H, m), 7.30 (2H, t, J = 7.83 Hz), 7.16 (1H, d, J = 8.00 Hz), 7.13 (1H, s), 7.00 (1H, s), 6.90 (1H, t, J = 7.30 Hz), 2.50 (3H, s), 2.33 (3H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ 191.2, 154.8, 146.0, 142.0, 140.7, 138.6, 137.8, 136.8, 132.6, 130.3, 129.4, 128.4, 128.1, 127.1, 127.0, 126.5, 120.7, 117.0, 102.1, 95.7, 21.3, 20.8; IR (KBr, cm^{-1}) ν 3285, 1599, 1561, 1518, 1501, 1473, 1437; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{26}H_{22}N_3OS$ 424.1484, found 424.1479.

(Z)-1-(2-(Phenylamino)-5H-benzo[e]pyrazolo[1,5-c][1,3]thiazin-5-ylidene)propan-2-one (**3l**)*:* isolated yield 127 mg (76%); yellowish green solid; mp 223−224 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.45 (1H, s), 8.10 (1H, d, J = 6.40 Hz), 7.65 (1H, d, J = 7.10 Hz), 7.61 (1H, d, J = 7.00 Hz), 7.49−7.45 (2H, m), 7.33 (2H, s), 7.17 (1H, s), 7.94−6.91 (2H, m); ^{13}C NMR (125 MHz, DMSO-d_6) δ 195.0, 154.7, 144.0, 141.9, 138.5, 130.3, 129.4, 127.8, 127.1, 126.3, 125.8, 120.6, 127.6, 117.0, 102.3, 95.5, 30.9; IR (KBr, cm^{-1}) ν 3307, 1632, 1601, 1567, 1483, 1441, 1306; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{19}H_{16}N_3OS$ 334.1014, found 334.1025.

(Z)-2-(2-(Phenylamino)-5H-benzo[e]pyrazolo[1,5-c][1,3]thiazin-5-ylidene)-1-(thiophene-2-yl)ethan-1-one (**3m**)*:* isolated yield 177 mg (88%); orange solid; mp 280−281 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.54 (1H, s), 8.15 (1H, d, J = 7.50 Hz), 7.95 (1H, d, J = 4.55 Hz), 7.82 (1H, d, J = 2.90 Hz), 7.76 (1H, s), 7.70−7.65 (3H, m), 7.54−7.46 (2H, m), 7.38 (2H, t, J = 7.55 Hz), 7.28 (1H, t, J = 3.98 Hz), 7.00 (1H, s), 6.94 (1H, t, J = 7.10 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 180.1, 155.0, 146.5, 146.3, 141.9, 138.7, 133.7, 130.5, 129.5, 129.4, 128.2, 127.0, 126.6, 126.0, 120.8, 120.6, 117.2, 98.4, 95.9; IR (KBr, cm^{-1}) ν 3334, 1601, 1576, 1558, 1475, 1438, 1401; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{22}H_{16}N_3OS_2$ 402.0735, found 402.0745.

(Z)-2-(2-Amino-5H-benzo[e]pyrazolo[1,5-c][1,3]thiazin-5-ylidene)-1-phenylethan-1-one (**3n**)*:* isolated yield 177 mg (88%); orange solid; mp >300 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.07 (1H, d, J = 7.60 Hz), 7.91 (2H, d, J = 7.30 Hz), 7.76 (1H, s), 7.70 (1H, d, J = 7.75 Hz), 7.61−754 (3H, m), 7.52−7.45 (2H, m), 6.71 (1H, s), 6.12 (2H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ 187.0, 159.3, 147.3, 139.4, 139.2, 132.4, 130.1, 129.2, 128.1, 127.5, 127.0, 126.2, 126.0, 120.9, 97.8, 95.2; IR (KBr, cm^{-1}) ν 3420, 3330, 1620, 1612, 1577, 1499, 1488, 1434, 1405; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{18}H_{14}N_3OS$ 320.0858, found 320.0852.

(Z)-2-(5H-Benzo[e]pyrazolo[1,5-c][1,3]thiazin-5-ylidene)-1-phenylethan-1-one (**3o**)*:* isolated yield 116 mg (76%); orange solid; mp 182−183 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.20−8.18 (3H, t, J = 6.43 Hz), 8.011 (2H, d, J = 7.25 Hz), 7.76 (1H, d, J = 7.40 Hz), 7.64 (1H, t, J = 6.92 Hz), 7.56 (2H, t, J = 7.45 Hz), 7.51 (3H, t, J = 9.10 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 187.7, 148.0, 144.3, 138.6, 133.0, 130.3, 129.3, 129.2, 127.9, 126.6, 126.2, 125.9, 121.3, 105.7, 101.1; IR (KBr, cm^{-1}) ν 1623, 1617, 1599, 1578, 1514,1469, 1399; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{18}H_{13}N_2OS$ 305.0749, found 305.0759.

(Z)-2-(8-Fluoro-2-(phenylamino)-5H-benzo[e]pyrazolo[1,5-c][1,3]thiazin-5-ylidene)-1-phenylethan-1-one (**3p**)*:* isolated yield 192 mg (93%); yellowish green solid; mp 269−270 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.54 (1H, s), 8.27 (1H, s), 7.98 (2H, d, J = 6.95 Hz), 7.92 (1H, s), 7.73 (1H, d, J = 8.30 Hz), 7.64−7.60 (5H, m), 7.36−7.35 (3H, m), 7.02 (1H, s), 6.94 (1H, t, J = 6.90 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 187.3, 162.5 (d, $^1J_{C-F}$ = 249.6 Hz), 155.0, 146.5, 141.9, 139.1, 138.2, 132.7, 129.5, 129.4, 127.7, 120.8, 117.6, 117.2, 116.0 (d, $^2J_{C-F}$ = 22.4 Hz), 112.7 (d, $^2J_{C-F}$ = 25.5 Hz), 98.8, 95.8; ^{19}F NMR (376 MHz, DMSO-d_6) δ −109.1; IR (KBr, cm^{-1}) ν 3329, 1599, 1599, 1523, 1497, 1478, 1424; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{24}H_{17}N_3OSF$ 414.1076, found 414.1089.

(Z)-1-(4-Chlorophenyl)-2-(8-fluoro-2-(phenylamino)-5H-benzo[e]pyrazolo[1,5-c][1,3]thiazin-5-ylidene)ethan-1-one (**3q**)*:* isolated yield 211 mg (94%); yellowish green solid; mp 297−298 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.53 (1H, s), 8.28 (1H, q, J = 8.40 Hz, J = 5.45 Hz), 7.98 (2H, d, J = 8.25 Hz), 7.88 (1H, s), 7.78 (1H, d, J = 7.60 Hz), 7.67 (2H, d, J = 5.25 Hz), 7.62 (2H, d, J = 7.95 Hz), 7.39−7.36 (3H, m), 7.03 (1H, s), 6.94 (1H, t, J = 7.25 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 186.1, 162.6 (d, $^1J_{C-F}$ = 248.8 Hz), 155.1, 147.1, 141.9, 138.3, 137.8, 137.6, 129.6, 129.3, 120.9, 117.6, 117.3, 116.2 (d, $^2J_{C-F}$ = 22.8 Hz), 112.7 (d, $^2J_{C-F}$ = 24.9 Hz), 98.5, 96.0; ^{19}F NMR (376 MHz, DMSO-d_6) δ −109.1; IR (KBr, cm^{-1}) ν 3303, 1602, 1552, 1516, 1495, 1480, 1426; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{24}H_{16}N_3OSClF$ 448.0687, found 448.0684.

(Z)-2-(8-Fluoro-2-(phenylamino)-5H-benzo[e]pyrazolo[1,5-c][1,3]thiazin-5-ylidene)-1-(4-methoxyphenyl)ethan-1-one (**3r**)*:* isolated yield 197 mg (89%); yellowish green solid; mp >300 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.51 (1H, s), 8.21 (1H, s), 7.94 (2H, d, J = 7.65 Hz), 7.88 (1H, s), 7.69 (1H, d, J = 8.10 Hz), 7.63 (2H, d, J = 7.05 Hz), 7.37−7.33 (3H, m), 7.11 (2H, d, J = 7.70 Hz), 6.98 (1H, s), 6.93 (1H, s), 3.86 (3H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ 186.1, 162.5 (d, $^1J_{C-F}$ = 248.6 Hz), 163.0, 154.8, 145.6, 142.0, 138.0, 131.7, 129.8, 129.5, 129.1, 120.7, 117.6, 117.1, 115.8 (d, $^2J_{C-F}$ = 24.9 Hz), 114.6, 112.5 (d, $^2J_{C-F}$ = 24.8 Hz), 98.8, 95.5, 56.0; ^{19}F NMR (376 MHz, DMSO-d_6) δ −109.3; IR (KBr, cm^{-1}) ν 3317, 1598, 1556, 1510, 1489, 1428; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{25}H_{19}N_3O_2SF$ 444.1182, found 444.1185.

(Z)-2-(8-Fluoro-2-((4-(trifluoromethyl)phenyl)amino)-5H-benzo[e]pyrazolo[1,5-c][1,3]thiazin-5-ylidene)-1-phenylethan-1-one (**3s**)*:* isolated yield 226 mg (94%); yellowish green solid; mp >300 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.02 (1H, s), 8.26 (1H, s), 8.00 (2H, d, J = 7.15 Hz), 7.94 (1H, s), 7.80−7.45 (3H, m), 7.72−7.71 (2H, m), 7.65−7.61 (3H, m), 7.37 (1H, s), 7.05 (1H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ 187.5, 162.6 (d, $^1J_{C-F}$ = 248.0 Hz), 154.2, 146.6, 145.3, 138.9, 138.4, 132.8, 129.9, 129.8, 129.4, 129.3, 129.2, 127.8, 126.7, 120.7, 117.5, 116.8, 116.0 (d, $^2J_{C-F}$ = 22.3 Hz), 112.7 (d, $^2J_{C-F}$ = 25.8 Hz), 99.2, 96.0; ^{19}F NMR (376 MHz, DMSO-d_6) δ −59.6 (3F, s), −109.0 (1F, s); IR (KBr, cm^{-1}) ν 3307, 1608, 1598, 1561, 1519, 1480, 1414, 1329, 1261, 1111, 1069, 998; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{25}H_{16}N_3OSF_4$ 482.0950, found 482.0962.

(Z)-2-(2-((4-Ethoxyphenyl)amino)-8-fluoro-5H-benzo[e]pyrazolo[1,5-c][1,3]thiazin-5-ylidene)-1-phenylethan-1-one (**3t**)*:* isolated yield 211 mg (92%); yellowish green solid; mp 271−272 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.28 (1H, s), 8.26 (1H, q, J = 8.76 Hz, J = 5.5 Hz), 7.97 (2H, d, J = 6.85 Hz), 7.90 (1H, s), 7.77 (1H, q, J = 9.10 Hz, J = 2.25 Hz), 7.64−7.59 (3H, m), 7.54 (2H, d, J = 8.90 Hz),

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7.39−7.35 (1H, m), 6.96 (1H, s), 6.95 (2H, s), 4.00 (2H, q, J = 6.93 Hz), 1.33 (3H, d, J = 6.95 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 187.2, 162.5 (d, $^1J_{C-F}$ = 248.4 Hz), 155.3, 153.2, 146.4, 139.0, 138.1, 135.2, 132.6, 129.7 (d, $^3J_{C-F}$ = 8.1 Hz), 129.3, 129.1 (d, $^3J_{C-F}$ = 8.1 Hz), 127.6, 118.7, 117.6, 116.0 (d, $^2J_{C-F}$ = 22.3 Hz), 115.4, 112.5 (d, $^2J_{C-F}$ = 25.6 Hz), 98.4, 95.5, 63.6, 15.2; ^{19}F NMR (376 MHz, DMSO-d_6) δ −109.2; IR (KBr, cm^{-1}) ν 3339, 1607, 1566, 1513, 1495, 1464, 1438, 1413; HRMS (ESI-TOF, [M + H]$^+$) calcd for $C_{26}H_{21}N_3O_2SF$ 458.1339, found 458.1342.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H, ^{19}F, and ^{13}C NMR spectra of all new compounds and X-ray data for compound **3k** in CIF format. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00288.

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Notes

The authors declare no competing financial interest.

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