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Three Component Divergent Reactions: Base-Controlled Amphiphilic Synthesis of Benzimidazole-Linked Thiazetidines and Fused Thiadiazines

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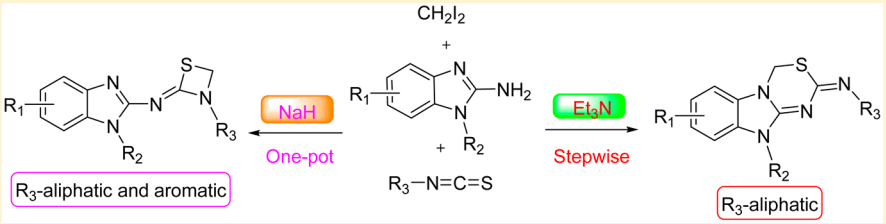
Supporting Information



ABSTRACT: A divergent reaction of 2-aminobenzimidazole with isothiocyanates and dihalomethanes has been developed for the selective synthesis of benzoimidazothiazetidine and benzoimidazothiadiazine. A single-pot reaction of 2-aminobenzimidazole in the presence of sodium hydride delivers benzoimidazothiazetidine, whereas triethylamine promotes the formation of benzoimidazothiadiazine via a sequential stepwise fashion. The reaction sequence involves the initial formation of thiourea followed by regioselective nucleophilic addition and intramolecular ring-closing with dihalo electrophiles. The observed regioselectivity of this reaction is governed by the nature of bases and the reaction sequence.

INTRODUCTION

Benzimidazoles are a class of important heterocycles that have attracted considerable attention because of their widespread applications in various domains.[1] In particular, polycyclic benzimidazole derivatives represent the range of eminent biologically and therapeutically active molecules, organic materials, and significant natural products.[2] A vast number of small molecules containing thiazetidine and thiadiazine skeletons have shown prominent biological and pharmaceutical applications as depicted in Figure 1. 1,3-Thiazetidin-2-ylidene directly linked with triazine (I) acts as a valuable herbicide. Similarly, 1,3-thiazetidine bearing oxadiazole core (II) exhibits promising antifungal and antibacterial activities.[3]

Likewise, six-membered 1,3,5-thiadiazines have been identified to possess significant applications in medicine and agriculture applications. 1,2,4-Triazole-fused thiadiazine (III) and its derivatives are recognized as antibacterial agents and insecticides.[4] Buprofezin(IV), a potent insecticide, was found as an active growth regulator on greenhouse whitefly and the brown planthopper.[5] Hence, we assumed that incorporating these scaffolds in a single molecule might be an effective strategy to discover novel entities with unusual biological properties. However, the synthesis of thiazetidines is very limited, and there is no report for the synthesis of benzoimidazothiazetidine or benzoimidazothiadiazine.[6] Diversity-oriented synthesis is a powerful tool for generating a collection of structurally complex molecules in a limited number of synthetic steps to meet the higher demand in chemical genetics and drug discovery.[7] In this context, multicomponent reactions (MCRs) constitute a significant role due to their high synthetic efficiency to construct a high level of molecular diversity in a step- and atom-economic manner.[8] However, most MCRs follow a single reaction pathway to furnish only one type of molecular scaffold. Consequently, development of novel MCRs for the selective formation of divergent products from the same participants is a worthy and challenging goal.[9,10]

Hence, we report herein the first systematic approach for the synthesis of benzimidazole-linked thiazetidine or fused thiadiazine through a three component reaction of 2-aminobenzimidazole, isothiocyanate, and diiodomethane. The present strategy explores the amphiphilic reactivity of 2-aminobenzimidazoles with isothiocyanates and dihalogen electrophiles (Scheme 1). Benzimidazole-linked thiazetidine **8** was obtained when the reaction was carried out in a single-pot operation using diiodomethane as a one carbon electrophile with sodium hydride. Both aromatic and aliphatic isothiocyanates were reacted successfully to deliver the product under these conditions. On the other hand, the reaction of isolated thiourea **7** with diiodomethane or dichloromethane in the presence of triethylamine yielded benzimidazole-fused thiadia-

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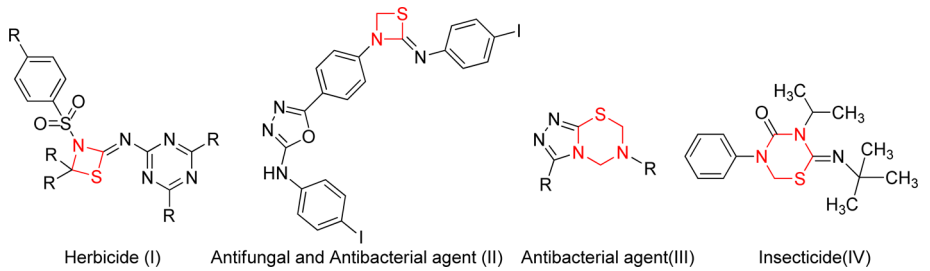
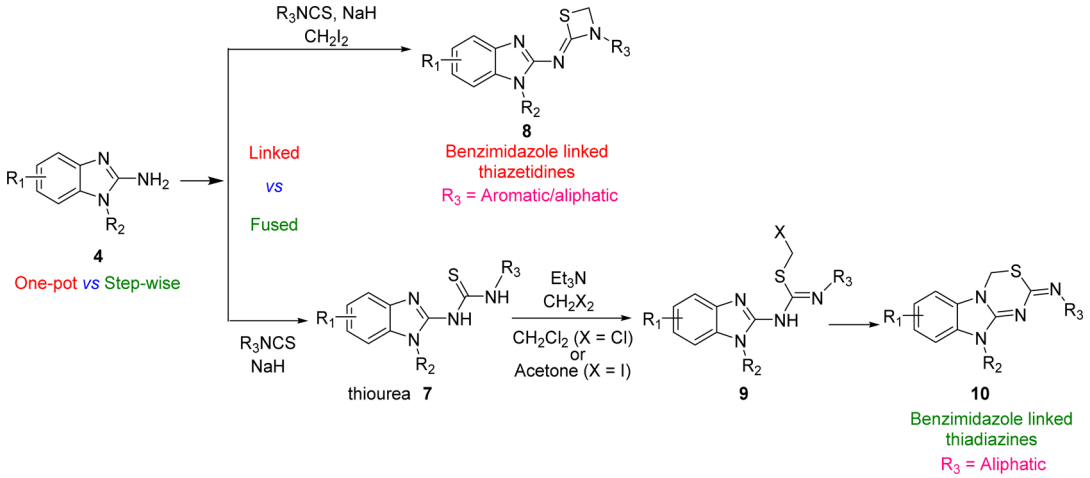
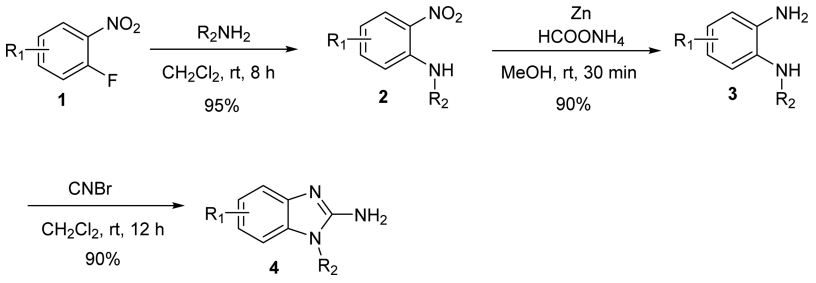


Figure 1. Biologically important thiazetidine and thiadiazine scaffolds.

Scheme 1. Regioselective Synthesis of Benzimidazole-Linked Thiazetidine 8 and Benzimidazole-Fused Thiadiazine 10



Scheme 2. Facile Synthesis of 2-Aminobenzimidazoles 4



zine **10**. Notably, only aliphatic isothiocyanates were feasible to furnish product **10** under this protocol. Under the strong basic conditions (NaH), the parent amine nitrogen is flanked exocyclic to the thiazetidine core and the other nitrogen is a part of thiazetidine. In contrast, the parent amine nitrogen is involved in a thiadiazine ring, and the other nitrogen stays exocyclic to thiadiazine in weak basic conditions (NEt_3). Hence, the product selectivity is dictated by the basicity of the parent amine and the reaction conditions (substrates and base) employed.

RESULTS AND DISCUSSION

Our work started with the facile synthesis of variously substituted 2-aminobenzimidazole **4** from 1-fluoro-2-nitrobenzene **1** by following the literature methods as represented in Scheme 2.[11]

Then, we carried out a three component reaction of **4a** with 1-isothiocyanato-3-methoxypropane **5a** and diiodomethane **6a** in the presence of Cs_2CO_3 in refluxing acetonitrile.

To our delight, desired product **8a** and thiourea **7a** were isolated in 35 and 20% yields, respectively. Encouraged by the results of the model reaction, the task of reaction optimization to improve the yield of **8a** was undertaken by varying the bases and solvents. The results for various optimization experiments are summarized in Table 1. Screening of various bases such as CS_2CO_3, K_2CO_3, Et_3N, and NaH under various solvents revealed that NaH in DMF gave the highest 69% yield (Table 1, entry 5). Next, we evaluated the suitability of different dihaloelectrophiles such as CH_2Br_2 and CH_2Cl_2 on the reactivity of **4a** in the presence of NaH. However, CH_2Br_2 was less reactive than that of CH_2I_2, and the product was obtained in a relatively lower yield (entries 7 and 8). It should be noted that, when employing dichloromethane as a reagent or solvent, the reaction did not generate any desired products (entries 9−11). With the optimized reaction conditions in hand (Table 1, entry 5), we first evaluated the scope for the formation of compound **8** by employing several substituted 2-aminobenzimidazoles and isothiocyanates. The reaction efficiency was not affected by the substituent groups on both

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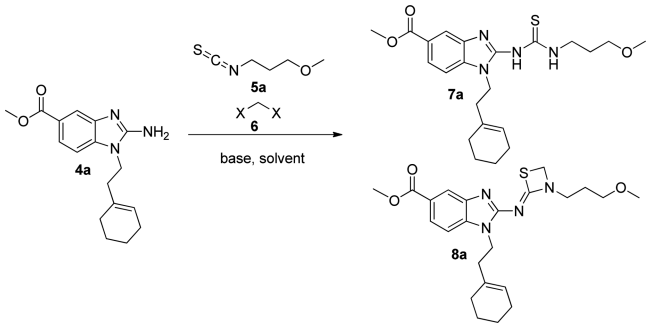
Table 1. Optimization of Reaction Conditions for the Synthesis of 8a[a]



entry	electrophile	base	solvent	temperature (°C)	time (h)	yield (%)[b] 7a	yield (%)[b] 8a
1	CH_2I_2	Cs_2CO_3	CH_3CN	reflux	12	20	35
2	CH_2I_2	K_2CO_3	CH_3CN	reflux	12	15	28
3	CH_2I_2	NEt_3	CH_3CN	reflux	12	15	0
4	CH_2I_2	NEt_3	acetone	rt	12	0	0
5	**CH_2I_2**	**NaH**	**CH_2I_2**	**rt**	**0.4**	**0**	**69**
6	CH_2I_2	NaH	THF	rt	1	12	36
7	CH_2Br_2	Cs_2CO_3	CH_3CN	reflux	12	22	28
8	CH_2Br_2	NaH	DMF	rt	0.4	0	52
9	CH_2Cl_2	NaH	CH_2Cl_2	rt	12	0	0
10[c]	CH_2Cl_2	NaH	DMF	90	0.4	50	0
11	CH_2Cl_2	NEt_3	CH_2Cl_2	reflux	12	10	0
12	CH_2I_2	KOtBu	CH_2I_2	rt	12	20	31

[a]Reaction conditions: **4a** (0.3 mmol), **5a** (0.45 mmol), CH_2I_2 (0.9 mmol), base (0.9 mmol), solvent (2 mL) at the specified temperature. [b]Isolated yield. [c]Under microwave irradiation.

benzimidazole and isothiocyanates. The electron-withdrawing and -donating groups were well tolerated under these reaction conditions and proceeded smoothly to give the corresponding derivatives in good yields. In particular, both aromatic as well as aliphatic isothiocyanates furnished the products smoothly with moderate yields (Scheme 3). Further, the substrate scope of this three component reaction was expanded by employing substituted 2-aminobenzoxazoles as a suitable substrate (Scheme 3, entries **8m** and **8n**).

In addition to the spectroscopic analysis, the structure of **8c** is assured by X-ray crystallographic analysis, and the ORTEP diagram is represented in Figure 2.[13] The benzimidazole and the four-membered thiazetidine were tethered through an exocyclic imine bridge in an angular orientation.

Further, we carried out this multicomponent one-pot reaction in a sequential stepwise pathway to understand its unique mechanism (Table 2). Hence, we performed a model reaction using isolated urea **7i** and CH_2Cl_2 in the presence of various bases as shown in Table 2. Employing inorganic bases such as K_2CO_3, Cs_2CO_3, or NaH did not give any product formation. Surprisingly, when we treated triethylamine as a base, no thiazetidines **8** was isolated, but an unprecedented benzimidazole-fused thiadiazine **10i** accompanied by unreactive **7i** were obtained (entry 5). The conversion was improved to 95% when diiodomethane was used as an electrophile (entry 9). Interestingly, treatment of NaH as a base delivered only thiazetidines **8** under this stepwise protocol (entry 7). Hence, the optimized conditions to selectively obtain product **10** are identified as the employment of triethylamine as a base and CH_2I_2 as an electrophile in acetone for 24 h at room temperature (entry 9).

Next we focused on the substrate scope for the formation of benzimidazole-fused thiadiazines **10** (Scheme 4). All of the aliphatic isothiocyanates smoothly delivered product **10** with moderate to high yields. On the contrary, aromatic isothiocyanates (entries **8o** and **8p**) were converted to thiazetidines **8** with lower yields under these conditions. Notably, no product formation was observed when 4-nitrophenyl isothiocyanate was employed (entry **8j**). Hence, in this stepwise protocol, using triethylamine as a base, the product outcome is dictated by the electronic nature of isothiocyanates; aliphatic isothiocyanates delivered thiadiazines **10** and aromatic isothiocyanates furnished thiazetidines **8**.

In contrast, sodium hydride selectively promotes the formation of thiazetidines **8** in both one-pot and stepwise protocols irrespective of the electronic nature of isothiocyanates (both aromatic and aliphatic). On the basis of the experimental observation, a plausible mechanism for the formation of benzoimidazothiazetidine and benzoimidazothiadiazine is outlined in Scheme 5.[6]

The first step is the formation of thiourea **7** through the reaction of 2-aminobenzimidazole **4** and isothiocyanate **5** in a one-pot or stepwise fashion. This preformed thiourea **7** acts as a common intermediate for the S-alkylation with diiodomethane under the basic conditions to obtain compound **9**, which shows base-controlled divergent cyclization. In the presence of NaH, the subsequent intramolecular ring closure of **9** is aided by the selective deprotonation of parent amine nitrogen to furnish four membered thiazetidines **8**. On the other hand, employing triethylamine in acetone promotes the formation of six-membered thiadiazines **10**. Hence, the main difference in reactivity is probably caused by the ability of a base to abstract slightly acidic hydrogen in **9** as represented in

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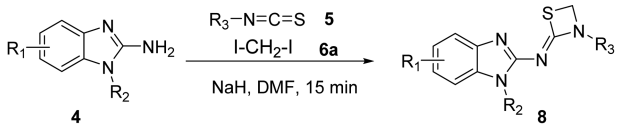
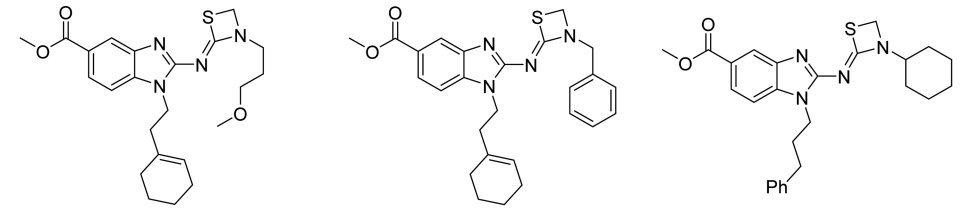
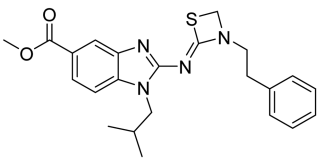
Scheme 3. One-Pot Synthesis of Benzimidazothiazetidine 8

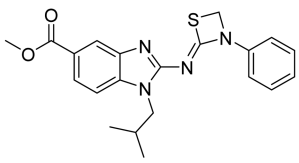


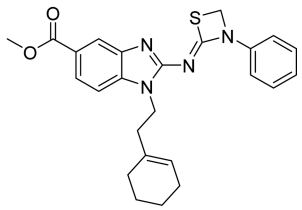

8a, 69%

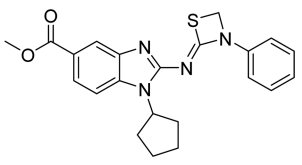
8b, 67%

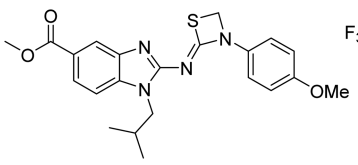
8c, 65%

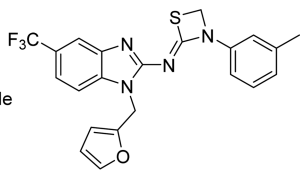

8d, 66%

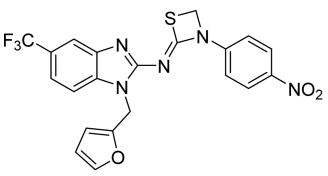

8e, 59%

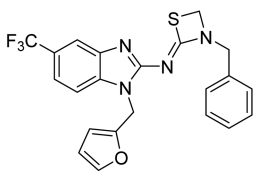

8f, 65%

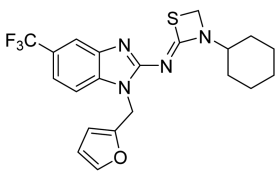

8g, 63%


8h, 61%


8i, 65%


8j, 67%


8k, 67%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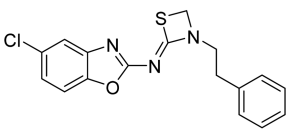
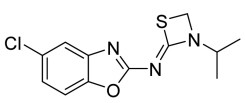
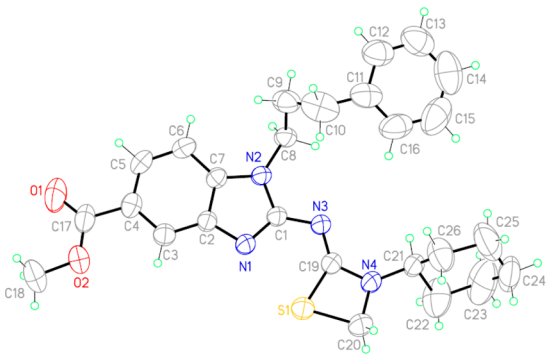

8m, 64%


8n, 62%



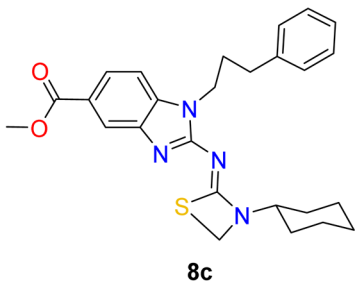

8c

Figure 2. ORTEP diagram of **8c**.

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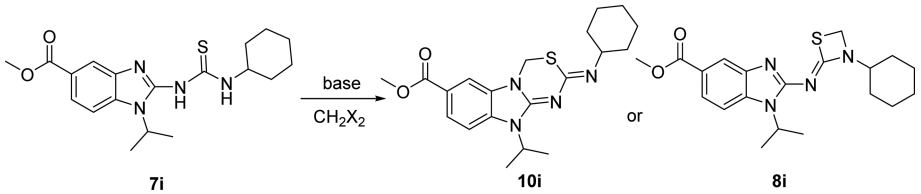
Table 2. Optimization of Reaction Conditions for the Synthesis of 10i[a]



7i 10i 8i

entry	electrophile[a]	base (equiv)	temperature (°C)	time (h)	yield (%)[b] 10i	yield (%)[b] 8i
1	CH_2Cl_2	K_2CO_3(5)	40	24	0	0
2	CH_2Cl_2	Cs_2CO_3(5)	40	24	0	0
3	CH_2Cl_2	NaH(5)	rt	8	0	0
4	CH_2Cl_2	NEt_3(5)	rt	24	12	0
5	CH_2Cl_2	NEt_3(10)	rt	8	49	0
6	CH_2I_2	K_2CO_3(5)	rt	24	0	0
7	**CH_2I_2**	**NaH(5)**	**rt**	**0.5**	**0**	**92**
8	CH_2I_2	NEt_3(3)	rt	24	67	0
9	**CH_2I_2**	**NEt_3(7)**	**rt**	**24**	**95**	**0**
10	CH_2I_2	Pyridine	rt	48	0	0
11	CH_2I_2	DIPEA(10)	rt	48	0	0

[a]CH_2Cl_2 is used as solvent and reagent. Acetone is used as a solvent when CH_2I_2 (1.5 equiv) is employed as an electrophile. [b]Isolated yields.

Scheme 5. Although the strong base NaH could form a more reactive and nucleophilic anion, much weaker triethylamine could assist only as a general base catalyst. In addition, a possible driving force for the observed selectivity could be the resonance stabilization of the resulting anion with the aromatic group on isothiocyanates. All of the prepared compounds of **8** and **10** were characterized by proton NMR (the characteristic $-CH_2$ proton resonates at 4.6 ppm for compound **8** and compound **10** shows at 5.9 ppm, and C-13 carbon NMR (the characteristic $-CH_2$ carbon resonates at 46.5 ppm for compound **8** and compound **10** shows at 52.8 ppm).

In addition, the structure of **10f** was unambiguously confirmed by X-ray crystallographic analysis as shown in Figure 3.[12] The thiadiazine skeleton is twisted and fused with the benzimidazole ring, which brought the characteristic methylene protons in close proximity to account for the deshielding effect consistently observed in all compounds **10**.[13]

CONCLUSIONS

In conclusion, we have developed a three component reaction of 2-aminobenzimidazole, isothiocyanate, and diiodomethane for the regioselective synthesis of benzoimidazothiazetidine and benzoimidazothiadiazine. In this selective protocol, the one-pot conditions resulted in the formation benzoimidazothiazetidine, whereas a stepwise sequential reaction furnished benzoimidazothiadiazine. The salient features of this strategy include milder reaction conditions, inexpensive reagents, high-atom economy, and efficacy of forming consecutive C−S and C−N bonds and two different unique heterocycles in a single synthetic operation. Further studies on the detailed reaction mechanism and their utility on other heterocycles for biological applications are underway.

EXPERIMENTAL SECTION

General Information. All of the solvents were distilled before use. All reactions were performed under an inert atmosphere with unpurified reagents and dry solvents. Analytical thin-layer chromatography (TLC) was performed using 0.25 mm silica gel-coated plates. Flash chromatography was performed using the indicated solvent and silica gel 60 (230−400 mesh). ^{1}H NMR, ^{13}C NMR, and NOE spectra were recorded at ambient temperature using 300, 400, and 600 MHz spectrometers. Chemical shifts are reported in parts per million (ppm) on the scale from an internal standard. IR spectra were recorded on an FT-IR instrument and are reported in wavenumbers (inverse centimeters). High-resolution mass spectra were recorded in ESI mode using a magnetic sector mass analyzer and TOF mass spectrometer.

*Experimental Procedure for the Synthesis of Methyl 1-(2-(Cyclohex-1-en-1-yl)ethyl)-2-((3-(3-methoxypropyl)-1,3-thiazetidin-2-ylidene)amino)-1H-benzo[d]imidazole-5-carboxylate (**8a**).* To a solution of methyl 2-amino-1-(2-(cyclohex-1-en-1-yl)ethyl)-1*H*-benzo[*d*]imidazole-5-carboxylate **4a** (0.1 g, 0.334 mmol) and 1-isothiocyanato-3-methoxypropane **5a** (0.065 g, 0.501 mmol) in DMF (8 mL) were added NaH (0.024 g, 1.002 mmol) followed by the addition of diiodomethane (0.268 g, 1.002 mmol). The resulting reaction mixture was stirred at room temperature for 15 min. After completion of the reaction, the reaction mixture was quenched with cold water (10 mL), extracted with EtOAc (2 × 20 mL), and washed with brine solution (30 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (10% EtOAc in hexane) to afford methyl 1-(2-(cyclohex-1-en-1-yl)ethyl)-2-((3-(3-methoxypropyl)-1,3-thiazetidin-2-ylidene)amino)-1*H*-benzo[*d*]imidazole-5-carboxylate **8a** as an off-white solid (0.102 g, 69%).

*Experimental Procedure for the Synthesis of Methyl 10-Isobutyl-2-(isopropylimino)-4,10-dihydro-2H-benzo[4,5]imidazo[1,2-c][1,3,5]thiadiazine-7-carboxylate (**10a**).* To a solution of methyl 2-amino-1-isobutyl-1*H*-benzo[*d*]imidazole-5-carboxylate **4a** (0.2 g, 0.808 mmol) and 2-isothiocyanatopropane (0.122 g, 1.212 mmol) in DMF (8 mL) was added NaH (0.058 g, 2.424 mmol), and the resulting reaction mixture was stirred at room temperature for 15 min. After completion of the reaction, the reaction mixture was quenched with cold water (10 mL), extracted with EtOAc (2 × 20 mL), and washed with brine solution (30 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (5% EtOAc in hexane) to afford methyl 1-isobutyl-2-(3-isopropylthioureido)-1*H*-benzo[*d*]imidazole-5-carboxylate **7a** (0.259 g, 92%) as a white solid. In the next step, to a solution of methyl 1-isobutyl-2-(3-isopropylthioureido)-1*H*-benzo[*d*]imidazole-5-carboxylate **7a** (0.1 g, 0.287 mmol) in acetone (10 mL) were added triethylamine (0.203 g, 2.011 mmol) and diiodomethane (0.115 g, 0.430 mmol). The resulting reaction mixture was allowed to stir at room temperature for 30 min.

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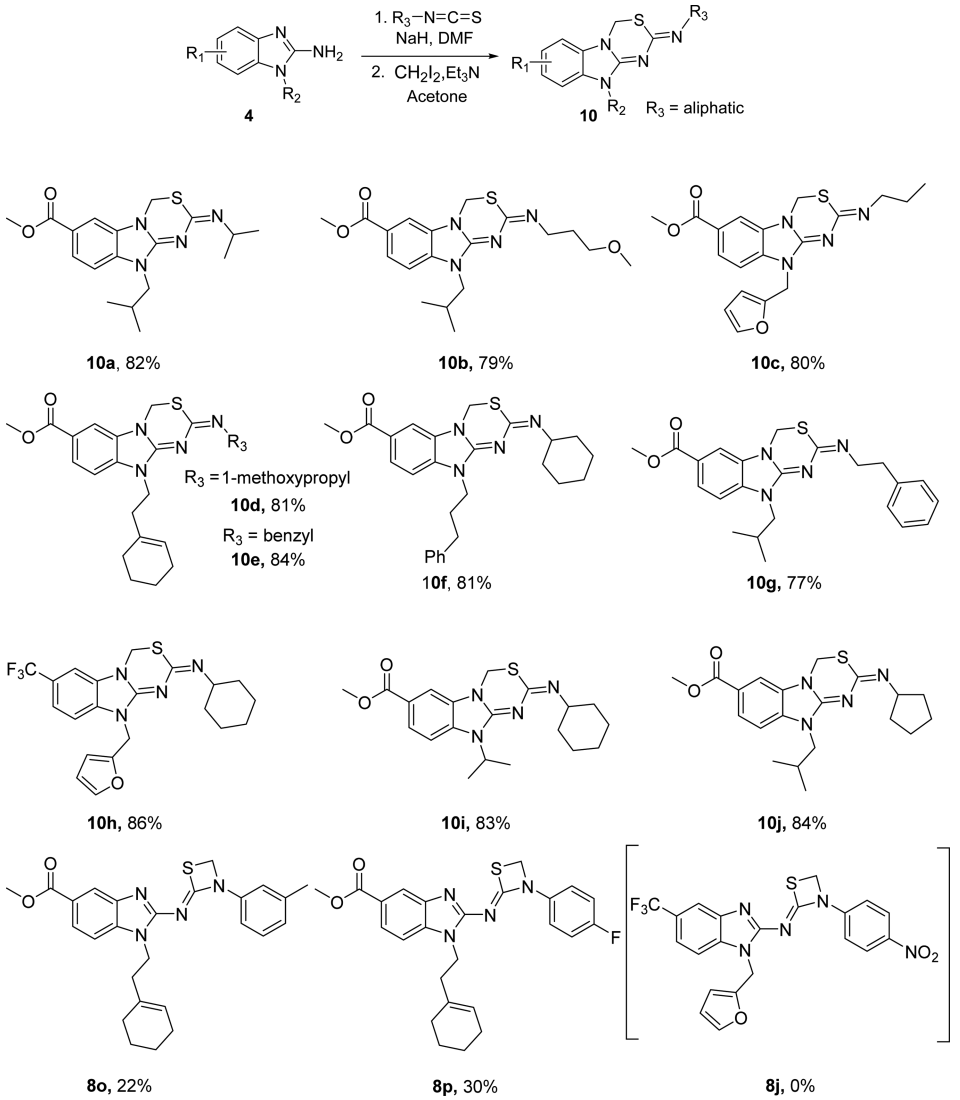
Scheme 4. Synthesis of Benzimidazothiadiazine 10 via a Stepwise Protocol



After completion of the reaction, the solvent was evaporated, diluted with ethyl acetate (15 mL), and washed with water (2 × 20 mL) followed by brine solution (10 mL). The organic extract was dried over $MgSO_4$, filtered, and concentrated under reduced pressure The crude product was purified by column chromatography (10% EtOAc in hexane) to afford methyl 10-isobutyl-2-(isopropylimino)-4,10-dihydro-2H-benzo[4,5]imidazo[1,2-*c*][1,3,5]thiadiazine-7-carboxylate **10a** as a white solid (0.084 g, 82%).

Methyl 1-(2-(Cyclohex-1-en-1-yl)ethyl)-2-((3-(3-methoxypropyl)-1,3-thiazetidin-2-ylidene)amino)-1H-benzo[d]imidazole-5-carboxylate ***8a***. White solid; yield = 0.12 g, 69%; mp 65−67 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 1.6 Hz, 1H), 7.82 (dd, J = 8.4, 1.6 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 5.23 (t, J = 6.9 Hz, 1H), 4.55 (s, 2H), 4.13 (t, J = 6.9, Hz, 2H), 3.88 (s, 3H), 3.50 (t, J = 6.9 Hz, 2H), 3.45 (t, J = 6.9 Hz, 2H), 3.32 (s, 3H), 2.32 (t, J = 7.3 Hz, 2H), 1.97 (t, J = 7.3 Hz, 2H), 1.95−1.89 (m, 2H), 1.89−1.77 (m, 2H), 1.61−1.51 (m, 2H), 1.50−1.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 22.8, 25.1, 27.7, 28.2, 37.3, 41.14, 43.9, 50.2, 51.7, 58.7, 69.6, 107.8, 119.6, 122.2, 122.9, 123.9, 133.8, 37.16, 141.6, 156.7, 163.7, 168.0; FT-IR (neat) 2873, 1709, 1503, 1438, 1113, 767, 749 cm^{-1}; MS (ESI) m/z 443 (MH^+); HRMS (ESI, m/z) calcd $C_{23}H_{30}N_4O_3S$ $[M + H]^+$ 443.2111, found 443.2124.

Methyl 2-((3-Benzyl-1,3-thiazetidin-2-ylidene)amino)-1-(2-(cyclohex-1-en-1-yl)ethyl)-1H-benzo[d]imidazole-5-carboxylate ***8b***. Pale yellow solid; yield = 0.102 g, 67%; mp 122−124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.44−7.26 (m, 5H), 7.18 (d, J = 8.4 Hz, 1H), 5.24 (t, J = 6.9 Hz, 1H), 4.60 (s, 2H), 4.45 (s, 2H), 4.17 (t, J = 7.4 Hz, 2H), 3.89 (s, 3H), 2.35 (t, J = 7.4 Hz, 2H), 1.97 (d, J = 6.8 Hz, 2H), 1.83−1.72 (m, 2H), 1.62−1.50 (m, 2H), 1.46−1.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 22.8, 25.1, 28.2, 37.4, 41.2, 49.4, 50.3, 51.7, 107.9, 119.6, 122.3, 123.0, 124.0, 128.1, 128.7, 128.9, 133.8, 134.8, 137.1, 141.6, 156.6, 164.0, 168.0; FT-IR (neat) 2993, 1709, 1503, 1438, 1296, 816, 787 cm^{-1}; MS (ESI) m/z 461 (MH^+); HRMS (ESI, m/z) calcd $C_{26}H_{28}N_4O_2S$ $[M + H]^+$ 461.2006, found 461.2013.

Methyl 2-((3-Cyclohexyl-1,3-thiazetidin-2-ylidene)amino)-1-(3-phenylpropyl)-1H-benzo[d]imidazole-5-carboxylate ***8c***. White solid; yield = 0.097 g, 65%; mp 165−167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.51−6.82 (m, 6H), 4.52 (s, 2H), 4.13 (t, J = 7.1 Hz, 2H), 3.91 (s, 3H), 2.66 (m, 1H), 2.13 (t, J = 7.6 Hz, 2H), 2.00 (d, J = 11.1 Hz, 2H), 1.83 (d, J = 12.2 Hz, 2H), 1.68 (d, J = 12.7 Hz, 2H), 1.17 (t, J = 12.3 Hz, 2H); ^{13}C NMR (100 MHz, CDCl3) δ 24.9, 24.9, 25.3, 29.9, 29.94, 30.5, 33.0, 41.8, 41.8, 46.8, 51.8, 55.3, 107.7, 119.5, 122.2, 123.0, 126.0, 126.0, 128.2, 128.3, 128.3, 128.4, 137.2, 141.1, 141.7, 157.1, 162.9, 168.1; FT-IR (neat) 2933, 2855, 1711, 1627, 1505, 1296, 1218, 1003, 819, 768 cm^{-1}; MS (ESI) m/z 463 (MH^+); HRMS (ESI, m/z) calcd $C_{26}H_{31}N_4O_2S$ $[M + H]^+$ 463.2162, found 463.2165.

Methyl 1-Isobutyl-2-((3-phenethyl-1,3-thiazetidin-2-ylidene)-amino)-1H-benzo[d]imidazole-5-carboxylate ***8d***. Off-white solid; yield = 0.112 g, 66%; mp 149−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 1.6 Hz, 1H), 7.83 (dd, J = 8.4, 1.6 Hz, 1H), 7.31

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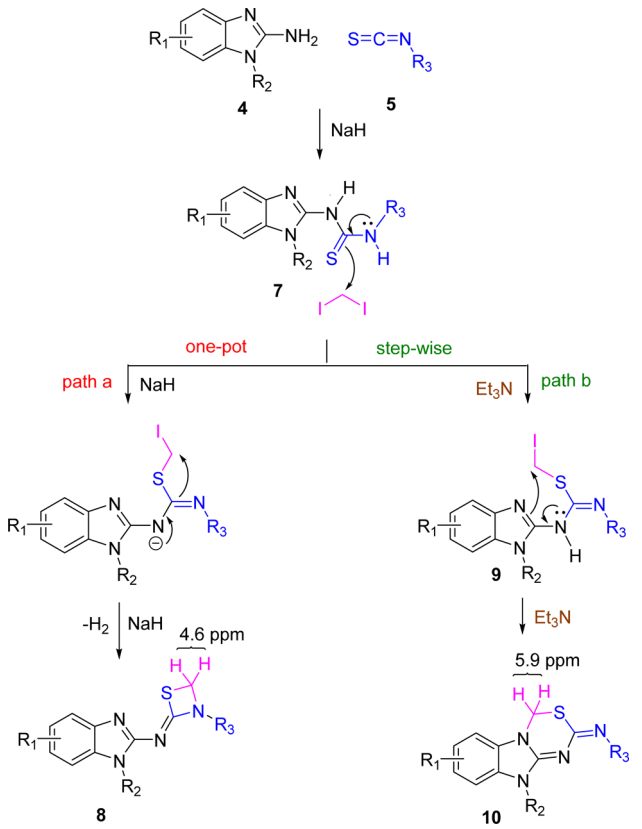
Scheme 5. Plausible Mechanism for the Formation of 8 and 10



(d, J = 8.4 Hz, 1H), 7.27−7.19 (m, 4H), 7.16 (d, J = 8.4 Hz, 1H), 4.31 (s, 2H), 3.90 (d, J = 7.0 Hz, 2H), 3.88 (s, 3H), 3.64 (t, J = 7.0 Hz, 2H), 2.98 (t, J = 7.0 Hz, 2H), 2.22 (m, 1H), 0.92 (d, J = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 28.8, 33.9, 48.2, 49.7, 50.6, 51.7, 108.0, 119.6, 122.2, 22.9, 126.8, 128.5, 128.8, 137.6, 138.2, 141.5, 157.0, 163.4, 168.0; FT-IR (neat) 2955, 2870, 1710, 1588, 1439, 1297, 1109, 768, 750 cm^{-1}; MS (ESI) m/z 423 (MH^+); HRMS (ESI, m/z) calcd $C_{23}H_{26}N_4O_2S$ $[M + H]^+$ 423.1849, found 423.1849.

Methyl 1-Isobutyl-2-((3-phenyl-1,3-thiazetidin-2-ylidene)amino)-1H-benzo[d]imidazole-5-carboxylate ***8e.*** Brown solid; yield = 0.094 g, 59%; 167−170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.38 (t, J = 7.8 Hz, 2H), 7.29 (m, 1H), 7.11 (t, J = 7.5 Hz, 2H), 4.93 (s, 2H), 3.99 (d, J = 7.3 Hz, 2H), 3.90 (s, 3H), 2.29 (m, 1H), 0.97 (d, J = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 29.0, 29.6, 48.5, 50.1, 51.8, 108.3, 116.0, 120.1, 122.7, 123.3, 123.7, 129.2, 137.5, 139.9, 141.3, 156.3, 159.6, 167.9; FT-IR (neat) 2955, 1710, 1625, 1500, 1324, 1245, 894, 768, 750 cm^{-1}; MS (ESI) m/z 395 (MH^+); HRMS (ESI, m/z) calcd $C_{21}H_{22}N_4O_2S$ $[M + H]^+$ 395.1536, found 395.1538.

Methyl 1-(2-(Cyclohex-1-en-1-yl)ethyl)-2-((3-phenyl-1,3-thiazetidin-2-ylidene)amino)-1H-benzo[d]imidazole-5-carboxylate ***8f.*** White solid; yield = 0.097 g, 65%; mp 200−201 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 1.6 Hz, 1H), 7.88 (dd, J = 8.4, 1.6 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.38 (t, J = 7.8 Hz, 2H), 7.29 (m, 1H), 7.11 (t, J = 7.8 Hz, 2H), 5.32 (t, J = 7.4 Hz, 1H), 4.95 (s, 2H), 4.25 (t, J = 7.4 Hz, 2H), 3.91 (s, 3H), 2.42 (t, J = 7.4 Hz, 2H), 2.01 (t, J = 7.4 Hz, 2H), 1.93−1.78 (m, 2H), 1.51−1.36 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 22.8, 25.2, 28.3, 37.6, 41.8, 48.4, 51.8, 108.1, 116.0, 120.1, 122.7, 123.3, 123.7, 124.3, 129.1, 133.8, 137.0, 139.8, 141.4, 156.0, 167.9; FT-IR (neat) 2922, 2851, 1713, 1623, 1494, 1296, 1089, 766, 689 cm^{-1}; MS (ESI) m/z 447 (MH^+); HRMS (ESI, m/z) calcd $C_{25}H_{26}N_4O_2S$ $[M + H]^+$ 447.1849, found 447.1845.

Methyl 1-Cyclopentyl-2-((3-phenyl-1,3-thiazetidin-2-ylidene)-amino)-1H-benzo[d]imidazole-5-carboxylate ***8g.*** Off-white solid; yield = 63%; mp 116−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 1.6 Hz, 1H), 7.85 (dd, J = 8.4, 1.6 Hz, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.43−7.32 (m, 2H), 7.30−7.10 (m, 2H), 5.11 (p, J = 8.9 Hz, 1H), 4.87 (s, 2H), 3.90 (s, 3H), 2.27−2.20 (m, 2H), 2.19−1.94 (m, 4H), 1.81−1.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 30.1, 48.6, 51.8, 55.2, 109.3, 116.1, 120.2, 122.4, 123.1, 123.7, 129.2, 136.1, 139.8, 141.6, 156.1, 159.8, 167.9; FT-IR (neat) 2997, 2871, 1711, 1623, 1580, 1492, 1362, 1300, 767, 688 cm^{-1}; MS (ESI) m/z 407 (MH^+); HRMS (ESI, m/z) calcd $C_{22}H_{22}N_4O_2S$ $[M + H]^+$ 407.1536, found 407.1538.

Methyl 1-Isobutyl-2-((3-(4-methoxyphenyl)-1,3-thiazetidin-2-ylidene)amino)-1H-benzo[d]imidazole-5-carboxylate ***8h.*** Off-white solid; yield = 0.105 g, 61%; mp 141−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 1.6 Hz, 1H), 7.86 (dd, J = 8.4, 1.6 Hz, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 8.9 Hz, 2H), 4.86 (s, 2H), 3.94 (d, J = 7.3 Hz, 2H), 3.93 (s, 3H), 3.89 (s, 3H), 2.27 (m, 1H), 0.95 (d, J = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 29.0, 48.6, 50.0, 51.8, 55.5, 108.2, 114.3, 117.4, 119.9, 122.6, 123.2, 133.6, 137.5, 141.4, 155.9, 156.5, 159.1, 167.9; FT-IR (neat) 2955, 2870, 1710, 1625, 1500, 1324, 1245, 894, 750, 768 cm^{-1}; MS (ESI) m/z 425 (MH^+); HRMS (ESI, m/z) calcd $C_{22}H_{24}N_4O_3S$ $[M + H]^+$ 425.1645, found 425.1647.

N-(1-(Furan-2-ylmethyl)-5-(trifluoromethyl)-1H-benzo[d]-imidazol-2-yl)-3-(m-tolyl)-1,3-thiazetidin-2-imine ***8i.*** White solid; yield = 65%; mp 187−190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.43−7.30 (m, 6H), 6.95 (d, J = 7.5 Hz, 1H), 6.31−6.27 (m, 2H), 5.36 (s, 2H), 4.92 (s, 2H), 2.39 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 39.2, 48.5, 108.37, 109.0, 110.5, 113.4, 116.7, 115.4 (q, $^3J_{C-F}$ = 4.5 Hz), 118.0 (q, $^3J_{C-F}$ = 3.02 Hz), 124.7, 129.1, 135.5, 139.2, 139.7, 141.46, 142.5, 149.6, 155.9, 124.1 (q, $^2J_{C-F}$ = 31.7 Hz), 160.2; FT-IR (neat) 2916, 2849, 1625, 1446, 1324, 735, 685, 661 cm^{-1}; MS (ESI) m/z 443 (MH^+); HRMS (ESI, m/z) calcd $C_{22}H_{17}F_3N_4OS$ $[M + H]^+$ 443.1148, found 443.1152.

N-(1-(Furan-2-ylmethyl)-N-(3-(4-nitrophenyl)-1,3-thiazetidin-2-ylidene)-5-(trifluoromethyl)-1H-benzo[d]imidazol-2-amine ***8j.*** Yellow solid; yield = 67%; mp 199−202 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 8.7 Hz, 2H), 7.90 (s, 1H), 7.73 (d, J = 8.7 Hz, 2H), 7.42−7.24 (m, 3H), 6.27 (dd, J = 2.1, 1.3, 1H), 6.19 (d, J = 3.2, 1H), 5.39 (s, 2H), 5.03 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 39.4, 49.2, 108.5, 109.3, 110.5, 115.8, 115.9, 124.3, 118.6 (q, $^3J_{C-F}$ = 3.01 Hz), 125.4, 126.2, 135.4, 141.1, 142.8, 143.0, 144.2, 149.1, 154.9, 160.6; FT-IR (neat) 2917, 2850, 1629, 1583, 1330, 1103, 812, 747,

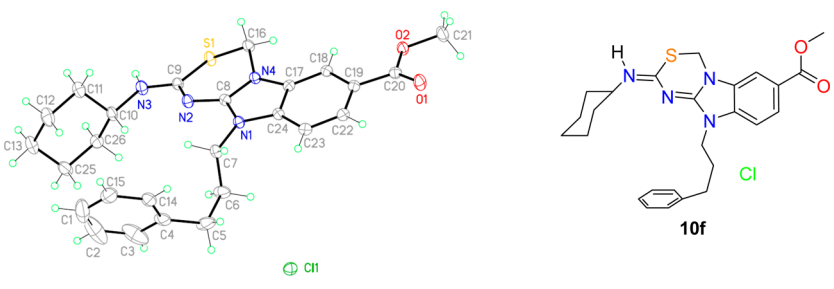


Figure 3. ORTEP diagram of compound **10f**.

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664 cm^{-1}; MS (ESI) m/z 474 (MH^+); HRMS (ESI, m/z) calcd $C_{21}H_{14}F_3N_5O_3S$ $[M + H]^+$ 474.0845, found 474.0842.

N-(3-Benzyl-1,3-thiazetidin-2-ylidene)-1-(furan-2-ylmethyl)-5-(trifluoromethyl)-1H-benzo[d]imidazol-2-amine ***8k***. White solid; yield = 67%; mp 123−125 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.39−7.30 (m, 8H), 6.27 (dd, J = 3.2, 1.8 Hz, 1H), 6.19 (d, J = 3.2 Hz, 1H), 5.31 (s, 2H), 4.64 (s, 2H), 4.47 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 39.0, 49.5, 50.4, 108.2, 108.8, 110.4, 115.0 (q, $^3J_{C-F}$ = 4.5 Hz), 117.6 (q, $^3J_{C-F}$ = 3.01 Hz), 128.2, 128.8, 129.0, 134.7, 135.5, 141.6, 142.4, 149.7, 156.5, 123.7 (q, $^2J_{C-F}$ = 31.7 Hz), 164.6; FT-IR (neat) 2918, 2850, 1629, 1583, 1371, 796, 701 cm^{-1}; MS (ESI) m/z 443 (MH^+); HRMS (ESI, m/z) calcd $C_{22}H_{17}F_3N_4OS$ $[M + H]^+$ 443.1148, found 443.1149.

N-(3-Cyclohexyl-1,3-thiazetidin-2-ylidene)-1-(furan-2-ylmethyl)-5-(trifluoromethyl)-1H-benzo[d]imidazol-2-amine ***8l***. White solid; yield = 69%; mp 161−163 °C; ^1H NMR (400 MHz, CDCl3) δ 7.79 (s, 1H), 7.29 (m, 3H), 6.27 (dd, J = 3.2, 1.8 Hz, 1H), 6.20 (d, J = 3.2 Hz, 1H), 5.27 (s, 2H), 4.52 (s, 2H), 3.99−3.58 (m, 1H), 2.06−1.98 (m, 2H), 1.88−1.79 (m, 2H), 1.74−1.62 (m, 2H), 1.51−1.16 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 24.9, 25.2, 29.9, 39.0, 46.9, 55.4, 108.1, 108.6, 110.4, 114.8 (q, $^3J_{C-F}$ = 4.1 Hz), 117.3 (q, $^3J_{C-F}$ = 3.8 Hz), 135.5, 141.7, 142.3, 149.9, 156.8, 123.5 (q, $^2J_{C-F}$ = 32.0), 163.3, 125.1 (q, $^1J_{C-F}$ = 271.8); FT-IR (neat) 2937, 2856, 1624, 1509, 1252, 1109, 1049, 679, 660 cm^{-1}; MS (ESI) m/z 435 (MH^+); HRMS (ESI, m/z) calcd $C_{21}H_{21}F_3N_4OS$ $[M + H]^+$ 435.1465, found 435.1461.

5-Chloro-N-(3-phenethyl-1,3-thiazetidin-2-ylidene)benzo[d]-oxazol-2-amine ***8m***. Off-white solid; yield = 0.13 g, 64%; mp 170−173 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 2.1 Hz, 1H), 7.31 (t, J = 8.5 Hz, 1H), 7.28−7.18 (m, 5H), 7.09 (dd, J = 8.5, 2.1 Hz, 1H), 4.26 (s, 2H), 3.71 (t, J = 7.0 Hz, 2H), 2.99 (t, J = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.9, 48.3, 50.2, 110.1, 117.7, 122.4, 126.9, 128.5, 128.9, 129.0, 137.8, 143.4, 146.9, 165.2, 166.1; FT-IR (neat) 2917, 2849, 1629, 1529, 1445, 1400 cm^{-1}; MS (ESI) m/z 344 (MH^+); HRMS (ESI, m/z) calcd $C_{17}H_{14}ClN_3OS$ $[M + H]^+$ 344.0619, found 344.0612.

5-Chloro-N-(3-isopropyl-1,3-thiazetidin-2-ylidene)benzo[d]-oxazol-2-amine ***8n***. Off-white solid; yield = 0.103 g, 62%; mp 140−141 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 2.2 Hz, 1H), 7.21 (d, J = 8.5 Hz, 1H), 7.06 (dd, J = 8.5, 2.2 Hz, 1H), 4.49 (s, 2H), 4.19 (sept, J = 6.7 Hz, 1H), 1.23 (d, J = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6, 19.6, 45.6, 48.0, 110.0, 117.6, 122.2, 128.9, 143.4, 146.8, 165.4; FT-IR (neat) 2981, 2906, 1604, 1448, 1287, 997, 801 cm^{-1}; MS (ESI) m/z 282 (MH^+); HRMS (ESI, m/z) calcd $C_{12}H_{12}ClN_3OS$ $[M + H]^+$ 282.0462, found 282.0466.

Methyl 1-(2-(Cyclohex-1-en-1-yl)ethyl)-2-((3-(m-tolyl)-1,3-thiazetidin-2-ylidene)amino)-1H-benzo[d]imidazole-5-carboxylate ***8o***. Off-white solid; yield = 0.034 g, 22%; mp 170−171 °C; ^1H NMR (400 MHz, CDCl3) δ 8.32 (d, J = 1.5 Hz, 1H), 7.88 (dt, J = 8.4, 1.1 Hz, 1H), 7.45 (s, 1H), 7.37 (dd, J = 8.1, 2.1 Hz, 1H), 7.29−7.19 (m, 4H), 6.94 (d, J = 7.5 Hz, 1H), 5.33 (s, 1H), 4.92 (s, 2H), 4.25 (dd, J = 8.2, 6.7 Hz, 2H), 3.91 (s, 3H), 2.42 (t, J = 7.6 Hz, 2H), 2.01 (s,3H), 1.87 (d, J = 5.0 Hz, 2H), 1.57−1.50 (m, 2H), 1.47 (ddt, J = 7.8, 5.7, 2.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 159.6, 156.1, 141.4, 139.8, 139.2, 137.1, 133.8, 128.9, 124.5, 124.1, 123.2, 122.7, 120.1, 116.7, 113.1, 108.1, 51.8, 48.4, 41.7, 37.5, 28.3, 25.1, 22.7, 22.1, 21.6; FT-IR (neat) 2926, 1712, 1629, 1504, 1297, 749 cm^{-1}; MS (ESI) m/z 461 (MH^+); HRMS (ESI, m/z) calcd $C_{26}H_{29}N_4O_2S$ $[M + H]^+$ 461.2006, found 461.2005.

Methyl 1-(2-(Cyclohex-1-en-1-yl)ethyl)-2-((3-(4-fluorophenyl)-1,3-thiazetidin-2-ylidene)amino)-1H-benzo[d]imidazole-5-carboxylate ***8p***. White solid; yield = 0.046 g, 30%; mp 159−162 °C; ^1H NMR (400 MHz, CDCl3) δ 8.32 (d, J = 1.6 Hz, 1H), 7.89 (dd, J = 8.4, 1.6 Hz, 1H), 7.58 (dd, J = 9.1, 4.5 Hz, 2H), 7.24 (s, 2H), 7.12−7.02 (m, 2H), 5.30 (d, J = 3.8 Hz, 1H), 4.93 (s, 2H), 4.25 (t, J = 7.4 Hz, 2H), 3.90 (s, 3H), 2.40 (t, J = 7.4 Hz, 2H), 1.99 (d, J = 7.2 Hz, 2H), 1.91−1.78 (m, 2H), 1.51−1.42 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 22.8, 25.2, 28.3, 37.5, 41.7, 48.6, 51.8, 108.17, 109.9, 115.8, 116.0, 117.5, 117.5, 120.1, 122.7, 123.3, 124.3, 133.7, 137.0, 141.3, 155.9, 158.8 (d, $^1J_{C-F}$ = 244.4) 167.9; FT-IR (neat) 2995, 1712, 1629, 1504, 1297, 749 cm^{-1}; MS (ESI) m/z 465 (MH^+); HRMS (ESI, m/z) calcd $C_{25}H_{25}FN_4O_2S$ $[M + H]^+$ 465.1755, found 465.1737.

Methyl 10-Isobutyl-2-(isopropylimino)-4,10-dihydro-2H-benzo-[4,5]imidazo[1,2-c][1,3,5]thiadiazine-7-carboxylate ***10a***. White solid; yield = 0.084 g, 82%; mp 227−230 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 1.4 Hz, 1H), 8.10 (dd, J = 8.5, 1.4 Hz, 1H), 7.37 (d, J = 8.5 Hz, 1H), 5.82 (s, 2H), 4.48 (sept, J = 6.6 Hz, 1H), 3.99 (d, J = 7.4 Hz, 2H), 3.95 (s, 3H), 2.20 (m, 1H), 1.44 (d, J = 6.6 Hz, 6H), 1.00 (d, J = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 18.9, 20.5, 28.2, 40.3, 46.3, 49.9, 51.6, 111.1, 111.9, 126.1, 126.6, 128.1, 133.4, 151.1, 161.7, 165.9; FT-IR (neat) 2960, 2916, 1708, 1547, 1497, 1297, 1202, 1014, 807, 721 cm^{-1}; MS (ESI) m/z 361 ($M + H)^+$; HRMS (ESI, m/z) calcd $C_{18}H_{24}N_4O_2S$ $[M + H]^+$ 361.1693, found 361.1698.

Methyl 10-Isobutyl-2-((3-methoxypropyl)imino)-4,10-dihydro-2H-benzo[4,5]imidazo[1,2-c][1,3,5]thiadiazine-7-carboxylate ***10b***. White solid; yield = 0.081 g, 79%; mp 212−214 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, J = 1.4 Hz, 1H), 8.12 (dd, J = 8.5, 1.4 Hz, 1H), 7.41 (d, J = 8.5 Hz, 1H), 5.97 (s, 2H), 4.03 (d, J = 7.4 Hz, 2H), 3.97 (s, 3H), 3.80 (t, J = 6.6 Hz, 2H), 3.52 (t, J = 6.6 Hz, 2H), 3.35 (s, 3H), 2.29 (m, 1H), 2.09 (quint, J = 6.6 Hz, 2H), 1.02 (d, J = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 162.8, 150.9, 132.9, 128.2, 127.0, 126.6, 113.0, 110.1, 69.8, 58.6, 52.6, 50.4, 41.7, 41.2, 28.6, 28.3, 20.1, 20.1; FT-IR (neat) 2922, 1728, 1566, 1519, 1253, 1017, 784 cm^{-1}; MS (ESI) m/z 391 (MH^+); HRMS (ESI, m/z) calcd $C_{19}H_{26}N_4O_3S$ $[M + H]^+$ 391.1798, found 391.1805.

Methyl 10-(Furan-2-ylmethyl)-2-(propylimino)-4,10-dihydro-2H-benzo[4,5]imidazo[1,2-c][1,3,5]thiadiazine-7-carboxylate ***10c***. Pale yellow; yield = 0.082 g, 80%; mp 205−207 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.42 (s, J = 1.4 Hz 1H), 8.11 (dd, J = 8.5, 1.4 Hz, 1H), 7.57 (d, J = 8.5 Hz, 1H), 7.39 (dd, J = 2.4, 1.9 Hz, 1H), 6.48 (dd, J = 3.3, 1.9 Hz, 1H), 6.38 (dd, J = 3.3, 1.9 Hz, 1H), 5.90 (s, 2H), 5.39 (s, 2H), 3.94 (s, 3H), 3.74 (t, J = 7.4, 2H), 1.92−1.80 (m, 2H), 1.03 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 22.0, 39.4, 41.7, 45.8, 52.5, 110.4, 110.6, 110.8, 112.7, 126.7, 127.1, 128.1, 132.3, 143.6, 146.6, 150.6, 162.9, 165.8; FT-IR (neat) 2915, 2948, 1718, 1552, 1458, 1251, 767, 637 cm^{-1}; MS (ESI) m/z 385 (MH^+); HRMS (ESI, m/z) calcd $C_{19}H_{20}N_4O_3S$ $[M + H]^+$ 385.1329, found 385.1334.

Methyl 10-(2-(Cyclohex-1-en-1-yl)ethyl)-2-((3-methoxypropyl)-imino)-4,10-dihydro-2H-benzo[4,5]imidazo[1,2-c][1,3,5]-thiadiazine-7-carboxylate ***10d***. White solid; yield = 0.083 g, 81%; mp 199−203 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 1.5 Hz, 1H), 8.09 (dd, J = 8.5, 1.4 Hz, 1H), 7.37 (d, J = 8.5 Hz, 1H), 5.91 (s, 2H), 5.15 (t, J = 3.5 Hz, 1H), 4.25 (t, J = 7.0 Hz, 2H), 3.93 (s, 3H), 3.77 (t, J = 7.2 Hz, 2H), 3.48 (t, J = 7.2 Hz, 2H), 3.30 (s, 3H), 2.40 (t, J = 7.2 Hz, 2H), 1.99−2.08 (m, 4H), 1.85−1.72 (m, 2H), 1.59−1.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 22.6, 25.1, 28.0, 28.5, 36.3, 41.3, 41.7, 41.8, 52.5, 58.6, 69.8, 110.0, 113.2, 125.6, 126.5, 127.0, 128.1, 132.3, 132.4, 150.7, 162.6, 165.9; FT-IR (neat) 2923, 2853, 1719, 1555, 1251, 1193, 765, 734 cm^{-1}; MS (ESI) m/z 443 (MH^+); HRMS (ESI, m/z) calcd $C_{23}H_{30}N_4O_3S$ $[M + H]^+$ 443.2111, found 443.2116.

Methyl 2-(Benzylimino)-10-(2-(cyclohex-1-en-1-yl)ethyl)-4,10-dihydro-2H-benzo[4,5]imidazo[1,2-c][1,3,5]thiadiazine-7-carboxylate ***10e***. White solid; yield = 0.086 g, 84%; mp 212−213 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 1.3 Hz, 1H), 8.09 (dd, J = 8.6, 1.4 Hz, 1H), 7.52−7.43 (m, 2H), 7.35 (d, J = 8.9 Hz, 1H), 7.30−7.22 (m, 2H), 7.20 (d, J = 7.0 Hz, 1H), 5.83 (s, 2H), 5.18 (s, 1H), 4.82 (s, 2H), 4.19 (t, J = 7.2 Hz, 2H), 3.94 (s, 3H), 2.32 (t, J = 7.2 Hz, 2H), 1.92−1.82 (m, 4H), 1.63−1.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 25.1, 28.2, 36.1, 41.6, 41.9, 47.1, 52.6, 110.1, 113.0, 125.3, 126.6, 127.1, 127.5, 128.0, 128.3, 128.5, 132.3, 132.4, 136.5, 150.5, 162.9, 165.8, 21.8; FT-IR (neat) 2924, 2853, 1719, 1551, 1252, 1193, 798, 698 cm^{-1}; MS (ESI) m/z 461 (MH^+); HRMS (ESI, m/z) calcd $C_{26}H_{28}N_4O_2S$ $[M + H]^+$ 461.2006, found 461.2013.

Methyl 2-(Cyclohexylimino)-10-(3-phenylpropyl)-2,10-dihydro-4H-benzo[4,5]imidazo[1,2-c][1,3,5]thiadiazine-7-carboxylate ***10f***. White solid; yield = 0.083 g, 81%; mp 219−221 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 1.4 Hz, 1H), 8.07 (dd, J = 8.5, 1.4 Hz, 1H), 7.45−6.90 (m, 6H), 5.85 (s, 2H), 4.20 (t, J = 7.2 Hz, 2H), 4.07 (dtd, J = 11.2, 7.2, 3.6 Hz, 1H), 3.94 (s, 3H), 2.75 (t, J = 7.3 Hz, 2H), 2.24 (p, J = 7.3 Hz, 2H), 2.07−1.91 (m, 2H), 1.96−1.52 (m, 6H), 1.28 (tt, J = 8.7, 5.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 25.1,

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29.1, 31.6, 32.9, 41.5, 42.8, 52.6, 54.5, 109.7, 112.9, 126.5, 126.9, 128.0, 128.2, 128.5, 132.4, 139.5, 150.6, 161.4, 165.9; FT-IR (neat) 2916, 2849, 1732, 1625, 1445, 1324, 1109, 881, 735 cm^{-1}; MS (ESI) m/z 463 (MH^+); HRMS (ESI, m/z) calcd $C_{26}H_{31}N_4O_2S$ $[M + H]^+$ 463.2162, found 463.2165.

Methyl 10-Isobutyl-2-(phenethylimino)-4,10-dihydro-2H-benzo-[4,5]imidazo[1,2-c][1,3,5]thiadiazine-7-carboxylate ***10g***. White solid; yield = 0.079 g, 77%; mp 208−210 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 1.5 Hz, 1H), 8.07 (dd, J = 8.6, 1.5 Hz, 1H), 7.36 (d, J = 8.6 Hz, 1H), 7.29−7.19 (m, 4H), 7.15 (m, 1H), 5.96 (s, 2H), 3.94 (d, J = 7.0 Hz, 2H), 3.92 (s, 3H), 3.88 (t, J = 7.9 Hz, 2H), 3.14 (t, J = 7.9 Hz 2H), 2.21 (m, 1H), 0.96 (d, J = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 28.3, 35.0, 41.7, 45.2, 50.4, 52.6, 76.7, 77.0, 77.3, 110.2, 113.1, 126.4, 126.6, 127.0, 128.1, 128.5, 128.8, 132.8, 138.4, 150.9, 162.9, 165.8; FT-IR (neat) 2952, 2925, 1719, 1553, 1458, 1183, 765 cm^{-1}; MS (ESI) m/z 423 (MH^+); HRMS (ESI, m/z) calcd $C_{23}H_{26}N_4O_2S$ $[M + H]^+$ 423.1849, found 423.1851.

N-(10-(Furan-2-ylmethyl)-7-(trifluoromethyl)-4,10-dihydro-2H-benzo[4,5]imidazo[1,2-c][1,3,5]thiadiazin-2-ylidene)-cyclohexanamine ***10h***. White solid; yield = 0.088 g, 86%; mp 252−254 °C; ^1H NMR (400 MHz, CD_3OD) δ 8.15 (d, J = 1.4 Hz, 1H), 7.94 (dd, J = 8.6, 1.4 Hz, 1H), 7.35 (d, J = 8.6 Hz, 1H), 7.46 (dd, J = 1.9, 0.8 Hz, 1H), 6.58 (dd, J = 3.3, 0.8 Hz, 1H), 6.40 (dd, J = 3.3, 0.8 Hz, 1H), 5.69 (s, 2H), 5.55 (s, 2H), 4.33 (m, 1H), 2.12−2.05 (m, 2H), 1.90−1.78 (m, 2H), 1.79 (m, 1H), 1.40−1.38 (m, 4H), 1.35 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 24.3, 24.5, 24.9, 31.5, 32.3, 39.0, 40.4, 53.5, 108.4, 109.8, 110.3, 111.9, 121.7, 122.6, 126.9, 128.2, 131.9, 143.4, 147.4, 150.9, 162.1; FT-IR (neat) 2934, 2856, 1556, 1507, 1487, 1063, 1012, 742 cm^{-1}; MS (ESI) m/z 435 (MH^+); HRMS (ESI, m/z) calcd $C_{21}H_{21}F_3N_4OS$ $[M + H]^+$ 435.1461, found 435.1467.

Methyl 2-(Cyclohexylimino)-10-isopropyl-4,10-dihydro-2H-benzo[4,5]imidazo[1,2-c][1,3,5]thiadiazine-7-carboxylate ***10i***. White solid; yield = 0.085 g, 83%; mp 191−194 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 1.4 Hz, 1H), 8.06 (dd, J = 8.7, 1.4 Hz, 1H), 7.48 (d, J = 8.6 Hz, 1H), 5.87 (s, 2H), 4.97 (p, J = 7.0 Hz, 1H), 4.10 (m, 1H), 3.93 (s, 3H), 1.21−1.90 (m, 4H), 1.80−1.71(m, 2H), 1.66 (d, J = 7.0 Hz, 6H), 1.40−1.17 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 24.9, 25.0, 30.8, 31.6, 41.4, 48.2, 52.5, 54.5, 110.9, 112.9, 126.2, 126.6, 128.5, 131.5, 150.1, 161.2, 165.9; FT-IR (neat) 2931, 2854, 1720, 1550, 1478, 1292, 971, 890, 817 cm^{-1}; MS (ESI) m/z 387 (MH^+); HRMS (ESI, m/z) calcd $C_{20}H_{26}N_4O_2S$ $[M + H]^+$ 387.1849, found 387.1853.

Methyl 2-(Cyclopentylimino)-10-isobutyl-4,10-dihydro-2H-benzo[4,5]imidazo[1,2-c][1,3,5]thiadiazine-7-carboxylate ***10j***. White solid; yield = 0.086 g, 84%; mp 232−234 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.08 (d, J = 8.5 Hz, 1H), 7.36 (d, J = 8.6 Hz, 1H), 5.88 (s, 2H), 4.51 (p, J = 6.8 Hz, 1H), 3.99 (d, J = 7.4 Hz, 2H), 3.94 (s, 3H), 2.26 (m, 1H), 2.09−2.01 (m, 4H), 1.98−1.90 (m, 2H), 1.62−1.56 (m, 2H), 0.99 (d, J = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 24.2, 28.4, 29.6, 32.2, 41.5, 50.4, 52.6, 56.5, 110.0, 112.9, 126.5, 127.0, 128.2, 132.9, 150.8, 161.6, 165.8; FT-IR (neat) 2954, 2872, 1722, 1547, 1501, 1251, 878, 736 cm^{-1}; MS (ESI) m/z 387 (MH^+); HRMS (ESI, m/z) calcd $C_{20}H_{26}N_4O_2S$ $[M + H]^+$ 387.1849, found 387.1855.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01586.

^1H, ^{13}C, LRMS, HRMS, and IR spectra (PDF)
X-ray crystal data of **8c** (CIF)
X-ray crystal data of **10f** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Lai, M. Y.; Chen, C. H.; Huang, W. S.; Lin, J. T.; Ke, T. H.; Chen, L. Y.; Tsai, M. H.; Wu, C. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 581. (b) Jin, Z. *Nat. Prod. Rep.* **2011**, *28*, 1143. (c) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev.* **2013**, *113*, 3084. (d) Fahsi, K.; Dutremez, S. G.; Vioux, A.; Viau, L. *J. Mater. Chem. A* **2013**, *1*, 4451.

(2) (a) Hauel, N. H.; Nar, H.; Priepke, H.; Ries, U.; Stassen, J.; Wienen, W. *J. Med. Chem.* **2002**, *45*, 1757. (b) Hranjec, M.; Piantanida, I.; Kralj, M.; Suman, L.; Pavelic, K.; Karminski-Zamola, G. *J. Med. Chem.* **2008**, *51*, 4899. (c) Hamdy, N. A.; Eldeen, A. M. G; Aziz, H. A. A.; Fakhr, I. M. I. *Eur. J. Med. Chem.* **2010**, *45*, 463. (d) Yuan, G.; Liu, H.; Gao, J.; Yang, K.; Niu, Q.; Mao, H.; Wang, X.; Lv, X. *J. Org. Chem.* **2014**, *79*, 1749.

(3) (a) Field, L.; Sweetman, B. J.; Bellas, M. *J. Med. Chem.* **1969**, *18*, 624. (b) Heimer, N. E.; Field, L. *J. Org. Chem.* **1970**, *35*, 1668. (c) Gordeev, M. F.; Gordon, E. M.; Patel, D. V. *J. Org. Chem.* **1997**, *62*, 8177. (d) Nakayama, J.; Ishii, A. *Adv. Heterocycl. Chem.* **2000**, *77*, 221.

(4) (a) Coburn, R. A.; Ho, C. H.; Bronstein, M. L. *J. Med. Chem.* **1982**, *25*, 481. (b) Shobana, N.; Farid, P. *Comprehensive Heterocyclic Chemistry III*; Pergamon: Oxford, 2008; Vol. *9*, p 457. (c) Dotsenko, V. V.; Frolov, K. A.; Pekhtereva, T. M.; Papaianina, O. S.; Suykov, S. Y.; Krivokolysko, S. G. *ACS Comb. Sci.* **2014**, *16*, 543.

(5) (a) Kanno, H. *Pure Appl. Chem.* **1987**, *59*, 1027. (b) Wang, Z. Y.; You, T. P.; Shi, H. J.; Shi, H. X. *Molecules* **1996**, *1*, 89. (c) Wang, Z. Y.; Shi, H. X.; Shi, H. J. *Synth. Commun.* **2001**, *31*, 2841.

(6) (a) Ried, W.; Mösinger, W. M. O. *Justus Liebigs Ann. Chem.* **1973**, *1973*, 1362. (b) Okajima, N.; Okada, Y. *J. Heterocycl. Chem.* **1991**, *28*, 177.

(7) (a) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46. (b) O'Connor, C. J.; Beckmann, H. S. G.; Spring, D. R. *Chem. Soc. Rev.* **2012**, *41*, 4444. (c) Ibbeson, B. M.; Laraia, L.; Alza, E.; O'Connor, C. J.; Tan, Y. S.; Davies, H. M. L.; McKenzie, G.; Venkitaraman, A. R.; Spring, D. R. *Nat. Commun.* **2014**, *5*, 4155.

(8) (a) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6234. (b) Yu, J.; Shi, F.; Gong, L. Z. *Acc. Chem. Res.* **2011**, *44*, 1156. (c) Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083. (d) de Graaff, C.; Ruijter, E.; Orru, R. V. A. *Chem. Soc. Rev.* **2012**, *41*, 3969.

(9) (a) Zhu, Y. G.; Zhai, C. W.; Yang, L. P.; Hu, W. H. *Eur. J. Org. Chem.* **2011**, *2011*, 1113. (b) Jing, C.; Xing, D.; Qian, Y.; Shi, T.; Zhao, Y.; Hu, W. *Angew. Chem., Int. Ed.* **2013**, *52*, 9289. (c) Selvaraju, M.; Sun, C. M. *ACS Comb. Sci.* **2015**, *17*, 182. (d) Dhole, S.; Selvaraju, M.; Maiti, B.; Chanda, K.; Sun, C. M. *ACS Comb. Sci.* **2015**, *17*, 310.

(10) Xu, X. F.; Doyle, M. P. *Chin. Chem. Lett.* **2015**, *26*, 227.

(11) (a) Chen, C. H.; Yellol, G. S.; Lin, P. T.; Sun, C. M. *Org. Lett.* **2011**, *13*, 5120. (b) Selvaraju, M.; Shiu, W. S.; Kulkarni, M. V.; Sun, C. M. *RSC Adv.* **2013**, *3*, 22314.

(12) Compound **10f** was directly obtained as a hydrochloride salt when dichloromethane was employed as an electrophile during the optimization studies.

(13) CCDC 849746 and 1463873 contain the supplementary crystallographic data for compounds **8c** and **10f**, respectively. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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