

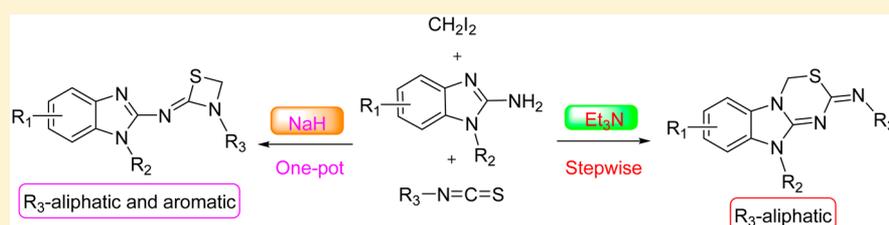
Three Component Divergent Reactions: Base-Controlled Amphiphilic Synthesis of Benzimidazole-Linked Thiazetidines and Fused Thiadiazines

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S Supporting Information



ABSTRACT: A divergent reaction of 2-aminobenzimidazole with isothiocyanates and dihalomethanes has been developed for the selective synthesis of benzoimidazothiazetidino and benzoimidazothiadiazino. A single-pot reaction of 2-aminobenzimidazole in the presence of sodium hydride delivers benzoimidazothiazetidino, whereas triethylamine promotes the formation of benzoimidazothiadiazino 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 thiazetidino and thiadiazino skeletons have shown prominent biological and pharmaceutical applications as depicted in Figure 1. 1,3-Thiazetidino-2-ylidene directly linked with triazine (I) acts as a valuable herbicide. Similarly, 1,3-thiazetidino 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 thiadiazino (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 benzoimidazothiazetidino or benzoimidazothiadiazino.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 thiazetidino or fused thiadiazino through a three component reaction of 2-aminobenzimidazole, isothiocyanate, and dihalomethane. The present strategy explores the amphiphilic reactivity of 2-aminobenzimidazoles with isothiocyanates and dihalogen electrophiles (Scheme 1). Benzimidazole-linked thiazetidino 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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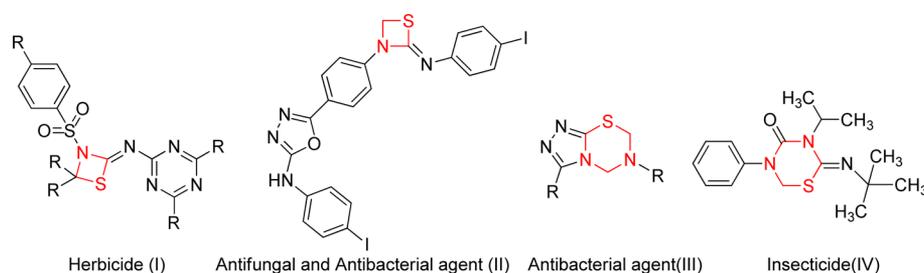
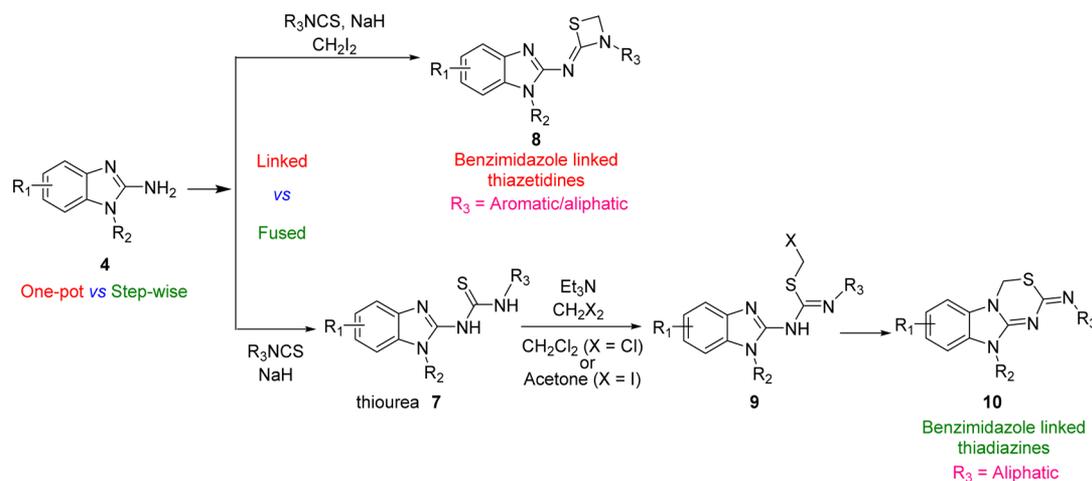
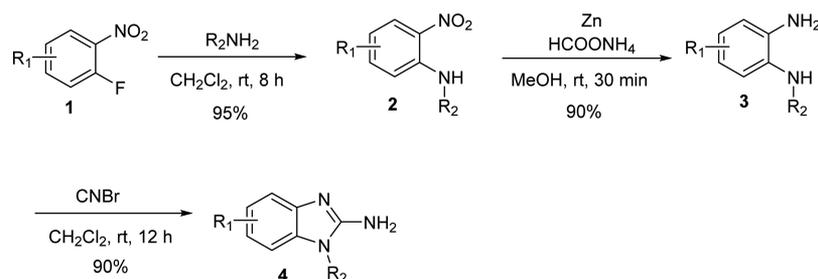


Figure 1. Biologically important thiazetidine and thiadiazine scaffolds.

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



Scheme 2. Facile Synthesis of 2-Aminobenzimidazoles 4



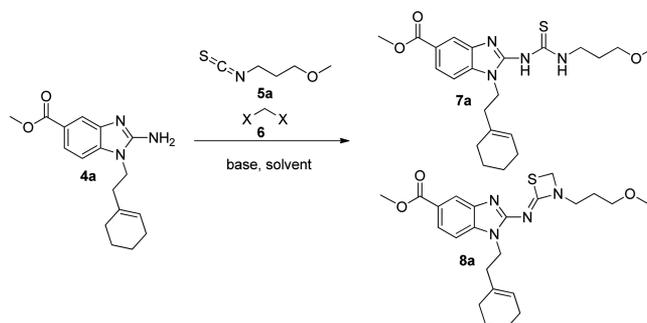
zine 10. Notably, only aliphatic isothiocyanates were feasible to furnish product 10 under this protocol. Under the strong basic conditions (NaH), the parent amine nitrogen is flanked exocyclic to the thiazetidine core and the other nitrogen is a part of thiazetidine. In contrast, the parent amine nitrogen 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

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

entry	electrophile	base	solvent	temperature (°C)	time (h)	yield (%) ^b	
						7a	8a
1	CH ₂ I ₂	Cs ₂ CO ₃	CH ₃ CN	reflux	12	20	35
2	CH ₂ I ₂	K ₂ CO ₃	CH ₃ CN	reflux	12	15	28
3	CH ₂ I ₂	NEt ₃	CH ₃ CN	reflux	12	15	0
4	CH ₂ I ₂	NEt ₃	acetone	rt	12	0	0
5	CH ₂ I ₂	NaH	CH ₂ I ₂	rt	0.4	0	69
6	CH ₂ I ₂	NaH	THF	rt	1	12	36
7	CH ₂ Br ₂	Cs ₂ CO ₃	CH ₃ CN	reflux	12	22	28
8	CH ₂ Br ₂	NaH	DMF	rt	0.4	0	52
9	CH ₂ Cl ₂	NaH	CH ₂ Cl ₂	rt	12	0	0
10 ^c	CH ₂ Cl ₂	NaH	DMF	90	0.4	50	0
11	CH ₂ Cl ₂	NEt ₃	CH ₂ Cl ₂	reflux	12	10	0
12	CH ₂ I ₂	KOtBu	CH ₂ I ₂	rt	12	20	31

^aReaction conditions: 4a (0.3 mmol), 5a (0.45 mmol), CH₂I₂ (0.9 mmol), base (0.9 mmol), solvent (2 mL) at the specified temperature. ^bIsolated yield. ^cUnder 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 CH₂Cl₂ in the presence of various bases as shown in Table 2. Employing inorganic bases such as K₂CO₃, Cs₂CO₃, 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 CH₂I₂ 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

Scheme 3. One-Pot Synthesis of Benzimidazothiazetidines 8

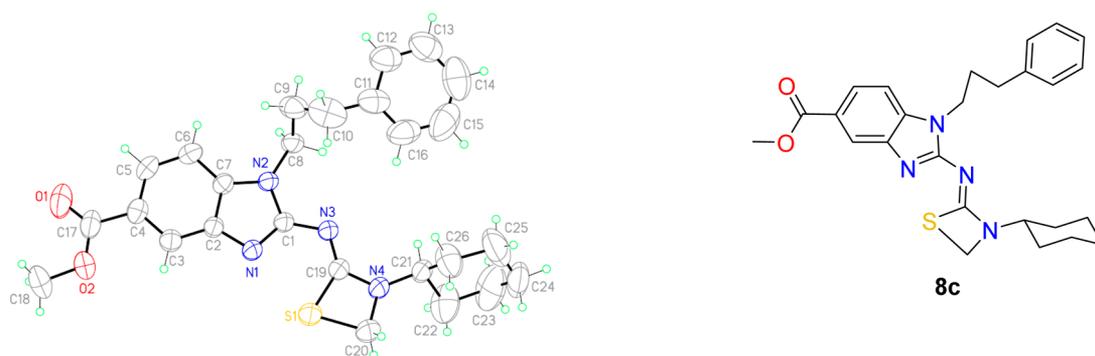
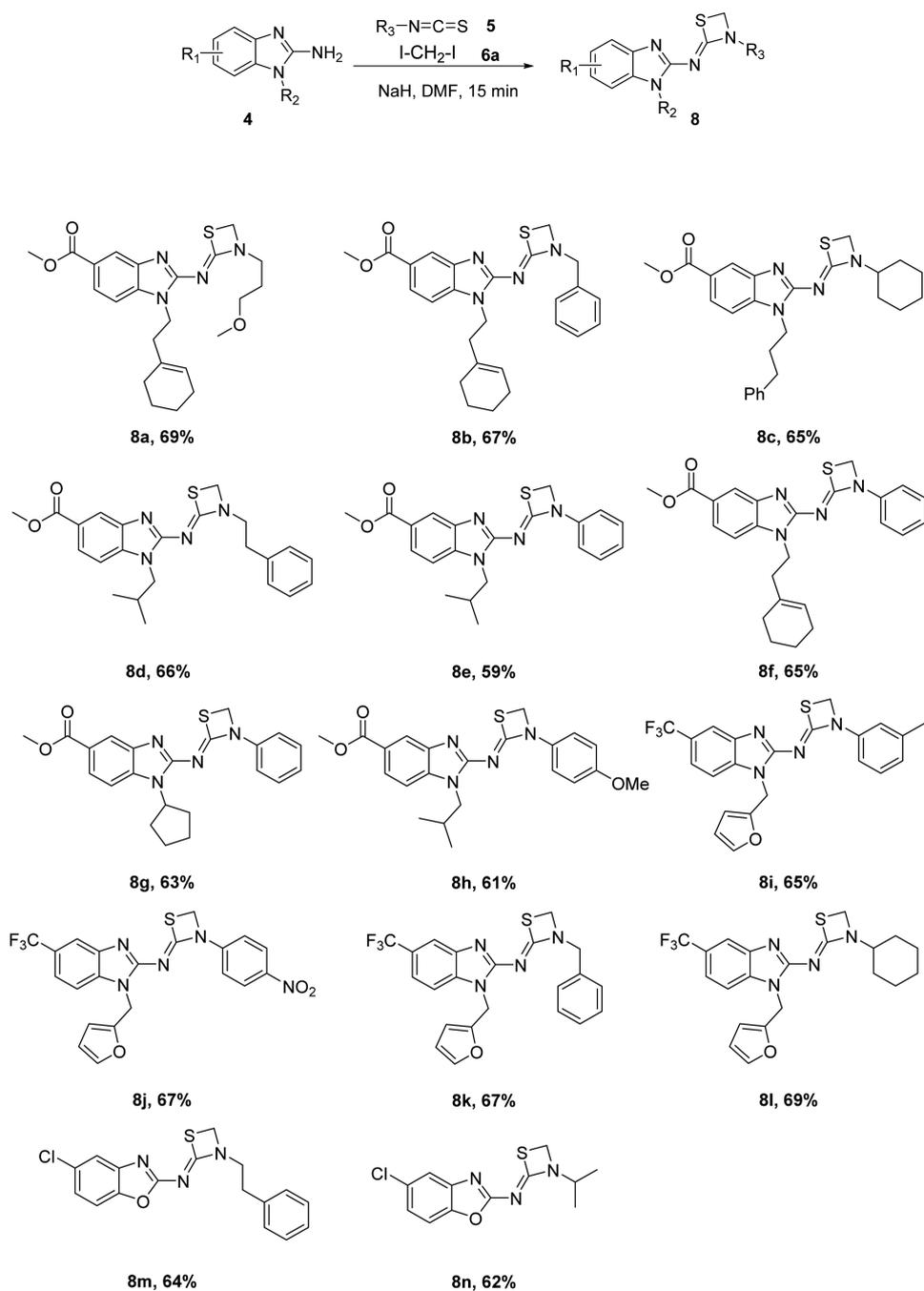
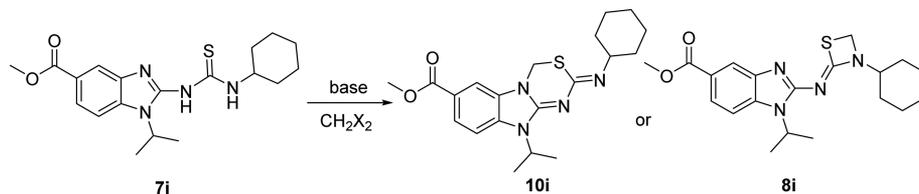


Figure 2. ORTEP diagram of 8c.

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

entry	electrophile ^a	base (equiv)	temperature (°C)	time (h)	yield (%) ^b	
					10i	8i
1	CH ₂ Cl ₂	K ₂ CO ₃ (5)	40	24	0	0
2	CH ₂ Cl ₂	Cs ₂ CO ₃ (5)	40	24	0	0
3	CH ₂ Cl ₂	NaH(5)	rt	8	0	0
4	CH ₂ Cl ₂	NEt ₃ (5)	rt	24	12	0
5	CH ₂ Cl ₂	NEt ₃ (10)	rt	8	49	0
6	CH ₂ I ₂	K ₂ CO ₃ (5)	rt	24	0	0
7	CH ₂ I ₂	NaH(5)	rt	0.5	0	92
8	CH ₂ I ₂	NEt ₃ (3)	rt	24	67	0
9	CH ₂ I ₂	NEt ₃ (7)	rt	24	95	0
10	CH ₂ I ₂	Pyridine	rt	48	0	0
11	CH ₂ I ₂	DIPEA(10)	rt	48	0	0

^aCH₂Cl₂ is used as solvent and reagent. Acetone is used as a solvent when CH₂I₂ (1.5 equiv) is employed as an electrophile. ^bIsolated 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 –CH₂ proton resonates at 4.6 ppm for compound **8** and compound **10** shows at 5.9 ppm, and C-13 carbon NMR (the characteristic –CH₂ 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

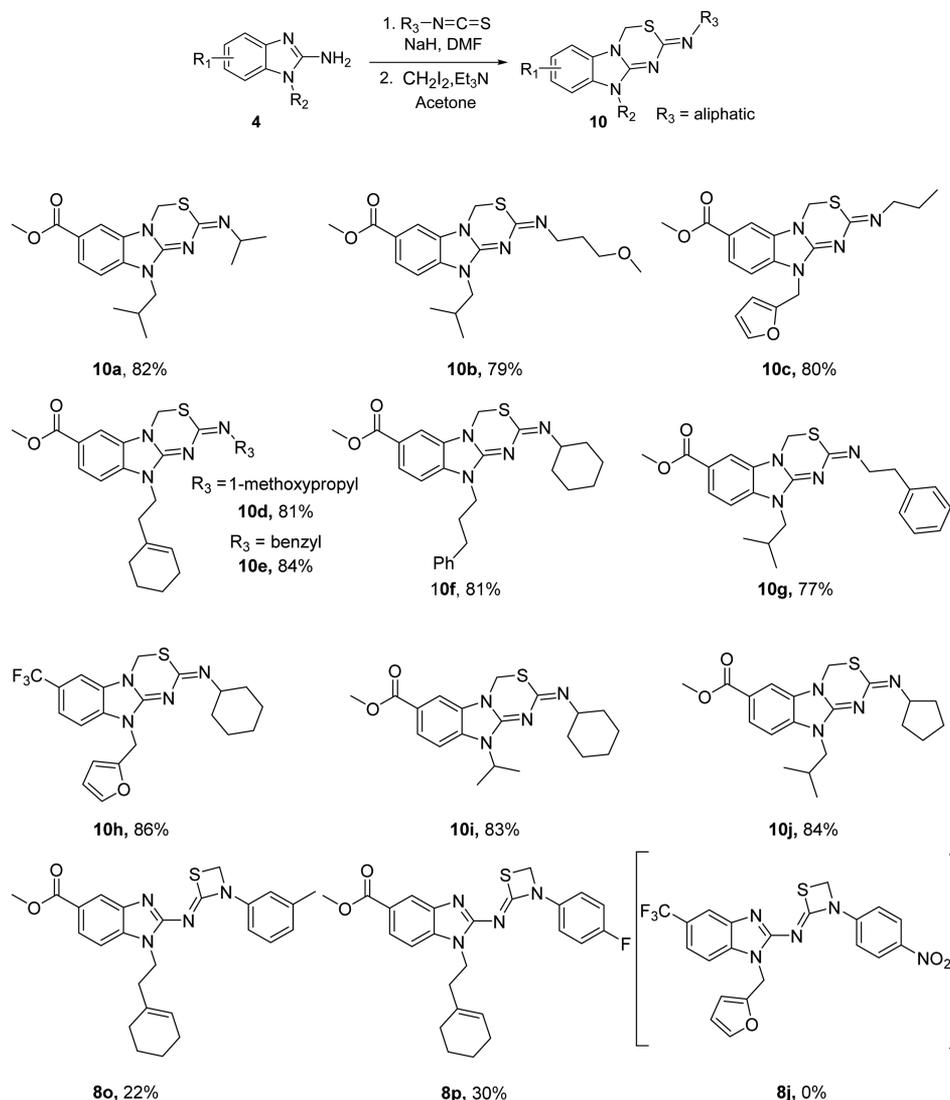
General Information. All of the solvents were distilled before use. All reactions were performed under an inert atmosphere with unpurified reagents and dry solvents. Analytical thin-layer chromatography (TLC) was performed using 0.25 mm silica gel-coated plates. Flash chromatography was performed using the indicated solvent and

silica gel 60 (230–400 mesh). ¹H NMR, ¹³C 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)-1H-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 MgSO₄, 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)-1H-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-1H-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 MgSO₄, 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)-1H-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)-1H-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.

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%).

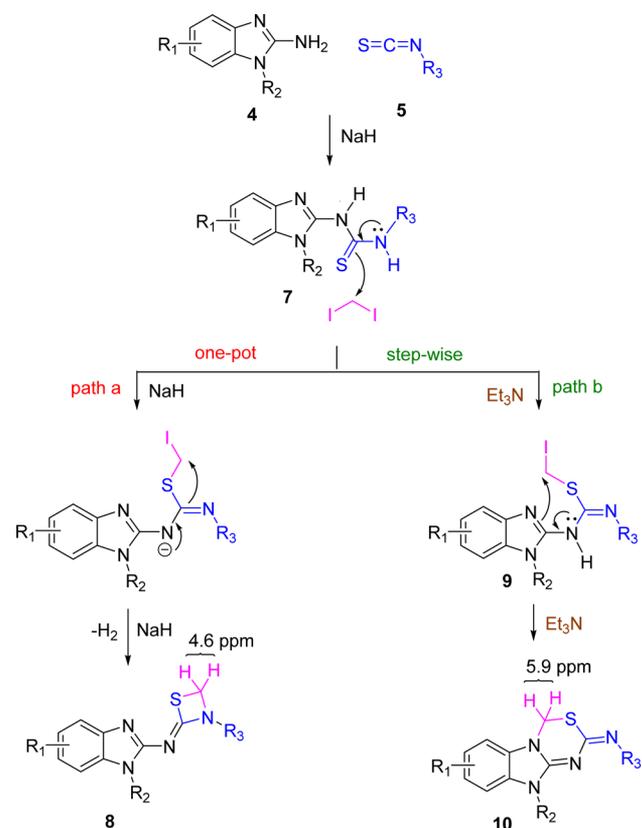
Methyl 1-(2-(Cyclohex-1-en-1-yl)ethyl)-2-((3-(3-methoxypropyl)-1,3-thiazetidin-2-ylidene)amino)-1H-benzo[d]imidazole-5-carboxylate 8a. White solid; yield = 0.12 g, 69%; mp 65–67 °C; 1H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, $J = 1.6$ Hz, 1H), 7.82 (dd, $J = 8.4, 1.6$ Hz, 1H), 7.15 (d, $J = 8.4$ Hz, 1H), 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; 1H 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; 1H 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, $CDCl_3$) 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; 1H 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

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 $\text{C}_{23}\text{H}_{26}\text{N}_4\text{O}_2\text{S}$ [$\text{M} + \text{H}$] $^+$ 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%; mp 167–170 °C; ^1H 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 $\text{C}_{21}\text{H}_{22}\text{N}_4\text{O}_2\text{S}$ [$\text{M} + \text{H}$] $^+$ 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.

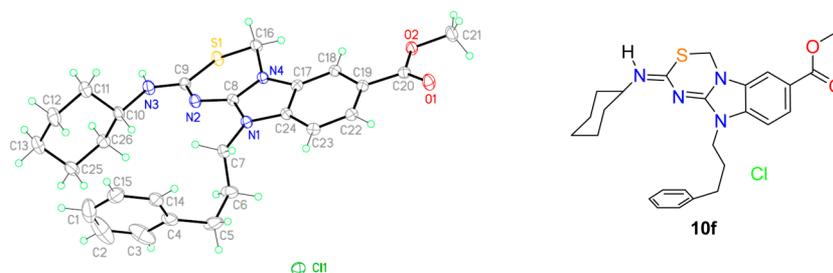
White solid; yield = 0.097 g, 65%; mp 200–201 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.32 (d, $J = 1.6$ Hz, 1H), 7.88 (dd, $J = 8.4, 1.6$ Hz, 1H), 7.62 (d, $J = 8.4$ Hz, 1H), 7.38 (t, $J = 7.8$ Hz, 2H), 7.29 (m, 1H), 7.11 (t, $J = 7.8$ Hz, 2H), 5.32 (t, $J = 7.4$ Hz, 1H), 4.95 (s, 2H), 4.25 (t, $J = 7.4$ Hz, 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 $\text{C}_{25}\text{H}_{26}\text{N}_4\text{O}_2\text{S}$ [$\text{M} + \text{H}$] $^+$ 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; ^1H 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 $\text{C}_{22}\text{H}_{22}\text{N}_4\text{O}_2\text{S}$ [$\text{M} + \text{H}$] $^+$ 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; ^1H 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 $\text{C}_{22}\text{H}_{24}\text{N}_4\text{O}_3\text{S}$ [$\text{M} + \text{H}$] $^+$ 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; ^1H 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, $^3J_{\text{C-F}} = 4.5$ Hz), 118.0 (q, $^3J_{\text{C-F}} = 3.02$ Hz), 124.7, 129.1, 135.5, 139.2, 139.7, 141.46, 142.5, 149.6, 155.9, 124.1 (q, $^3J_{\text{C-F}} = 31.7$ 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 $\text{C}_{22}\text{H}_{17}\text{F}_3\text{N}_4\text{OS}$ [$\text{M} + \text{H}$] $^+$ 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; ^1H 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, $^3J_{\text{C-F}} = 3.01$ 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**.

664 cm^{-1} ; MS (ESI) m/z 474 (MH^+); HRMS (ESI, m/z) calcd $\text{C}_{21}\text{H}_{14}\text{F}_3\text{N}_5\text{O}_3\text{S}$ [$\text{M} + \text{H}$] $^+$ 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, $^3J_{\text{C-F}} = 4.5$ Hz), 117.6 (q, $^3J_{\text{C-F}} = 3.01$ Hz), 128.2, 128.8, 129.0, 134.7, 135.5, 141.6, 142.4, 149.7, 156.5, 123.7 (q, $^2J_{\text{C-F}} = 31.7$ 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 $\text{C}_{22}\text{H}_{17}\text{F}_3\text{N}_4\text{O}_3\text{S}$ [$\text{M} + \text{H}$] $^+$ 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, CDCl_3) 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, $^3J_{\text{C-F}} = 4.1$ Hz), 117.3 (q, $^3J_{\text{C-F}} = 3.8$ Hz), 135.5, 141.7, 142.3, 149.9, 156.8, 123.5 (q, $^2J_{\text{C-F}} = 32.0$), 163.3, 125.1 (q, $^1J_{\text{C-F}} = 271.8$); 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 $\text{C}_{21}\text{H}_{21}\text{F}_3\text{N}_4\text{O}_3\text{S}$ [$\text{M} + \text{H}$] $^+$ 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 $\text{C}_{17}\text{H}_{14}\text{ClN}_3\text{O}_3\text{S}$ [$\text{M} + \text{H}$] $^+$ 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 $\text{C}_{12}\text{H}_{12}\text{ClN}_3\text{O}_3\text{S}$ [$\text{M} + \text{H}$] $^+$ 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, CDCl_3) 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 $\text{C}_{26}\text{H}_{29}\text{N}_4\text{O}_2\text{S}$ [$\text{M} + \text{H}$] $^+$ 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, CDCl_3) 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, $^1J_{\text{C-F}} = 244.4$) 167.9; FT-IR (neat) 2995, 1712, 1629, 1504,

1297, 749 cm^{-1} ; MS (ESI) m/z 465 (MH^+); HRMS (ESI, m/z) calcd $\text{C}_{25}\text{H}_{25}\text{FN}_4\text{O}_2\text{S}$ [$\text{M} + \text{H}$] $^+$ 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 ($\text{M} + \text{H}$) $^+$; HRMS (ESI, m/z) calcd $\text{C}_{18}\text{H}_{24}\text{N}_4\text{O}_2\text{S}$ [$\text{M} + \text{H}$] $^+$ 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 $\text{C}_{19}\text{H}_{26}\text{N}_4\text{O}_3\text{S}$ [$\text{M} + \text{H}$] $^+$ 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, $J = 7.4, 2\text{H}$), 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 $\text{C}_{19}\text{H}_{20}\text{N}_4\text{O}_3\text{S}$ [$\text{M} + \text{H}$] $^+$ 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 $\text{C}_{23}\text{H}_{30}\text{N}_4\text{O}_3\text{S}$ [$\text{M} + \text{H}$] $^+$ 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 $\text{C}_{26}\text{H}_{28}\text{N}_4\text{O}_2\text{S}$ [$\text{M} + \text{H}$] $^+$ 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,

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 $\text{C}_{26}\text{H}_{31}\text{N}_4\text{O}_2\text{S}$ [$\text{M} + \text{H}$] $^+$ 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 $^{\circ}\text{C}$; ^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 $\text{C}_{23}\text{H}_{26}\text{N}_4\text{O}_2\text{S}$ [$\text{M} + \text{H}$] $^+$ 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 $^{\circ}\text{C}$; ^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 $\text{C}_{21}\text{H}_{21}\text{F}_3\text{N}_4\text{OS}$ [$\text{M} + \text{H}$] $^+$ 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 $^{\circ}\text{C}$; ^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 $\text{C}_{20}\text{H}_{26}\text{N}_4\text{O}_2\text{S}$ [$\text{M} + \text{H}$] $^+$ 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 $^{\circ}\text{C}$; ^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 $\text{C}_{20}\text{H}_{26}\text{N}_4\text{O}_2\text{S}$ [$\text{M} + \text{H}$] $^+$ 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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- (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.