JOC*Article*

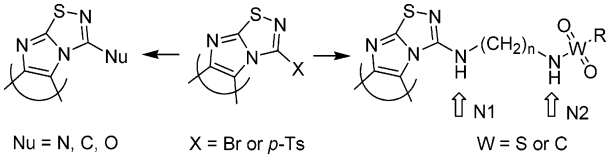
# Synthesis of 3-Substituted Bicyclic Imidazo[1,2-*d*][1,2,4]thiadiazoles and Tricyclic Benzo[4,5]imidazo[1,2-*d*][1,2,4]thiadiazoles

Regis Leung-Toung,* Tim F. Tam, Yanqing Zhao, Craig D. Simpson, Wanren Li, Denis Desilets, and Khashayar Karimian

*Medicinal Chemistry Department, ApoPharma, Inc., 400 Ormont Drive, Toronto, ON M9L 1N9, Canada*

*rleung@apotex.ca*

*Received April 14, 2005*




A versatile synthetic route to potentially useful fused-ring [1,2,4]thiadiazole scaffolds (e.g., **7a** and **10b**) via exchange reactions of the precursor [1,2,4]thiadiazol-3-(2*H*)one derivatives (e.g., **6** and **9**) with appropriately substituted nitriles (e.g., cyanogen bromide or *p*-toluenesulfonyl cyanide) under mild conditions is described. For example, the tricyclic 3-bromo [1,2,4]THD derivative (**7a**) underwent $S_NAr$ substitution with a variety of nucleophiles, which included amines, malonate esters and alcohols. Likewise, the bicyclic 3-*p*-tosyl [1,2,4]THD (**10b**) was employed as a template in reaction with diamines, and the resulting substituted diamines (e.g., **12a** or **12e**) were further selectively derivatized at the N1 and/or N2 positions in a linear fashion. The X-ray crystal structure of the 3-methyl bicyclic [1,2,4]THD (**21**) was obtained, and selective methylation at the N1 position via a protection−alkylation−deprotection protocol, as illustrated in Scheme 6, was confirmed. Alternatively, a short convergent synthesis of N1-functionalized derivatives from the reaction of **10b** with appropriately substituted secondary amines was also developed. Hence, these synthetic strategies were advantageously exploited to provide access to a variety of diversely derivatized 3-substituted fused-ring [1,2,4]thiadiazole derivatives.

## Introduction

Monocyclic [1,2,4]thiadiazoles ([1,2,4]THDs) have been widely claimed to be useful insecticidal, herbicidal and fungicidal agents.[1] For example, 5-ethoxy-3-(trichloromethyl)-[1,2,4]thiadiazole (**1**) is a soil fungicide marketed as *etridiazole* or *terrazole* (Figure 1).[2]

In recent years, many biologically active [1,2,4]THDs exhibiting interesting medicinal properties for the potential treatment of human diseases have been disclosed.[3−9] The injectable cephalosporin antibiotic cefozopran hydrochloride (**2**), which has a monocyclic THD group was launched as *Firstcin* in Japan in 1995 (Figure 1).[10] However, the role and importance of the THD moiety in all of those compounds, with regards to the mechanism of the biological response of the targeted enzymes, are not clearly understood at the molecular level.

* To whom correspondence should be addressed. Phone: 416-749-9300 ext 8120. Fax: 416-401-3845.

(1) (a) Franz, J. E.; Dhingra, O. P. *Compr. Heterocycl. Chem. I* **1984**, *6*, 463−511. (b) Wilkins, D. J.; Bradley, P. A. *Compr. Heterocycl. Chem. II* **1996**, *4*, 307−354. (c) Kurzer, F. *Adv. Heterocycl. Chem*. **1982**, *32*, 285−398.

(2) The CAS Registry No. for terrazole is 25-931-59.

(3) (a) Unangst, P. C.; Shrum, G. P.; Connor, D. T.; Dyer, R. D.; Schrier, D. J. *J. Med. Chem.* **1992**, *35*, 3691−3698. (b) Song, Y.; Connor, D. T.; Sercel, A. D.; Sorenson, R. J.; Doubleday: R.; Unangst, P. C.; Roth, B. D.; Beylin, V. G.; Gilbertsen, R. B.; Chan, K.; Schrier, D. J.; Guglietta, A.; Bornemeier, D. A.; Dyer, R. D. *J. Med. Chem*. **1999**, *42*, 1161−1169.

(4) Smith, C. W.; Chakrabarti, J. K.; Williamson, W. R. N. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1673−1678.

(5) Yousif, N. M. *Egypt. J. Chem*. **1989**, *32*, 597−605.

(6) (a) van Muijlwijk-Koezen, J. E.; Timmerman, H.; Vollinga, R. C.; Frijtag von Drabbe Kunzel, J.; de Groote, M.; Visser, S.; Ijzerman, A. P. *J. Med. Chem.* **2001**, *44*, 749−762. (b) van den Nieuwendijk, A. M.; Pietra, D.; Heitman, L.; Göblyös, A.; Ijzerman, A. P. *J. Med. Chem*. **2004**, *47*, 663−672. (c) Göblyös, A.; de Vries, H.; Brussee, J.; Ijzerman, A. P. *J. Med. Chem*. **2005**, *48*, 1145−1151.

(7) Antonio, Y.; Camargo, C.; Galeazzi, E.; Iriarte, J.; Guzman, M.; Muchowski, J. M.; Gerrity, K.; Liu, F.; Miller, L. M.; Strosberg, A. M. *J. Med. Chem*. **1978**, *21*, 123−126.

(8) MacLeod, A. M.; Baker, R.; Freedman, S. B.; Patel, S.; Merchant, K. J.; Ros, M.; Saunders J. *J. Med. Chem*. **1990**, *33*, 2052−2059.

(9) Collins, I.; Moyes, C.; Davey, W. B.; Rowley, M.; Bromidge, F. A.; Quirk, K.; Atack, J. R.; McKernan, R. M.; Thompson, S. A.; Wafford, K.; Dawson, G. R.; Pike, A.; Sohal, B.; Tsou, N. N.; Ball, R. G.; Castro, J. L. *J. Med. Chem*. **2002**, *45*, 1887−1900.

(10) Cheng, X.-M. *Annual Reports in Medicinal Chem*istry; Bristol, J. A., Ed.; Academic Press: London, 1996; *Vol. 31*, Chapter 34, pp 337−355; in particular p 339.

10.1021/jo0507486 CCC: $30.25 
Published on Web 07/12/2005

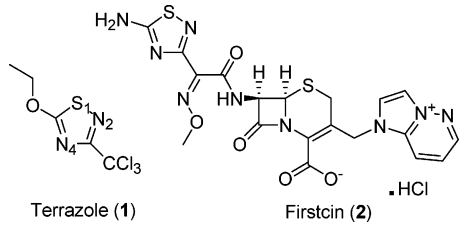
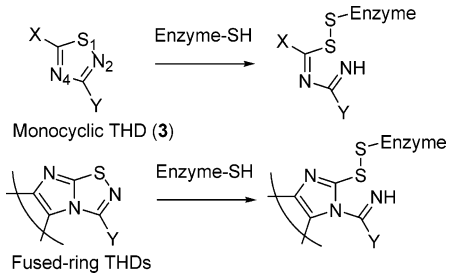



**FIGURE 1.** Examples of commercial monocyclic [1,2,4]THD derivatives.

**SCHEME 1. Mechanism of Inhibition of Cysteine Residues of Biomolecules by [1,2,4]THDs**




Early on, in our discovery program on the design of novel inhibitors targeting cysteine residues of biomolecules,[11,12] we recognized the advantage of employing the [1,2,4]THD heterocycle[13] as the thiol trapping electrophile via S−S bond formation with concomitant N−S ring opening (Scheme 1). Contrary to the commonly reported electrophilic "warheads" (e.g., epoxides, chloromethyl ketones, vinyl sulfones, and aldehydes),[11] the [1,2,4]THD heterocycle displayed lack of reactivity (N−S bond cleavage) toward nucleophiles such as amines and alcohols, but reacted with thiols.[1,14]

Substituents at the C3- (Y) and C5- (X) positions in the monocyclic THD (**3**) can be modified to tune enzyme affinity and reactivity of the N−S bond toward the incoming thiol nucleophile,[15] whereas an appropriate C3 substituent (Y) in the fused-ring bicyclic THD (**4**) and tricyclic THD (**5**) can enhance both enzyme affinity and reactivity (Figure 2). Therefore, enzyme-specific and/or active site-directed inhibitors can be designed through a judicious choice of substituents (recognition arm), and THD "warhead" (monocyclic vs fused).

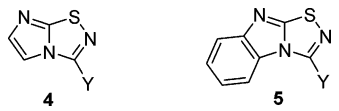



**FIGURE 2.** Fused-ring bicyclic (**4**) and tricyclic (**5**) [1,2,4]THD scaffolds.

We[13,15] and others[16] have recently disclosed the use of novel inhibitors based on the monocyclic [1,2,4]THD scaffold for targeting cysteine proteases (cathepsin B[15a] and guinea pig liver transglutaminase[16]) through S−S bond formation (Scheme 1). Interestingly, suitably 3-substituted bicyclic THD derivatives are potent, selective, and active-site directed inhibitors of plasma transglutaminase (FXIIIa),[17] while 3-substituted tricyclic THD derivatives are preferred for the inhibition of certain enzymes such as the proton pump ($H^+/K^+$ ATPase).[18]

At the time we started our medicinal chemistry efforts, the chemistry of monocyclic [1,2,4]THDs were well documented,[1] whereas that of fused-ring bicyclic and tricyclic THDs remained largely unknown apart from a few sparse publications.[19−21] However, we required an array of 3-substituted fused-ring THD analogues for structure−activity relationship (SAR) studies in biological systems. We reasoned that [1,2,4]THD scaffolds with a good leaving group (e.g., Br or *p*-Ts) at the 3-position would readily undergo nucleophilic substitution via an $S_NAr$ mechanism.[22] In addition, the resulting suitably substituted [1,2,4]THD derivatives could serve as templates for further synthetic manipulation, and hence provide access to a rich diversity of fused-ring [1,2,4]-THDs. Herein, we discuss our strategies and results on the synthesis of 3-substituted bicyclic and tricyclic THD compounds using the 3-bromo or 3-*p*-tosyl substituted THD scaffolds.

## Results and Discussion

**Preparation of Fused-Ring [1,2,4]Thiadiazole Scaffolds.** In our hands, a solution of 2-butylbenzo[4,5]-

(11) (a) For recent reviews on cysteine proteases, see the following: Leung-Toung, R.; Li, W.; Tam, T. F.; Karimian, K. *Curr. Med. Chem.* **2002**, *9*, 979−1002. (b) Powers, J. C.; Asgian, J. L.; Ekici, Ö. D.; James, K. L. *Chem. Rev*. **2002**, *12*, 4639−4750. (c) Donkor, I. O. *Curr. Med. Chem*. **2000**, *7,* 1171−1188. (d) Talanian, R. V.; Brady, K. D.; Cryns, V. L. *J. Med. Chem*. **2000**, *43,* 3351−3371.

(12) For a review on inhibitors targeting the cysteine residues of biomolecules, see the following: Scozzafava, A.; Casini, A.; Supuran, C. T. *Curr. Med. Chem*. **2002**, *9*, 1167−1185.

(13) Bryson, S.; Pai, E. F.; Desilets, D.; Li W.; Tam T.; Karimian K. *Evidence for the formation of a disulfide bond between cysteine proteases and 1,2,4-thiadiazoles*; PENCE AGM 2000 Meeting, Montebello, Quebec, Canada, June 24−26, 2000; PENCE, Inc.: Edmonton, 2000.

(14) (a) Crook, S.; Sykes, P. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1791−1796. (b) Hagiwara, K.; Hashimoto, S.; Shimoda, S. *J. Pestic. Sci*. **1992**, *17*, 251−259. (c) Newton, C. G.; Ollis, D. W. *J. Chem. Soc., Perkin Trans. 1* **1984**, 75−84.

(15) (a) Leung-Toung, R.; Wodzinska, J.; Li, W.; Lowrie, J.; Kukreja, R.; Desilets, D.; Karimian, K.; Tam, T. F. *Bioorg. Med. Chem*. **2003**, *11*, 5529−5537. (b) Karimian, K.; Tam, T. F.; Leung-Toung, R. C. S. H.; Li, W.; Bryson, S.; Wodzinska, J. M. WO0190095, 2001.

(16) Marrano, C.; de Macedo, P.; Gagnon, P.; Lapierre, D.; Gravel, C.; Keillor, J. W. *Bioorg. Med. Chem*. **2001**, *9*, 3231−3241.

(17) (a) Leung-Toung, R.; Tam, T. F.; Wodzinska, M. J.; Zhao, Y.; Lowrie, J.; Simpson, D. C.; Karimian, K.; Spino, M. *J. Med. Chem.* **2005**, 48, 2266−2269. (b) Tam, T. F.; Karimian, K.; Leung-Toung, R. C. S. H.; Zhao, Y.; Wodzinska, J. M.; Li, W.; Lowrie, J. N. US patent application 20030225007A1, 2003.

(18) (a) Tam, F. T.; Leung-Toung, R.; Li, W.; Spino, M.; Karimian, K. *Mini-Rev. Med. Chem.* **2005**, *5*, 367−379. (b) Tam, T.; Li, W.; Leung-Toung, R.; Karimian, K. *IDrugs* **2000**, *3*, 1064−1074. (c) Karimian, K.; Tam, T. F.; Desilets, D.; Lee, S.; Cappelletto, T.; Li, W. US patent 5,677,302, 1997.

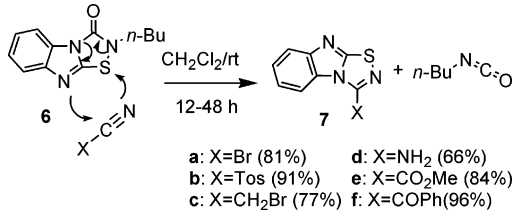
(19) Haugwitz, R. D.; Toeplitz, B.; Gougoudas, J. Z. *J. Chem. Soc., Chem. Commun*. **1977**, 736−737.

(20) (a) Martin, D.; Tittelbach, F. *Tetrahedron* **1983**, *39*, 2311−2314. (b) Martin, D.; Wenzel, A. *J. Prakt. Chem.* **1978**, *320*, 677−684. (c) Martin, D.; Tittelbach, F. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1007−1013;

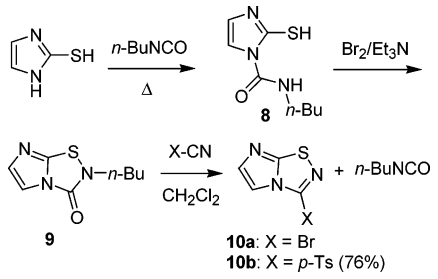
(21) Pentimalli, L.; Milani, G.; Biavati, F. *Gazz. Chim. Ital*. **1977**, *107*, 1−5.

(22) For examples of $S_NAr$ substitution in heterocycles, see the following: (a) Chauvière, G. Bouteille, B.; Enanga, B.; de Albuquerque, C.; Croft, S. L.; Dumas, M.; Périé, J. *J. Med. Chem*. **2003**, *46*, 427−440. (b) Song, Y.; Connor, D. T.; Sercel, A. D.; Sorenson, R. J.; Doubleday: R.; Unangst, P. C.; Roth, B. D.; Beylin, V. G.; Gilbertsen, R. B.; Chan, K.; Schrier, D. J.; Guglietta, A.; Bornemeier, D. A.; Dyer, R. D. *J. Med. Chem*. **1999**, *42*, 1161−1169. (c) Zhang, Z.; Yin, Z.; Kadow, J. F.; Meanwell, N. A.; Wang, T. *J. Org. Chem.* **2004**, *69*, 1360−1363. (d) Guillier, F.; Roussel, P.; Moser, H.; Kane, P.; Bradley, M. *Chem. Eur. J*. **1999**, *5*, 3450−3458. (e) Liu, J.; Janeba, Z.; Robins, M. J. *Org. Lett*. **2004**, *6*, 2917−2919.

**SCHEME 2. Preparation of Tricyclic [1,2,4]THD Scaffolds (7a–f)**




**SCHEME 3. Preparation of Bicyclic [1,2,4]THD Scaffolds (10a,b)**

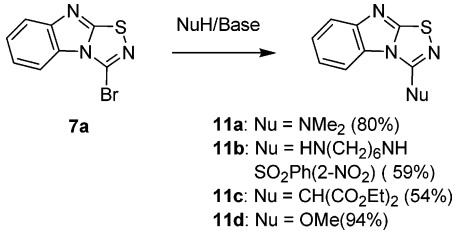



imidazo[1,2-*d*][1,2,4]thiadiazol-3(2*H*)-one (**6**), prepared according to the procedure previously described by Martin and Wenzel,[20a] in dichloromethane underwent exchange reaction with cyanogen bromide smoothly at room temperature with extrusion of *n*-butyl isocyanate. The tricyclic 3-bromo THD (**7a**) precipitated out and was isolated by simple suction filtration in good yield (81%). No further purification was required after the solid was washed with dichloromethane. The exchange reaction could be extended to a variety of substituted nitriles (e.g., bromoacetonitrile, cyanamide), and its scope is illustrated with the straightforward preparation of the tricyclic [1,2,4]THD scaffolds **7b**–**f**, as depicted in Scheme 2.

The bicyclic 3-substituted [1,2,4]THD scaffolds (**10a**,**b**) were prepared as shown in Scheme 3, following a similar pathway as that for the tricyclic analogues. The condensation product (**8**) from 2-mercaptoimidazole and *n*-butyl isocyanate[23] was subjected to oxidative ring closure with bromine and triethylamine at ice cold temperature to afford 2-butyl-imidazo[1,2-*d*][1,2,4]thiadiazol-3(2*H*)-one (**9**) in >70% combined yield, consistently. However, the exchange reaction of **9** with cyanogen bromide under standard conditions was rather problematic, as production of the bromo compound **10a** was unpredictable. For example, in one instance, **10a** was isolated in 91% yield, while only insoluble unidentified solid material was obtained in other experiments under similar conditions. Gratifyingly, **9** underwent exchange reaction with *p*-toluenesulfonyl cyanide[24] smoothly to afford **10b** in >75% yield, consistently.

**Derivatization of [1,2,4]THD Scaffolds.** The tricyclic bromo THD (**7a**) underwent nucleophilic substitution uneventfully with aqueous dimethylamine or with sodium methoxide in methanol, under mild conditions, and

**SCHEME 4. Nucleophilic Displacement Reactions of Tricyclic [1,2,4]THD Scaffold (7a)**




the corresponding 3-substituted THDs (**11a**) and (**11d**) were readily isolated in good yields (Scheme 4). Similarly, other nucleophiles such as *N*-(6-aminohexyl)-2-nitrobenzene sulfonamide and diethyl malonate in the presence of triethylamine also afforded substituted THDs **11b** and **11c**, respectively, in modest unoptimized yields. In the case of diethyl malonate, extended refluxing (36 h) in THF was needed for the completion of the reaction. Thus, derivatization of the tricyclic 3-bromo THD scaffold (**7a**) with nitrogen, carbon, and oxygen nucleophiles is shown to be feasible.

However, synthesis of the analogous bicyclic 3-bromo THD scaffold (**10a**) was unreliable and, hence, precluded access to 3-substituted bicyclic THD derivatives via this route. Alternatively, it is documented that heterocyclic vinyl sulfones underwent nucleophilic $S_NAr$ substitution with a variety of nucleophiles including amines.[22] Indeed, *N*-(6-aminohexyl)-1-naphthylsulfonamide reacted with the 3-*p*-tosyl-substituted THD (**10b**), under mild conditions, in dimethylformamide, and in the presence of triethylamine to afford **12a** in 69% yield, after purification by column chromatography.

We then based our strategy for the derivatization of **10b** with diamines, as illustrated in Scheme 5. The synthesis of THD derivatives via route 1 was preferred when the sulfonyl R group was fixed (e.g., 2-$NO_2$-Ph) and *n* was varied ($n = 3-7$). The reaction medium was usually dimethylformamide, with triethylamine as base (Table 1, **12b**–**f**, entries 2–6). Conversely, with *n* fixed (e.g., $n = 4$ or 6), route 2 was preferred for the preparation of THDs with different sulfonyl moieties (Table 1, entries 8–14). The sulfonyl R moiety could be aromatic, heterocyclic (**12m**, entry 13), or aliphatic (**12n**, entry 14), and the nature of the substituents influenced the choice of reaction medium. We noticed that reactions involving 1,5-diaminopentane and its THD derivatives were usually sluggish and more difficult, and yields were lower as compared to other analogues (entry 4).[25] Other reagents besides sulfonyl halides were employed, and compounds **13** and **14** are examples of THD derivatives that could be prepared from acylation of **16** with 2-nitrobenzoyl chloride and from alkylation with the activated 2-chloro-3-nitropyridine, respectively (entries 15, 16).

The THD template **15** or **16** (Scheme 5) could be prepared directly from the reaction of **10b** with at least 4–5 equiv of the respective diamines. In some cases, formation of disubstituted products were non-negligible.

(23) Other isocyanates (methyl, ethyl, propyl) work equally well. However, we settled for *n*-butyl isocyanate because of cost and safety (higher bp) considerations and commercial availability in kilogram quantity.

(24) For a preparative procedure for *p*-TsCN, see the following, Vrijland, M. S. A. In *Organic Syntheses*; Noland, W. E., Ed; John Wiley & Sons, Inc.: Toronto, 1988; Collect. Vol. VI, pp 727–730.

(25) We do not have a reasonable explanation for this observation. However, we also noted that 1,3-, 1,4-, and 1,6-alkyldiamines are available reasonably cheaply in kg's quantities from commercial suppliers, but 1,5-diaminopentane is supplied in small quantities (25 g bottle) and is relatively much more expensive.

**SCHEME 5. Functionalization of Bicyclic [1,2,4]THD Scaffold 10b with Diamines**

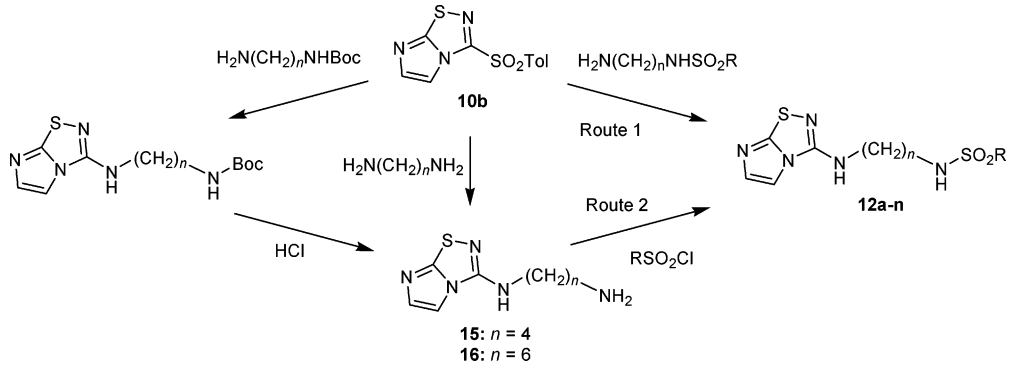
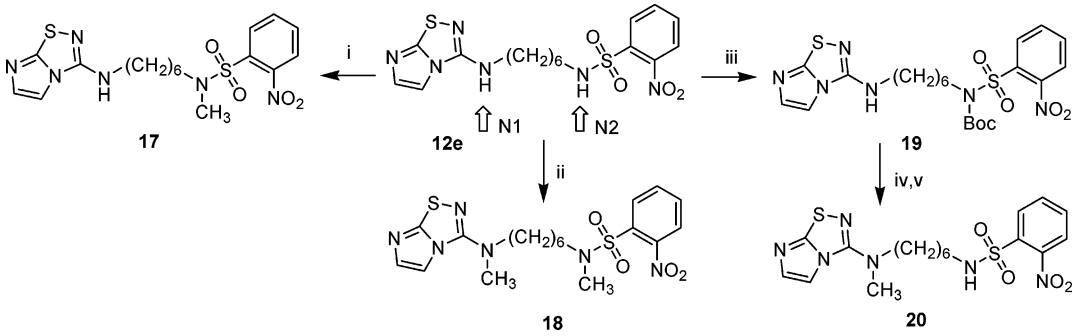



**TABLE 1. Diamine Derivatives from the 3-*p*-Tosyl-Substituted Bicyclic Scaffold (10b)**

| entry | compd | *n* | R | yield (%) | entry | compd | *n* | R | yield (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **12a** | 6 | 1-naphthyl | 69[a] | 9 | **12i** | 6 | 2-CN-Ph | 62 |
| 2 | **12b** | 3 | 2-$NO_2$-Ph | 82 | 10 | **12j** | 6 | 2,4-di-Br-Ph | 89 |
| 3 | **12c** | 4 | 2-$NO_2$-Ph | 65 | 11 | **12k** | 6 | 2-$NO_2$-4-CN-Ph | 48 |
| 4 | **12d** | 5 | 2-$NO_2$-Ph | 24 | 12 | **12l** | 6 | 2-$NO_2$-4-COOH-Ph | 73 |
| 5 | **12e**[b] | 6 | 2-$NO_2$-Ph | 58[c] | 13 | **12m** | 6 | 5-[3-Br-2-Cl-Py] | 45 |
| 6 | **12f** | 7 | 2-$NO_2$-Ph | 79 | 14 | **12n** | 6 | $CH_3$ | 75 |
| 7 | **12g** | 6 | 2-$NH_2$-Ph | 65 | 15 | **13**[d] | 6 | 2-$NO_2$-Bz | 63 |
| 8 | **12h** | 6 | 3-COOH-Ph | 80 | 16 | **14**[e] | 6 | 3-$NO_2$−2-Py | 43 |

[a] 91% yield via route 2. [b] For spectral data, see ref 17. [c] 70% yield from route 2. [d] Acylating agent is 2-nitrobenzoyl chloride. [e] Alkylating agent is 2-chloro-3-nitropyridine.

**SCHEME 6. Selective Methylation at N1 and N2 Positions of Bicyclic THD (12e)[a]**




[a] Reagents and conditions: (i) 3 equiv of $CH_3I$, 7.5 equiv of $K_2CO_3$, acetone; (ii) excess $CH_3I$, solid $K_2CO_3$, powder KOH, cat. *n*-$Bu_4N^+I^-$, toluene; (iii) 1.5 equiv of $Boc_2O$, cat. DMAP/$CH_3CN$; (iv) excess $CH_3I$, solid $K_2CO_3$, powder KOH, cat. *n*-$Bu_4N^+HSO_4^-$, toluene/$CH_2Cl_2$ (5/1, v/v); (v) HCl(g), MeOH, then neutralize.

Then, access to **15** or **16**, from **10b** via a Boc protection−substitution−deprotection protocol was desirable.

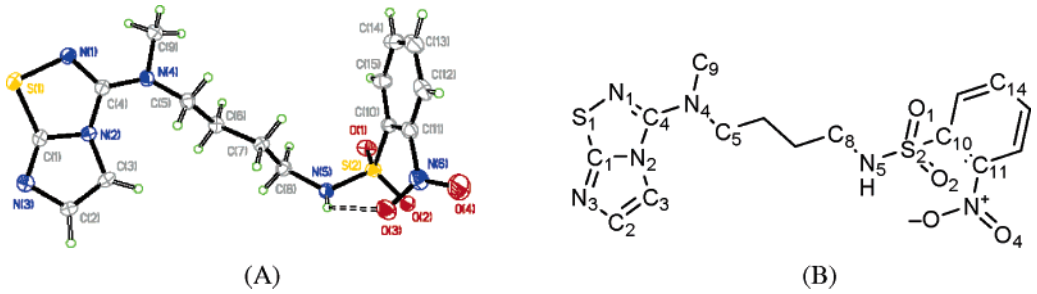
The aqueous solubilities of most of these compounds at pH 7.4 and at ambient temperature are in the 10 $\mu$M range; for example, the solubility of **12e** is 13 $\mu$g/mL.[17a] However, the solubility can reach mM range in other media such as in Cremophor (e.g., solubility of **12a** in 25% Cremophor EL is 0.38 mg/mL at rt and at native pH), or in mixtures of poly(ethylene glycol) (PEG)/ethanol/saline (e.g., solubility of **12a** in 60%PEG400/10%ethanol/30%saline is 0.42 mg/mL at rt and at native pH).

It is quite apparent that the two nitrogens (e.g., N1 and N2 of **12e**, Scheme 6) could be different in their reactivities with electrophiles. This is further supported by the calculated p$K_a$'s,[26] which clearly suggested that these nitrogens could be selectively exploited for further synthetic elaboration. Indeed, reaction of **12e** with iodomethane in the presence of potassium carbonate in acetone at room temperature afforded the N2-methyl compound **17**, exclusively, in 76% yield, after purification by column chromatography. When the reaction condition was slightly modified by the addition of powdered potassium hydroxide, both N1 and N2 were methylated, and **18** was isolated in 88% yield. Based on these results, a route to selectively introduce a methyl substituent at the N1 position via a Boc protection−alkylation−deprotection protocol was employed successfully (Scheme 6).[17a] Products **17**-**20** were characterized by 2D-NMR, including HSQC and HMBC experiments.[27]

We have recently determined the single-crystal X-ray structure of **21** (Figure 3), a homologue of **20** but with a

(26) Single p$K_a$ calculations of compound **12e** using ACD/Labs software were performed: p$K_a$ of N1 was calculated to be −2.21 ($NH_2^+$) and that of N2 was 10.72 (NH).

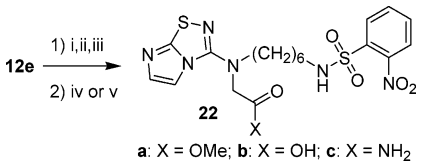
(27) Braun, S.; Kalinowski, H.-O.; Berger, S. *150 and More Basic NMR Experiments: A Practical Course*, 2nd expanded ed.; Wiley-VCH: Toronto, 1998.



(A) (B)

**FIGURE 3.** (A) X-ray crystal structure of 3-methyl bicyclic [1,2,4]thiadiazole (**21**). Color code: blue (N), gray (C), red (O), yellow (S), green (H). (B) ChemDraw structure of **21** with corresponding atom labeling.

**SCHEME 7. Selective Functionalization at the N1 Position of 12e**[a]




[a] Reagents and conditions: (i) 1.5 equiv of $Boc_2O$, 0.5 equiv of DMAP, $CH_3CN$; (ii) excess $BrCH_2CO_2CH_3$, solid $K_2CO_3$, powder KOH, cat. $n$-$Bu_4N^+I^-$, toluene; (iii) HCl(g), MeOH, then neutralize; (iv) for **22b**: 2 N NaOH, MeOH; then neutralize; (v) for **22c**: $NH_3$ gas, MeOH/$CH_2Cl_2$.

$(CH_2)_4$ spacer, obtained via the protection−alkylation−deprotection route. Thus, unequivocal proof that methylation occurred at the N1 position has been established, which also confirmed the conclusions reached from the 2D-NMR experiments. Some of the salient features of this molecule include the C(1)−S(1) and N(1)−S(1) bond lengths of 1.730 and 1.693 Å, respectively, which are slightly longer than the C−S (1.707 Å) and N−S (1.649 Å) bond lengths of monocyclic [1,2,4]thiadiazole.[1a] Accessibility to the sulfur atom of the bicyclic [1,2,4]THD ring is clearly not hampered by the methyl substituent at the N(4) nitrogen (Figure 3),[11,17,18] which is also referred to as the N1 position in the text. In addition, the aromatic ring bearing the nitro group is almost perpendicular to the plane of the bicyclic thiadiazole-spacer group.

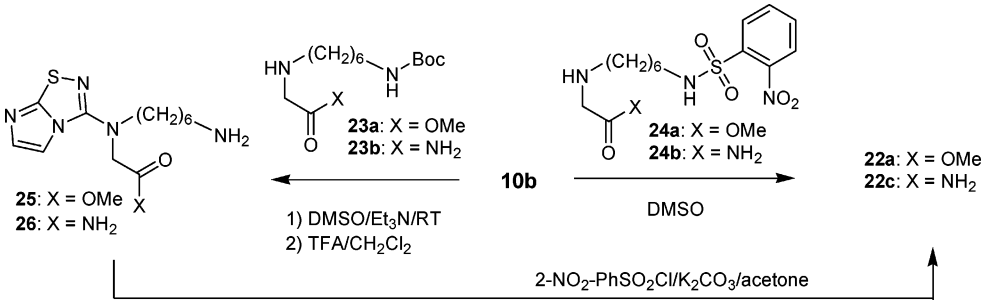
Other electrophiles were also employed using this pathway. For example, the methyl glycinate moiety was effectively introduced at the N1 position in the conversion of **12e** to **22a** (Scheme 7). The ester group provided a handle for other functional group interconversion such as transformation to the acid **22b** (79% yield) or the amide **22c** (91% yield).

While the synthetic route described above (Scheme 7) provided access to a wide variety of N1-functionalized [1,2,4]THDs, it suffered from several shortcomings. Namely, the synthesis was linear, and the THD moiety, which is the expensive part, was carried on in all the steps to the final product (e.g., Scheme 7). To address these issues, a disconnection at the 3-position of the THD was desirable from a retro-synthetic perspective. Consequently, this approach necessitated a nucleophilic displacement of the 3-*p*-tosyl group of **10b** with a secondary amine (e.g., **23**, **24**) as depicted in Scheme 8.

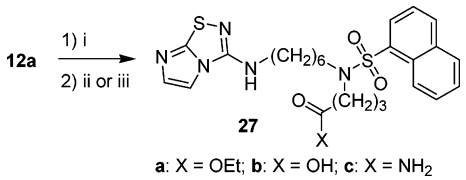
However, our initial efforts to react **10b** with the secondary amine **24a** under standard conditions (DMF/$Et_3N$/rt) were unsuccessful, as mainly starting materials were detected by TLC or by HPLC. Under more vigorous conditions (warming up to 100 °C), the formation of unidentified byproducts were observed, and the expected product **22a** was not detected, either by HPLC or by MS. The reaction was attempted in several different solvents, including DMPU, dichloromethane, and *i*-PrOH, without success. We were, eventually, gratified to find out that the reaction between **10b** and excess amine **24a**, when carried out in DMSO as solvent, yielded the desired product **22a** in reasonable yield (75%), after purification by column chromatography. With the appropriate choice of secondary amines, templates such as **25** and **26** were readily accessible, thereby allowing further derivatization at the N2 position (Scheme 8). This short synthetic strategy, thus, provided a convergent route to the N1-functionalized bicyclic [1,2,4]THDs.

As in the case of N1 derivatization, other electrophiles besides iodomethane could be employed for N2 functionalization. Accordingly, alkylation of **12a** with ethyl 4-bromobutyrate in the presence of potassium carbonate in acetone, under reflux conditions for 16 h, afforded compound **27a** in 72% yield, after purification by column chromatography. The ester moiety could further be transformed to other functionalities, such as the acid (**27b**) or the amide (**27c**) (Scheme 9).

**SCHEME 8. N1-Functionalized THD Derivatives: Substitution with Secondary Amines**

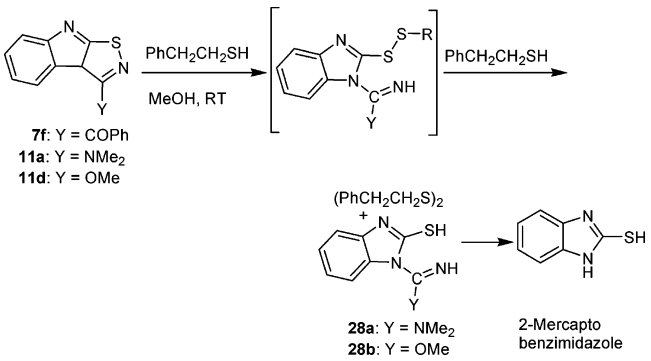


**SCHEME 9. Selective Functionalization at N2 Positions of 12a**[a]




[a] Reagents and conditions: (i) 2 equiv of $Br(CH_2)_3CO_2Et$, 7.1 equiv of $K_2CO_3$, acetone; (ii) for **27b**: 2 N NaOH/MeOH then neutralize; (iii) for **27c**: excess 28% aq $NH_4OH$, MeOH, rt, 16 h.

**SCHEME 10. Proposed Ring Opening of Tricyclic [1,2,4]THD Derivatives with Phenethyl Mercaptan**




**Stability of Fused-Ring [1,2,4]THDs.** Since we have an interest in the potential use of these compounds as cysteine protease inhibitors, we sought some information on the stability of these fused-ring [1,2,4]THD compounds under stress conditions in chemical systems and also in the presence of other nucleophiles.

Thus, a suspension of the tricyclic [1,2,4]THD derivative **7f** in the presence of 2.5 equiv. of phenethyl mercaptan in methanol slowly converted to 2-mercaptobenzimidazole (Scheme 10) over a period of 3 days at room temperature, as monitored by TLC ($CHCl_3$/MeOH as eluant, 100/2 ratio, v/v).[28] However, degradation of **7f** in the presence of a large excess of phenethyl mercaptan (25 equiv) occurred within ca. 2−3 h at room temperature. Interestingly, compounds **11a** and **11d** reacted with phenethyl mercaptan (25 equiv) in methanol at rt in less than 1 min to afford compounds **28a** and **28b**, respectively. After the mixture was stirred for another 2−3 h, compound **28b** further transformed to 2-mercaptobenzimidazole.

The results obtained can be rationalized via the proposed mechanism shown in Scheme 10.[14,18a] It involved the initial ring opening of the thiadiazole ring with phenethyl mercaptan to the disulfide intermediate. The latter then reacted with excess phenethyl mercaptan present to form phenethyl disulfide. Depending on the Y substituent, relatively stable intermediates such as **28a** or **28b** could be isolated and identified.[28] In the case of the latter, **28b** was further converted to 2-mercaptobenzimidazole.

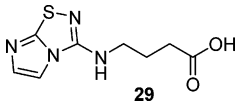



**FIGURE 4.** Structure of bicyclic THD **29**.

In contrast to its reactivity with phenethyl mercaptan, for example, the bicyclic [1,2,4]THD **12a** in dichloromethane solution was stable in the presence of 5 equiv. of *n*-butylamine at room temperature for 20 h. Additionally, **12a** was stable to acid or base in the pH range of 2−9.8 for at least 20 h at room temperature, as monitored by TLC (95/5 $CH_2Cl_2$/MeOH as eluant, $R_f = 0.21$), or by HPLC. However, about 60% of **12a** remained after stirring in a mixture of acetonitrile and 2 N sodium hydroxide (pH = 13.8) for 20 h, as monitored by HPLC. Nevertheless, stability of thiadiazole derivatives in strongly alkaline medium was dependent on the 3-substituent. For example, **29** (Figure 4) was stable at pH 13.7 for at least 20 h.

## Conclusion

A simple route to bicyclic and tricyclic 3-substituted [1,2,4]THD scaffolds is described.[29] The fused-ring templates (e.g., **7a** and **10b**) are advantageously used in substitution reactions with various nucleophiles that include amines, alcohols and malonate esters. With diamines as nucleophiles, further derivatization of the adducts can be selectively effected. As a result, an assortment of 3-substituted [1,2,4]THD derivatives is readily accessible.

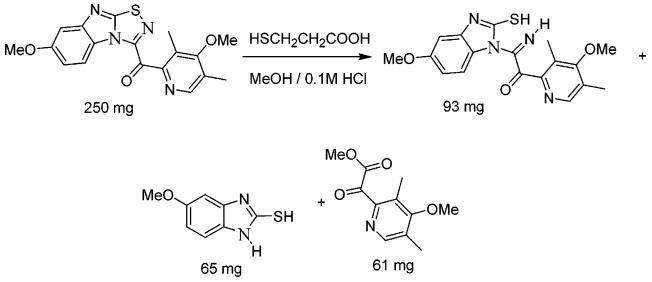
The fused-ring [1,2,4]THDs are stable in the presence of excess *n*-butylamine, and in buffers at the pH range of 2−9.8. However, their stabilities in strongly alkaline conditions (pH 13.7) are contingent on the nature of the 3-substituents. Additionally, the thiadiazoles decomposed in the presence of phenethyl mercaptan via heterocyclic N−S bond cleavage at rates that were dependent on the nature of the 3-substituents and the amount of phenethyl mercaptan used.

Results of studies of these classes of compounds in biological systems will be reported elsewhere.

## Experimental Section[17b,18c]

Usual workup and purification means that the organic layer was dried over $Na_2SO_4$, filtered, and evaporated to dryness. Chromatographic purification was then performed using the flash chromatography technique[30] on silica gel (Merck Kieselgel 60: 230−400 mesh) and the mixed solvent systems are indicated in the text. Reagents were purchased from com-

(28) Based on the experimental design (monitoring of 2-mercaptobenzimidazole), we cannot preclude the formation of an imine type intermediate like **28a** or **28b** in the case of **7f**. However, in a different system and different conditions, the intermediates shown below were isolated (see ref 18c):




(29) A major part of this work has been the subject of US patent 5,677,302, 1997 (ref 17b) and US patent application 20030225007A1, 2003 (ref 18c).

(30) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

mercial sources. 2-Mercaptoimidazole was purchased in bulk (kg quantity) from Lancaster, *n*-BuNCO (kg quantity) and *p*-TsCN (100's g) were supplied from Aldrich. 2-Butylbenzo-[4,5]imidazo[1,2-*d*][1,2,4]thiadiazol-3(2*H*)-one (**6**) was prepared according to the procedure reported by Martin and Wenzel.[20a]

**3-Bromobenzo[4,5]imidazo[1,2-*d*][1,2,4]thiadiazole (7a).** A mixture of **6** (5.00 g, 20.2 mmol) and cyanogen bromide (4.28 g, 40.4 mmol) in $CH_2Cl_2$ (100 mL) was stirred at room temperature rt for 26 h. The precipitate was collected by suction filtration and was thoroughly washed with $CH_2Cl_2$. Compound **7a** was obtained as a white powder (4.18 g): yield 81%; mp 189−190 °C; $^1$H NMR ($CDCl_3$) $\delta$: 8.23 (d, $J$ = 8.1 Hz, 1H), 7.82 (d, $J$ = 8.2 Hz, 1H), 7.52 (t, $J$ = 7.1 Hz, 1H) and 7.42 (d, $J$ = 7.2 Hz, 1H); $^{13}$C NMR (1:1 $CDCl_3$/DMSO-$d_6$) $\delta$ 162.8, 149.7, 129.2, 125.5, 122.2, 119.5, 117.3 and 111.3; IR (KBr) $\nu_{max}$ 1601 cm$^{-1}$; MS (CI) *m/z* 255 $[M + 1]^+$ (100), 254 (11, $M^+$), 148, 90; HRMS calcd for $C_8H_4N_3SBr$ 252.9309, found 252.9307. Anal. Calcd for $C_8H_4BrN_3S$: C, 37.81; H, 1.59; N, 16.54. Found: C, 37.44; H, 1.33; N, 16.57.

**2-Mercaptoimidazole-1-carboxylic Acid Butylamide (8).** A mixture of 2-mercaptoimidazole (24.4 g, 0.244 mol) and *n*-butyl isocyanate (48.3 g, 0.487 mol) was heated at 50 °C for 30 min or until the reaction was complete by TLC ($CH_2Cl_2$/MeOH, 95/5, v/v, $R_f$ of **8** = 0.22). The reaction mixture was then cooled to rt, and the solidified mass was triturated with hexanes (50 mL) for 30 min. The solid was filtered, washed with a minimum amount of hexane, and dried under reduced pressure to yield 45.0 g of **8** as beige crystals: yield 93%; mp 66−68 °C; $^1$H NMR ($CDCl_3$) $\delta$ 10.67 (br, 1H), 10.32 (br, 1H), 7.63 (s, 1H), 6.71 (s, 1H), 3.47 (br q, $J \approx$ 6.4 Hz, 2H, NHC$H_2$-$CH_2$),[31] 1.65 (quint, $J$ = 7.6 Hz, 2H, $NHCH_2CH_2CH_2$), 1.47 (sext, $J$ = 7.5 Hz, 2H, $CH_2CH_2CH_3$), 0.98 (t, $J$ = 7.3 Hz, 3H, $CH_3$); $^{13}$C NMR ($CDCl_3$) $\delta$: 160.9 (CS), 150.0(CO), 117.2 (CH), 113.8 (CH), 40.7($NCH_2$), 31.2, 20.3, 13.8($CH_3$); MS *m/z* 222 $[M + Na]^+$, 200 $[M + 1]^+$, 101 (100).

**2-Butylimidazo[1,2-*d*]-1,2,4-thiadiazole-3(2*H*)-one (9).** To an ice-cooled suspension of **8** (4.73 g, 23.7 mmol) in $CH_2Cl_2$ (15 mL) was added dropwise a bromine (3.79 g, 23.7 mmol) solution in $CH_2Cl_2$ (15 mL) under a blanket of nitrogen. After the addition was complete, a solution of $Et_3N$ (4.81 g, 47.5 mmol) in $CH_2Cl_2$ (15 mL) was added at such a rate that the temperature of the reaction mixture did not exceed 0 °C. The reaction mixture was maintained at 0 °C for an additional 2 h and then stirred at rt for 16 h. The mixture was diluted with $CH_2Cl_2$ (150 mL), and the organic layer was washed twice with water and then with brine. The organic fraction was dried over $MgSO_4$, filtered, and evaporated to dryness to afford 4.30 g of **9** as an off-white powder: yield 92%; mp 142−143 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.60 (s, 1H), 7.35 (s, 1H), 3.78 (t, $J$ = 7.2 Hz, 2H, $NCH_2CH_2$), 1.76 (quint, $J$ = 7.4 Hz, 2H, $CH_2CH_2CH_2$), 1.46 (sext, $J$ = 7.3 Hz, 2H, $CH_2CH_2CH_3$), 1.00 (t, $J$ = 7.4 Hz, 3H, $CH_3$); $^{13}$C NMR ($CDCl_3$) $\delta$ 147.2, 145.0, 133.7, 113.1, 44.8 ($NCH_2$), 31.1 ($NCH_2CH_2$), 19.7 ($CH_2CH_3$), 13.5 ($CH_3$); IR (KBr) $\nu_{max}$ 1702 (C=O) cm$^{-1}$; MS *m/z* 199 $[M + 1]^+$, 101 (100), 69. Anal. Calcd for $C_8H_{11}N_3OS$: C, 48.71; H, 5.62; N, 21.30. Found: C, 48.48; H, 5.44; N, 21.26.

**3-[(4-Methylphenyl)sulfonyl]imidazo[1,2-*d*][1,2,4]-thiadiazole (10b).** A mixture of **9** (34.5 g, 0.175 mol) and *p*-TsCN (36.2 g, 0.200 mol) in $CH_2Cl_2$ (600 mL) was stirred at rt for 16 h. The white solid was collected by suction filtration. The mother liquor was concentrated to ca. half-volume as more solid separated. The solid was again collected by filtration. The latter two steps were repeated twice more. The solids from the four crops were combined, then suspended in EtOAc (150 mL) and stirred at rt for about 30 min. Hexane (150 mL) was added, and the solid was collected by suction filtration. **10b** was dried to constant weight (37.0 g) under vacuum at 45 °C for 4 h: yield 76%; mp 185−186 °C; $^1$H NMR ($CDCl_3$) $\delta$ 8.08 (br s, 1H), 8.01 (d, $J$ = 7.9 Hz, 2H), 7.52 (br, 1H), 7.45 (d, $J$ = 7.9 Hz, 2H), 2.50 (s, 3H, $CH_3$); $^{13}$C NMR ($CDCl_3$ + few drops of $CD_3OD$) $\delta$ 159.6, 147.7, 145.4, 138.5 (CH), 133.2, 130.6 (2C, CH), 129.1 (2C, CH), 113.3 (CH), 21.8 ($CH_3$); MS *m/z* 280 $[M + 1]^+$, 239, 155, 99 (100). Anal. Calcd for $C_{11}H_9N_3O_2S_2$: C, 47.30; H, 3.25; N, 15.04. Found: C, 46.86; H, 3.31; N, 14.92.

**3-Dimethylaminobenzo[4,5]imidazo[1,2-*d*][1,2,4]-thiadiazole (11a).** To an ice-cooled mixture of **7a** (15.4 g, 0.060 mmol) in $CH_2Cl_2$ was added dimethylamine (40% solution in water, 5.44 g, 0.121 mol) dropwise. The resulting mixture was allowed to warm to rt and stirred for 16 h. The mixture was diluted with $CH_2Cl_2$ and then washed with water. The organic fraction was collected, dried ($Na_2SO_4$), filtered, and evaporated to dryness. Compound **11a** was obtained as a colorless crystalline solid (10.5 g): yield 80%; mp 102−104 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.72−7.76 (m, 2H), 7.41 (t, $J$ = 8.2 Hz, 1H), 7.27 (t, $J$ = 8.2 Hz, 1H) and 3.06 (s, 6H, 2C$H_3$); MS (EI) *m/z* 218 $[M]^+$, 177, 150, 90. Anal. Calcd for $C_{10}H_{10}N_4S$: C, 55.03; H, 4.62; N, 25.69. Found: C, 54.53; H, 4.90; N, 25.50.

***N*-[6-(Benzo[4,5]imidazo[1,2-*d*][1,2,4]thiadiazol-3-ylamino)hexyl]-2-nitrobenzenesulfonamide (11b).**: A mixture of **7a** (381 mg, 1.5 mmol), *N*-(6-aminohexyl)-2-nitrobenzene-sulfonamide (903 mg, 3.0 mmol), and $Et_3N$ (2.0 mL) in DMF (15 mL) was stirred at rt for 16 h. Volatiles were removed in vacuo, and the residue was partitioned between $CH_2Cl_2$ and a solution of 10% citric acid. After usual workup ($CH_2Cl_2$/EtOAc, 9/1 then 8/2, v/v, as eluant), **11b** was obtained as a light yellow solid (420 mg): yield 59%; mp 183−183 °C; $^1$H NMR ($CDCl_3$ + $CD_3OD$) $\delta$ 8.01−8.03 (m, 1H), 7.83 (d, $J$ = 8.1 Hz, 1H), 7.74−7.77 (m, 1H), 7.63−7.68 (m, 3H), 7.36 (t, $J$ = 7.7 Hz, 1H), 7.24 (t, $J$ = 7.8 Hz, 1H), 3.44 (t, $J$ = 7.1 Hz, 2H, $NCH_2CH_2$), 3.01 (t, $J$ = 6.8 Hz, 2H, $NCH_2CH_2$), 1.67 (br quint, 2H, NCH2C$H_2$-$CH_2$), 1.49 (br quint, 2H, $NCH_2CH_2CH_2$), 1.32−1.36 (m, 4H, 2C$H_2$); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 163.9 (C), 150.1 (C), 147.8 (C), 145.8 (C), 133.9 (CH), 132.9 (C), 132.5 (CH), 129.4 (CH), 128.2 (C), 124.31 (CH), 124.29 (CH), 120.9 (CH), 118.3 (CH), 111.9 (CH), 42.6 ($NCH_2$), 42.3 ($NCH_2$), 29.1 ($CH_2$), 28.4 ($CH_2$), 25.9 ($CH_2$), 25.7 ($CH_2$); MS *m/z* 475 $[M + 1]^+$, 327, 149. Anal. Calcd for $C_{20}H_{22}N_6O_4S_2$: C, 50.62; H, 4.67; N, 17.71. Found: C, 50.37; H, 5.10; N, 17.51.

**2-Benzo[4,5]imidazo[1,2-*d*][1,2,4]thiadiazol-3-ylmalonic Acid Diethyl Ester (11c).** A mixture of **7a** (0.20 g, 0.78 mmol), diethyl malonate (0.15 g, 0.94 mmol), and $Et_3N$ (0.13 mL, 0.94 mmol) in THF (8 mL) was refluxed under a nitrogen atmosphere for 36 h. The resulting mixture was extracted with EtOAc and washed with water followed by a 10% aqueous sodium sulfate solution. After usual workup (hexane/EtOAc, 65/35, v/v, as eluant), **11c** was obtained as a yellow oil (0.14 g): yield 54%; $^1$H NMR ($CDCl_3$) $\delta$ 9.48 (s, 1H), 8.06 (d, $J$ = 6.9 Hz, 1H), 7.64 (d, $J$ = 6.3 Hz, 1H), 7.31−7.35 (m, 2H), 4.39 (q, $J$ = 7.3 Hz, 4H, 2 O$CH_2$), 1.35 (t, $J$ = 7.4 Hz, 6H, 2 $CH_3$); $^{13}$C NMR ($CDCl_3$) $\delta$ 163.8, 153.7, 151.3, 149.4, 131.2, 124.9, 123.7, 119.0, 112.8, 69.6, 64.6, 13.7; IR (film) $\nu_{max}$ 1748 cm$^{-1}$; MS (EI) *m/z* 333 $[M]^+$ (100%), 215, 161; HRMS calcd for $C_{15}H_{15}N_3O_4S$ 333.0783, found 333.0794.

**3-Methoxybenzo[4,5]imidazo[1,2-*d*][1,2,4]thiadiazole (11d).** Sodium methoxide (0.967 g, 17.9 mmol) was added in one portion to an ice-cooled mixture of **7a** (4.55 g, 17.9 mmol) in methanol (50 mL). The cooling bath was removed, and the mixture was stirred for 4 h at rt. Volatile materials were removed in vacuo, and the residue was taken up in EtOAc and washed with water. The organic layer was dried over $Na_2SO_4$, filtered, and evaporated to yield 3.64 g of **11d** as colorless crystals: yield 94%; mp 172−175 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.83 (d, $J$ = 8.1 Hz, 1H), 7.75 (d, $J$ = 8.2 Hz, 1H), 7.42 (t, $J$ = 8.0 Hz, 1H), 7.27 (t, $J$ = 8.2 Hz, 1H), 4.32 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 163.2, 150.3, 148.1, 128.2, 124.9, 121.8, 119.2, 111.7, 57.5;

(31) We have noticed coupling with NH for $NHCH_2CH_2$ protons in the $^1$H NMR spectrum (showing a slightly unresolved q signal, or alternatively an unresolved dt signal) in cases when nonprotic deuterated solvents were used (e.g., **13** in DMSO or **8** in $CDCl_3$). However, t signal is observed in the presence of, or with addition of a protic deuterated solvent (e.g., **11b** in $CDCl_3$ + $CD_3OD$). For a literature example of the description of the multiplicity (br q or unresolved q) of a $NHCH_2CH_2$ and its associated $J$ value ($\approx$ 6 Hz), see: Grehn, L.; Ragnarsson, U. *J. Org. Chem*. **2002**, *67*, 6557−6559.

IR (KBr) $\nu_{max}$ 1595 cm$^{-1}$; MS (EI) *m/z* 205 [M]$^+$, 150, 90. Anal. Calcd for $C_9H_7N_3OS$: C, 52.67; H, 3.44; N, 20.49. Found: C, 52.28; H, 3.36; N, 20.45.

**Synthesis of Sulfonamides: Route 1. *N*-[6-(Imidazo-[1,2-*d*][1,2,4]thiadiazol-3-ylamino)hexyl]naphthalene-1-sulfonamide (12a).** A mixture of **10b** (3.94 g, 14.1 mmol), *N*-(6-aminohexyl)naphthalene-1-sulfonamide (6.50 g, 21.2 mmol), and $Et_3N$ (5.8 mL, 42 mmol) in DMF (75 mL) was stirred at rt overnight. Volatile materials were removed in vacuo, and the residue was partitioned between water (75 mL) and EtOAc (100 mL). The aqueous layer was extracted with EtOAc (100 mL). The combined organic fractions were then successively washed with a 10% citric acid solution (25 mL), water (50 mL), and a saturated sodium carbonate solution (25 mL). After usual workup (MeOH/$CH_2Cl_2$, 3/97, v/v, as eluant), **12a** was obtained as a white solid (5.10 g): yield 84%; mp 144−145 °C; $^1$H NMR ($CDCl_3$) $\delta$ 8.67 (d, $J$ = 7.7 Hz, 1H), 8.22 (t, $J$ = 6.9 Hz, 1H), 8.05 (d, $J$ = 7.8 Hz, 1H), 7.92 (d, $J$ = 7.2 Hz, 1H), 7.50−7.62 (m, 4H), 7.24−7.28 (m, 1H), 5.61−5.80 (br, 1H, N*H*), 5.18−5,32 (br, 1H, N*H*), 3.37 (br q, $J \approx$ 6.4 Hz, 2H, NHC$H_2$CH$_2$), 2.88 (br q, $J \approx$ 6.3 Hz, 2H, NHC$H_2$CH$_2$), 1.50 (br quint, 2H, NCH$_2$C$H_2$CH$_2$), 1.36 (br quint, 2H, NCH$_2$C$H_2$-CH$_2$), 1.15−1.25 (m, 4H, 2CH$_2$); $^{13}$C NMR ($CDCl_3$) $\delta$ 161.3, 158.8, 143.7, 137.2 (CH), 134.7, 134.3 (CH), 129.5 (CH), 129.1 (CH), 128.4 (CH), 128.1, 126.9 (CH), 124.4 (CH), 124.1 (CH), 109.5 (CH), 42.8 (N*C*H$_2$), 41.5 (N*C*H$_2$), 29.2 (CH$_2$), 28.7 (CH$_2$), 25.6 (CH$_2$), 25.5 (CH$_2$); MS *m/z* 430 [M + 1]$^+$, 388, 220. Anal. Calcd for $C_{20}H_{23}N_5O_2S_2$: C, 55.92; H, 5.40; N, 16.30. Found: C, 55.99; H, 5.61; N, 16.30.

**2-Amino-*N*-[6-(imidazo[1,2-*d*][1,2,4]thiadiazol-3-ylamino)hexyl]benzenesulfonamide (12g).** A mixture of *tert*-butyl 6-{[(2-nitrophenyl)sulfonyl]amino}hexylcarbamate (see preparation of **30a** in the Supporting Information) (5.00 g, 12.5 mmol) and Pd/C (0.400 g, 10% wet) in EtOH (150 mL) was hydrogenated at 50 psi pressure of hydrogen at ambient temperature for 16 h. Nitrogen gas was bubbled in the reaction mixture, and Celite was added. The mixture was filtered over a pad of Celite, and the cake was thoroughly washed with MeOH. The filtrate was cooled in an ice bath, and HCl gas was bubbled through for 25 min. The cooling bath was removed, and the resulting mixture was stirred at rt for 3 h. Volatiles were removed in vacuo, and the residue was partitioned between a 1 N NaOH solution and EtOAc. The aqueous layer was extracted with EtOAc, and the combined organic fractions were washed with brine, dried, filtered, and concentrated to a brown oil (3.30 g).

The 2-amino-*N*-(6-aminohexyl)benzenesulfonamide obtained above was used directly in reaction with **10b** to afford the desired compound **12g** as a light orange solid: yield 65%; mp 138−139 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 7.83−7.86 (m, 2H), 7.44−7.46 (m, 2H), 7.21−7.28 (m, 2H), 6.77−6.79 (m, 1H), 6.57−6.59 (m, 1H), 5.86 (br, 2H, N$H_2$), 3.31−3.35 (m, 2H, NHC$H_2$-CH$_2$, masked under HDO peak), 3.33 (br s, HDO), 2.70 (br unresolved q, 2H, NHC$H_2$CH$_2$), 1.54 (br quint, 2H, NCH$_2$C$H_2$-CH$_2$), 1.35 (br quint, 2H, NCH$_2$C$H_2$CH$_2$) and 1.20−1.28 (m, 4H, 2CH$_2$); $^{13}$C NMR ($CDCl_3$) $\delta$ 156.8 (C), 146.2 (C$_{ipso}$), 144.2 (C), 136.7 (CH), 133.3 (CH), 129.0 (CH), 120.0 (*C*NO$_2$), 116.8 (CH), 115.0 (CH), 111.3 (CH), 42.0 (N*C*H$_2$), 41.7 (N*C*H$_2$), 28.8 (CH$_2$), 28.5 (CH$_2$), 25.9 (CH$_2$), 25.7 (CH$_2$); MS *m/z* 395 [M + 1]$^+$, 378, 280. Anal. Calcd for $C_{16}H_{22}N_6O_2S_2$: C, 48.71; H, 5.62; N, 21.30. Found: C, 47.16; H, 5.56; N, 20.43 (adjusted for water content: Anal. Calcd for (**12g** hemihydrate) $C_{16}H_{22}N_6O_2S_2\cdot 0.5H_2O$: C, 47.62; H, 5.75; N, 20.83).

**Synthesis of sulfonamides: Route 2. 3-[6-(Imidazo[1,2-*d*][1,2,4]thiadiazol-3-ylamino)hexylsulfamoyl]benzoic Acid (12h).** A mixture of **16** (310 mg, 1.30 mmol), 3-chlorosulfonylbenzoic acid (314 mg, 1.40 mmol), and $Et_3N$ (0.70 mL, 5.2 mmol) in $CH_3CN$ (15 mL) was stirred at ambient temperature for overnight. Silica gel was added, and the mixture was evaporated to dryness. The residue was poured onto a wet prepacked silica gel column, and the product was eluted using a solvent mixture of MeOH/$CH_2Cl_2$ (30/70, v/v). Compound **12h** (440 mg) was obtained as a white solid: Yield 80%; mp >230 °C dec; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.57 (br t, $J \approx$ 6.9 Hz, 1H, N*H*), 8.10 (s, 1H), 7.94 (br t, $J \approx$ 7.1 Hz, 1H, N*H*), 7.87 (s, 1H), 7.71−7.78 (m, 2H), 7.40 (t, $J$ = 7.7 Hz, 1H), 7.30 (s, 1H), 3.30 (partially HDO masked, br q, 2H, $J \approx$ 5.8 Hz, 2H, NHC$H_2$-CH$_2$), 3.34 (br s, HDO), 2.50 (masked under DMSO signal, m, 2H, NHC$H_2$CH$_2$), 2.51 (br, DMSO), 1.63 (br quint, 2H, NCH$_2$C$H_2$CH$_2$), 1.55 (br quint, 2H, NCH$_2$C$H_2$CH$_2$), 1.30−1.40 (m, 4H, 2CH$_2$); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 165.8 (CO), 156.8 (C), 148.1 (C), 144.3 (C$_{ipso}$), 136.8 (CH), 134.4 (*C*CO), 128.0 (CH), 127.8 (CH), 127.4 (CH), 124.5 (CH), 111.4 (CH), 41.8 (N*C*H$_2$), 39.7 (N*C*H$_2$), 29.1 (CH$_2$), 28.6 (CH$_2$), 26.3 (CH$_2$), 26.2 (CH$_2$); MS *m/z* 424 [M + 1]$^+$, 326, 143 (100). Anal. Calcd for $C_{17}H_{21}N_5O_4S_2$: C, 48.21; H, 5.00; N, 16.54. Found: C, 42.63; H, 4.95; N, 14.66 (adjusted for water content: Anal. Calcd for $C_{17}H_{21}N_5O_4S_2\cdot 3H_2O$ (**12h** trihydrate): C, 42.85; H, 5.50; N, 14.70).

***N*-[6-(Imidazo[1,2-*d*][1,2,4]thiadiazol-3-ylamino)hexyl]-methanesulfonamide (12n).** A mixture of **16** (0.42 g, 1.5 mmol), methanesulfonyl chloride (0.12 mL, 1.5 mmol), and $K_2CO_3$ (0.50 g, 3.6 mmol) in acetone (25 mL) was stirred at rt for 16 h. The mixture was filtered over a pad of Celite, and the cake was thoroughly washed with small portions of acetone. Volatile materials were removed in vacuo, and the crude product was purified by column chromatography on silica gel using a mixture of MeOH/$CH_2Cl_2$ (5/95, v/v) as eluant. Compound **12n** (0.32 g) was obtained as a waxy white solid: yield 66%; mp 98−99 °C; $^1$H NMR (DMSO-$d_6$) $\delta$: 7.94 (br, 1H, NH), 7.86 (s, 1H), 7.31 (s, 1H), 6.94 (br, 1H, NH), 3.32−3.36 (m, 2H, masked by HDO peak), 3.35 (br s, HDO), 2.92 (br q, $J \approx$ 6.3 Hz, 2H, NHC$H_2$CH$_2$), 2.87 (s, 3H, C$H_3$), 1.62 (br quint, 2H, NCH$_2$C$H_2$CH$_2$), 1.46 (quint, $J \approx$ 6.6 Hz, 2H, NCH$_2$C$H_2$-CH$_2$), 1.30−1.40 (m, 4H, 2CH$_2$); $^{13}$C NMR (DMSO-$d_6$) $\delta$: 156.8 (C), 144.2 (C), 136.8 (CH), 111.2 (CH), 42.4 (N*C*H$_2$), 41.7 (N*C*H$_2$), 39.1 (CH$_3$), 29.4 (CH$_2$), 28.5 (CH$_2$), 26.0 (CH$_2$), 25.9 (CH$_2$); MS *m/z* 318 [M + 1]$^+$, 220 (100), 178, 108. Anal. Calcd for $C_{11}H_{19}N_5O_2S_2$: C, 41.62; H, 6.03; N, 22.06. Found: C, 42.12; H, 6.06; N, 21.58.

**Cyano-*N*-[6-(imidazo[1,2-*d*][1,2,4]thiadiazol-3-ylamino-)hexyl]benzenesulfonamide (12i):** yield 62%; mp 131−132 °C; $^1$H NMR ($CDCl_3$ + DMSO-$d_6$) $\delta$ 7.92 (br, 1H, N*H*), 7.70−7.74 (m, 1H), 7.60−7.65 (m, 2H), 7.56 (s, 1H), 7.10 (s, 1H), 7.00 (br, 1H, N*H*), 3.62 (br q, 2H, NHC$H_2$CH$_2$), 3.26 (br q, $J \approx$ 6.1 Hz, 2H, NHC$H_2$CH$_2$), 1.73 (br quint, 2H, NCH$_2$C$H_2$CH$_2$), 1.55 (br quint, 2H, NCH$_2$C$H_2$CH$_2$), 1.30−1.36 (m, 4H, 2CH$_2$); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 156.8 (C), 152.1 (C), 144.2 (C$_{ipso}$), 136.8 (CH), 135.8 (CH), 133.8 (CH), 132.8 (CH), 128.7 (CH), 116.2 (CN), 111.2 (CH), 109.0 (*C*CN), 42.5 (N*C*H$_2$), 41.7 (N*C*H$_2$), 29.0 (CH$_2$), 28.4 (CH$_2$), 26.0 (CH$_2$), 25.9 (CH$_2$); MS *m/z* 405 [M + 1]$^+$, 307 (100), 265, 183. Anal. Calcd for $C_{17}H_{20}N_6O_2S_2$: C, 50.48; H, 4.98; N, 20.78. Found: C, 50.75; H, 5.34; N, 20.48.

**2,4-Dibromo-*N*-[6-(imidazo[1,2-*d*][1,2,4]thiadiazol-3-ylamino)hexyl]benzene sulfonamide (12j):** yield 89%; mp 61−62 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.12 (s, 1H), 7.81−7.94 (m, 5H, 3 Ar-H + 2N*H*), 7.30 (s, 1H), 3.28−3.36 (HDO masked m, 2H, NHC$H_2$CH$_2$), 2.85 (br q, 2H, NHC$H_2$CH$_2$), 1.53 (br quint, 2H, NCH$_2$C$H_2$CH$_2$), 1.37 (br quint, 2H, NCH$_2$C$H_2$CH$_2$), 1.20−1.30 (m, 4H, 2CH$_2$); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.0 (C), 144.1 (C), 138.0 (C$_{ipso}$), 137.6 (CH), 137.2 (CH), 132.6 (CH), 131.3 (CH), 127.9 (CBr), 120.7 (CBr), 110.0 (CH), 43.1 (N*C*H$_2$), 42.5 (N*C*H$_2$), 29.4 (CH$_2$), 29.0 (CH$_2$), 26.1 (CH$_2$), 26.0 (CH$_2$); MS *m/z* 540 [M + 3]$^+$, 539 [M + 2]$^+$, 538 [M + 1]$^+$, 536, 438, 396. Anal. Calcd for $C_{16}H_{19}Br_2N_5O_2S_2$: C, 35.77; H, 3.56; N, 13.03. Found: C, 36.14; H, 3.78; N, 12.81.

***N*-Imidazo[1,2-*d*][1,2,4]thiadiazol-3-yl-*N*′-(3-nitropyridin-2-yl)-hexane-1,6-diamine (14).** Triethylamine (0.9 mL, 6.0 mmol) was added to a suspension of the HCl salt of **16** (0.38 g, 1.2 mmol) in DMF (40 mL) at ambient temperature. After 10 min, 2-chloro-3-nitropyridine (0.24 g, 1.5 mmol) was added all at once. The resulting mixture was stirred at rt over 2 days. After usual workup (MeOH/$CH_2Cl_2$, 10/90, v/v, as eluant), **14** was obtained as a solid (0.19 g): yield 43%; mp

147−148 °C; $^1$H NMR (DMSO-$d_6$) $\delta$: 8.67 (br, 2H), 8.41 (d, $J$ = 7.2 Hz, 1H), 7.88−7.94 (br m, 1H), 7.85 (s, 1H), 7.30 (s, 1H), 6.72−6.76 (m, 1H), 3.58 (br q, $J \approx$ 6.3 Hz, 2H, NHC$H_2$CH$_2$), 3.31−3.38 (m, 2H), 3.30 (br s, HDO), 1.60−1.70 (m, 4H, 2NCH$_2$C$H_2$), 1.35−1.45 (m, 4H, 2CH$_2$); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 156.8 (C), 156.1 (CH), 152.0 (C$_{ipso}$py), 144.2 (C), 136.8 (CH), 135.2 (CH), 127.2 (*C*NO$_2$), 111.6 (CH), 111.2 (CH), 41.7 (N*C*H$_2$), 40.6 (N*C*H$_2$), 28.7 (CH$_2$), 28.5 (CH$_2$), 26.18 (CH$_2$), 26.20 (CH$_2$); MS *m/z* 362 [M + 1]$^+$, 264 (100), 99. Anal. Calcd for $C_{15}H_{19}N_7O_2S$: C, 49.85; H, 5.30; N, 27.13. Found: C, 50.09; H, 5.30; N, 26.87.

**4-Cyano-*N*-[6-(imidazo[1,2-*d*][1,2,4]thiadiazol-3-ylamino)hexyl]-2-nitrobenzenesulfonamide (12k).** A mixture of the HCl salt of **16** (0.83 g, 3.0 mmol) and 4-cyano-2-nitrobenzenesulfonyl chloride (prepared according to GB patent 1,426,405) in $CH_2Cl_2$ (125 mL), water (40 mL), and 2 N NaOH (10 mL) was stirred at rt for 15 min. The organic layer was collected and successively washed with water, a 10% citric acid solution, and water. After usual workup (100% $CH_2Cl_2$ then 95/5 $CH_2Cl_2$/MeOH, v/v, as eluant), **12k** (0.65 g) was obtained as a light brown foamy solid: yield 48%; mp 62−65 °C; $^1$H NMR ($CDCl_3$) $\delta$ 8.05 (d, $J$ = 8.2 Hz, 1H), 7.88−7.92 (m, 1H), 7.81 (d, $J$ = 8.2 Hz, 1H), 7.66 (s, 1H), 7.30 (br, 2H, 2N*H*), 7.05 (s, 1H), 3.14 (br q, $J \approx$ 6.0 Hz, 2H, NHC$H_2$CH$_2$), 2.78 (br q, $J \approx$ 6.0 Hz, 2H, NHC$H_2$CH$_2$), 1.42 (br quint, $J \approx$ 6.4 Hz, 2H, NCH$_2$C$H_2$CH$_2$), 1.30 (br quint, $J \approx$ 6.4 Hz, 2H, NCH$_2$C$H_2$CH$_2$), 1.10−1.15 (m, 4H, 2CH$_2$); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 156.8 (C), 146.9 (C$_{ipso}$), 144.2 (C), 137.6 (CH), 136.9 (CH), 132.0 (CH), 130.6 (*C*NO$_2$), 118.3 (CN), 115.8 (CH), 111.2 (CH), 96.1 (*C*CN), 42.3 (N*C*H$_2$), 41.7 (N*C*H$_2$), 28.5 (CH$_2$), 28.0 (CH$_2$), 26.1 (CH$_2$), 26.0 (CH$_2$); MS *m/z* 450 [M + 1]$^+$, 352, 240, 99.

**4-[6-(Imidazo[1,2-*d*][1,2,4]thiadiazol-3-ylamino)hexylsulfamoyl]-3-nitrobenzoic Acid (12l).** A mixture of the HCl salt of **16** (1.40 g, 5.1 mmol) and 4-chlorosulfonyl-3-nitrobenzoic acid methyl ester (1.45 g, 5.2 mmol) in $CH_2Cl_2$ (50 mL), water (40 mL), and 2 N NaOH (10 mL) was stirred at rt for 90 min. The progress of reaction was monitored by TLC (8/2/0.5 $CH_2Cl_2$/MeOH/$NH_4OH$, v/v/v as eluant; $R_f$ of **12l** = 0.22). The aqueous layer was collected and acidified with a 10% citric acid solution as a dense precipitate separated. The solid was collected by suction filtration and dried under vacuum at 45 °C for 4 h. **12l** was obtained as a white solid (1.80 g): yield 73%; mp 172−175 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.37 (s, 1H), 8.33 (d, $J$ = 8.3 Hz, 1H), 8.23 (br t, $J \approx$ 5.1 Hz, 1H, N*H*), 8.11 (d, $J$ = 8.1 Hz, 1H), 7.89 (br t, $J \approx$ 5.0 Hz, 1H, N*H*), 7.85 (s, 1H), 7.30 (s, 1H), 3.30 (q, $J \approx$ 6.2 Hz, 2H, NHC$H_2$CH$_2$), 2.93 (q, $J \approx$ 6.3 Hz, 2H, NHC$H_2$CH$_2$), 1.54 (br quint, 2H, NCH$_2$C$H_2$CH$_2$), 1.44 (br quint, 2H, NCH$_2$C$H_2$CH$_2$), 1.25−1.30 (m, 4H, 2CH$_2$); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 164.6 (CO), 147.7 (C), 144.2 (C), 136.9 (CH), 136.2 (C), 135.9 (C), 132.9 (CH), 130.1 (CH), 124.9 (CH), 111.3 (CH), 42.7 (N*C*H$_2$), 41.6 (N*C*H$_2$), 29.1 (CH$_2$), 28.5 (CH$_2$), 25.9 (CH$_2$), 25.6 (CH$_2$); MS *m/z* 469 [M + 1]$^+$, 371, 259.

**5-Bromo-6-chloropyridine-3-sulfonic acid [6-(imidazo[1,2-*d*][1,2,4]thiadiazol-3-ylamino)hexyl]amide (12m):** yield 45%; mp 146−150 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.76 (s, 1H), 8.51 (s, 1H), 7.97 (br t, $J \approx$ 5.2 Hz, 1H, N*H*), 7.90 (br t, $J \approx$ 5.0 Hz, 1H, N*H*), 7.85 (s, 1H), 7.30 (s, 1H), 3.31−3.35 (masked under HDO peak, m, 2H, NHC$H_2$CH$_2$), 3.33 (br s, HDO), 2.85 (br q, $J \approx$ 5.6 Hz, 2H, NHC$H_2$CH$_2$), 1.57 (br quint, 2H, NCH$_2$C$H_2$CH$_2$), 1.40 (br quint, 2H, NCH$_2$C$H_2$CH$_2$), 1.20−1.30 (m, 4H, 2CH$_2$); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 156.8 (C), 152.9 (C), 145.9 (CH), 144.2 (C), 140.5 (CH), 137.3 (C), 136.8 (CH), 120.3 (C), 111.2 (CH), 42.5 (N*C*H$_2$), 41.7 (N*C*H$_2$), 29.0 (CH$_2$), 28.5 (CH$_2$), 25.9 (CH$_2$), 25.7 (CH$_2$); MS *m/z* 497 [M + 4]$^+$, 495 [M + 2]$^+$, 493 [M]$^+$, 395 (100), 353, 283. Anal. Calcd for $C_{15}H_{18}BrClN_6O_2S_2$: C, 36.48; H, 3.67; N, 17.02. Found: C, 37.08; H, 3.83; N, 17.02.

***N*-[6-(Imidazo[1,2-*d*][1,2,4]thiadiazol-3-ylamino)hexyl]-2-nitrobenzamide (13).** A mixture of **16** (0.24 g, 1.0 mmol), 2-nitrobenzoyl chloride (0.22 mg, 1.2 mmol), and $Et_3N$ (0.28 mL, 2.0 mmol) in $CH_2Cl_2$ (25 mL) was stirred at rt for 3 d. The mixture was quenched with a 10% citric acid solution. The organic fraction was collected and successively washed with water, a saturated $Na_2CO_3$ solution and water. The organic layer was dried over $Na_2SO_4$, filtered, and evaporated to dryness. A light yellow solid was obtained upon trituration with a small amount of $CH_2Cl_2$. The solid was collected by filtration, suspended in EtOAc, and the mixture was stirred for 10 min. **13** was collected as an off-white solid and was dried at 45 °C under vacuum for 2 h: yield 0.25 g (63%); mp 152−153 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.63 (br t, $J \approx$ 4.8 Hz, 1H, N*H*), 8.02 (d, $J$ = 8.0 Hz, 1H), 7.93 (br t, $J \approx$ 5.0 Hz, 1H, N*H*), 7.86 (s, 1H), 7.77 (t, $J$ = 7.3 Hz, 1H), 7.67 (t, $J$ = 7.7 Hz, 1H), 7.58 (d, $J$ = 7.4 Hz, 1H), 7.30 (s, 1H), 3.35 (partially masked, br q, $J \approx$ 6.6 Hz, 2H, NHC$H_2$CH$_2$), 3.33 (br s, HDO), 3.22 (br q, $J \approx$ 6.5 Hz, 2H, NHC$H_2$CH$_2$), 1.64 (br quint, $J \approx$ 6.4 Hz, 2H, NCH$_2$C$H_2$CH$_2$), 1.54 (br quint, $J \approx$ 6.2 Hz, 2H, NCH$_2$C$H_2$CH$_2$), 1.35−1.45 (m, 4H, 2CH$_2$); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 165.3 (CO), 156.9 (C), 147.1 (C), 144.2 (C), 136.8 (CH), 133.5 (CH), 132.9 (C), 130.5 (CH), 129.0 (CH), 124.0 (CH), 111.3 (CH), 41.8 (N*C*H$_2$), 39.0 (N*C*H$_2$), 28.7 (CH$_2$), 28.6 (CH$_2$), 26.2 (CH$_2$), 26.1 (CH$_2$); MS *m/z* 389 [M + 1]$^+$, 291, 143 (100).

**General Method for N2 Alkylation. *N*-[6-(Imidazo[1,2-*d*][1,2,4]thiadiazol-3-ylamino)hexyl]-*N*-methyl-2-nitrobenzenesulfonamide (17).** A mixture of **12e** (0.26 g, 0.60 mmol), $CH_3I$ (0.11 mL, 1.8 mmol), and potassium carbonate (0.62 g, 4.5 mmol) in acetone (15 mL) was stirred at ambient temperature for 16 h. The mixture was filtered through a pad of Celite, and the cake was thoroughly washed with acetone. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography on silica gel using a mixture of solvents (5% MeOH in $CH_2Cl_2$) as eluant thereby affording **17** (0.20 g) as a dense light yellow oil: yield 76%; $^1$H NMR ($CDCl_3$) $\delta$ 7.97 (d, $J$ = 6.8 Hz, 1H), 7.69−7.74 (m, 2H), 7.64−7.66 (m, 1H), 7.45 (s, 1H), 7.33 (s, 1H), 5.53 (br t, $J \approx$ 5.6 Hz, 1H, N*H*), 3.52 (br q, $J \approx$ 6 Hz, 2H, NHC$H_2$CH$_2$), 3.28 (t, $J$ = 6.6 Hz, 2H, NC$H_2$), 2.88 (s, 3H, NC$H_3$), 1.72 (br quint, $J \approx$ 6.4 Hz, 2H, NCH$_2$C$H_2$CH$_2$), 1.63 (br quint, $J \approx$ 6.4 Hz, 2H, NCH$_2$C$H_2$CH$_2$), 1.30−1.40 (m, 4H, 2CH$_2$); $^{13}$C NMR ($CDCl_3$) $\delta$ 158.9 (C), 148.4 (C), 144.1 (C), 137.3 (CH), 133.8 (CH), 132.2 (C), 131.8 (CH), 130.7 (CH), 124.3 (CH), 110.0 (CH), 49.7 (N*C*H$_2$), 42.2 (NH*C*H$_2$), 34.3 (CH$_3$), 28.9 (CH$_2$), 27.1 (CH$_2$), 25.8 (CH$_2$), 25.4 (CH$_2$); MS *m/z* 439[M + 1]$^+$, 341, 229; HPLC purity: Method 1: 94.9%, Method 2: 95.6%.

**4-[[6-(Imidazo[1,2-*d*][1,2,4]thiadiazol-3-ylamino)hexyl]-(naphthalene-1-sulfonyl)amino]butyric acid ethyl ester (27a):** 2 equiv of bromo compound, reflux for 16 h; yield 72%; $^1$H NMR ($CD_3OD$) $\delta$ 8.58 (d, $J$ = 11.2 Hz, 1H), 8.11−8.18 (m, 2H), 7.96 (d, $J$ = 10.8 Hz, 1H), 7.69 (d, $J$ = 1.8 Hz, 1H), 7.55−7.66 (m, 3H), 7.30 (d, $J$ = 2.0 Hz, 1H), 4.04 (q, $J$ = 9.6 Hz, 2H, OC$H_2$), 3.24−3.38 (m, 4H, 2CH$_2$), 2.23 (t, $J$ = 9.6 Hz, 2H, NCH$_2$), 1.78 (quint, $J$ = 9.6 Hz, 2H, CH$_2$C$H_2$CH$_2$), 1.39−1.53 (m, 4H, 2CH$_2$), 1.08−1.29 (m, 9H, 3CH$_2$ + CH$_3$); $^{13}$C NMR ($CD_3$OD) $\delta$ 174.7 (CO), 159.8, 146.1, 137.6 (CH), 136.4, 136.1, 135.6 (CH), 131.0 (CH), 130.3 (CH), 130.0, 129.2 (CH), 128.1 (CH), 126.2 (CH), 125.5 (CH), 111.9 (CH), 61.7 (OC$H_2$), 47.9 (N*C*H$_2$), 47.2 (N*C*H$_2$), 43.3 (N*C*H$_2$), 31.8, 29.7, 28.9, 27.4, 27.3, 24.5, 14.6 (*C*H$_3$); MS *m/z* 544 [M + 1]$^+$, 400, 210.

***N*-{6-[Imidazo[1,2-*d*][1,2,4]thiadiazol-3-yl(methyl)amino]hexyl}-*N*-methyl-2-nitrobenzenesulfonamide (18).** A mixture of **12e** (0.19 g, 0.44 mmol), $CH_3I$ (0.50 mL, 8.0 mmol), $K_2CO_3$ (1.0 g), powder KOH (1.0 g), and $n$-Bu$_4$N$^+$I$^-$ (0.15 g) in toluene (25 mL) was stirred at rt for ca. 10 min. The mixture was filtered over a pad of Celite, and the cake was thoroughly washed with acetone. The filtrate was soaked onto silica gel and evaporated to dryness. The solid was applied on top of a wet silica gel column and eluted with a solvent mixture of 5% MeOH in $CH_2Cl_2$ as eluant. Thus, **18** was obtained as a thick yellow oil (0.18 g): yield 88%; $^1$H NMR ($CDCl_3$) $\delta$ 7.97−7.99 (m, 1H), 7.67−7.70 (m, 2H), 7.60−7.62 (m, 1H), 7.50 (s, 1H), 7.28 (s, 1H), 3.46 (t, $J$ = 7.4 Hz, 2H, NC$H_2$), 3.23 (t, $J$ = 7.0 Hz, 2H, NC$H_2$), 3.16 (s, 3H, CH$_3$), 2.87 (s, 3H, CH$_3$), 1.68 (overlapping br quint, 2H, NCH$_2$C$H_2$CH$_2$), 1.62 (overlapping br quint, 2H, NCH$_2$C$H_2$CH$_2$), 1.37−1.40 (m, 4H, 2CH$_2$); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.6 (C), 148.4 (C), 147.0 (C), 137.8 (CH),

133.6 (CH), 132.4 (C), 131.7 (CH), 130.9 (CH), 124.2 (CH), 112.3 (CH), 51.8 (N*C*$H_2$), 49.9 (N*C*$H_2$), 37.6 (*C*$H_3$), 34.3 (*C*$H_3$), 27.6 ($CH_2$), 27.5 ($CH_2$), 26.3 ($CH_2$), 26.2 ($CH_2$); MS *m/z* 453 [M + 1]$^+$, 355 (100), 139.

**General Protection−Alkylation−Deprotection Procedures. *t*-Butyl [6-(imidazo[1,2-*d*][1,2,4]thiadiazol-3-ylamino)hexyl][(2-nitrophenyl)sulfonyl]carbamate (19).** A mixture of **12e** (0.48 g, 1.1 mmol), di-*tert*-butyl dicarbonate (0.38 g, 1.7 mmol), and DMAP (0.08 g, 0.61 mmol) in $CH_3CN$ (40 mL) was stirred at ambient temperature for 16 h. Volatile materials were removed in vacuo, and the residue was partitioned between EtOAc and a solution of 10% citric acid. After usual workup (4% MeOH in $CH_2Cl_2$ as eluant), **19** (500 mg) was obtained as a colorless oil: yield 84%; $^1$H NMR ($CDCl_3$) $\delta$ 8.25−8.35 (m, 1H), 7.77−7.80 (m, 3H), 7.46 (s, 1H), 7.32 (s, 1H), 5.73 (br, 1H, N*H*), 3.80 (t, $J$ = 6.9 hz, 2H, NC$H_2$), 3.53 (br q, $J \approx$ 6.1 Hz, 2H, NHC$H_2$C$H_2$), 1.65−1.80 (m, 4H, 2NC$H_2$C$H_2$), 1.40−1.50 (m, 4H, 2C$H_2$), 1.39 (s, 9H, *t*-Bu); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.1 (C), 150.5 (CO), 147.7 (C), 143.9 (C), 137.4 (CH), 134.4 (CH), 133.6 (CH), 133.3 (CH), 132.0 (C), 124.5 (CH), 109.6 (CH), 85.3 (OC*C*$H_3$), 48.0 (N*C*$H_2$), 42.5 (N*C*$H_2$), 29.8 ($CH_2$), 29.0 ($CH_2$), 28.0 (3*C*$H_3$), 26.2 ($CH_2$), 26.0 ($CH_2$); MS *m/z* 525.6 [M + 1]$^+$, 425 (100), 327, 285, 186.

***N*-{6-[Imidazo[1,2-*d*][1,2,4]thiadiazol-3-yl(methyl)amino]hexyl}-2-nitrobenzenesulfonamide (20).**[17a] A mixture of **19** (0.42 g, 0.80 mmol), $CH_3I$ (1.0 mL, 16 mmol), $K_2CO_3$ (2.5 g), powder KOH (2.5 g), and *n*-$Bu_4N^+HSO_4^-$ (0.05 g) in toluene (25 mL) and $CH_2Cl_2$ (5 mL) was stirred at rt for ca. 15 min. The mixture was filtered over a pad of Celite, and the cake was thoroughly washed with acetone. The filtrate was soaked onto silica gel and evaporated to dryness. The solid was applied on top of a wet prepacked silica gel column and eluted with a solvent mixture of 4% MeOH in $CH_2Cl_2$ as eluant. Thus, *tert*-butyl [6-(imidazo[1,2-*d*][1,2,4]thiadiazol-3-yl(methyl)amino)-hexyl][(2-nitrophenyl)sulfonyl]carbamate (**20a**) was obtained as a thick light yellow oil (0.35 g): yield 81%; $^1$H NMR ($CDCl_3$) $\delta$ 8.32−8.33 (m, 1H), 7.72−7.80 (m, 3H), 7.51 (s, 1H), 7.38 (s, 1H), 3.79 (t, $J$ = 7.2 Hz, 2H, N$CH_2$), 3.49 (t, $J$ = 7.4 Hz, 2H, N$CH_2$), 3.18 (s, 3H, $CH_3$), 1.70−1.80 (2 overlapping br quint, 4H, 2NCH$_2$C$H_2$C$H_2$), 1.42−1.52 (m, 4H, 2$CH_2$), 1.37 (s, 9H, *t*-Bu); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.6 (C), 150.5 (CO), 147.7 (C), 147.0 (C), 137.8 (CH), 134.3 (CH), 133.7 ($C_{ipso}$), 133.3 (CH), 131.9 (CH), 124.5 (CH), 111.2 (CH), 85.1 (O*C*CH$_3$), 51.8 (N*C*$H_2$), 48.0 (N*C*$H_2$), 37.6 ($CH_3$), 30.0 ($CH_2$), 28.0 (3$CH_3$), 27.7 ($CH_2$), 26.4 ($CH_2$), 26.3 ($CH_2$); MS *m/z* 539 [M + 1]$^+$, 341.

Compound **20a** obtained above (0.30 g, 0.56 mmol) was dissolved in MeOH (25 mL) and then cooled in ice. HCl gas was bubbled through the solution for ca. 6 min, and the resulting mixture was allowed to warm to rt and stirred for 16 h. Volatile materials were removed in vacuo and the residue was purified by column chromatography on silica gel using a solvent mixture of 5% MeOH in $CH_2Cl_2$ as eluant, thus affording **20** (0.24 g) as a light yellow oil: yield 98%.

***tert*-Butyl [6-(imidazo[1,2-*d*][1,2,4]thiadiazol-3-ylamino)butyl][(2-nitrophenyl)sulfonyl]carbamate (21a):** yield 86%; $^1$H NMR ($CDCl_3$) $\delta$ 8.27−8.33 (m, 1H), 7.70−7.78 (m, 3H), 7.55 (s, 1H), 7.44 (s, 1H), 7.32 (s, 1H), 5.83 (br t, $J \approx$ 5.5 Hz, 1H, NH), 3.82 (t, $J$ = 6.7 Hz, 2H, NC$H_2$CH$_2$), 3.57 (br q, $J \approx$ 6.2 Hz, 2H, NHC$H_2$CH$_2$), 1.86 (quint, $J$ = 7.4 Hz, 2H, NCH$_2$C$H_2$CH$_2$), 1.80 (quint, $J$ = 7.0 Hz, 2H, NCH$_2$C$H_2$CH$_2$), 1.36 (s, 9H, *t*-Bu); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.1 (C), 150.6 (C), 147.7 (C), 143.8 (C), 137.5 (CH), 134.5 (CH), 133.5 (C), 133.3 (CH), 132.0 (CH), 124.6 (CH), 109.6 (CH), 85.6 (O*C*CH3), 47.6 (N*C*$H_2$), 42.3 (N*C*$H_2$), 28.0 ($CH_3$), 27.4 ($CH_2$), 25.8 ($CH_2$); MS *m/z* 497 [M + 1]$^+$, 397 (100), 299. Anal. Calcd for $C_{19}H_{24}N_6O_6S_2$: C, 45.96; H, 4.87; N, 16.92. Found: C, 45.99; H, 5.03; N, 16.99.

Compound **21a** was methylated at the N1 position as described above to afford *tert*-butyl [6-(imidazo[1,2-*d*][1,2,4]-thiadiazol-3-yl(methyl)amino)butyl][(2-nitrophenyl)sulfonyl]-carbamate: yield 88%; $^1$H NMR ($CDCl_3$) $\delta$ 8.31−8.33 (m, 1H), 7.74−7.80 (m, 3H), 7.56 (s, 1H), 7.42 (s, 1H), 3.83 (br t, 2H, NC$H_2$), 3.55 (br t, 2H, NC$H_2$), 3.21 (s, 3H, $CH_3$), 1.82−1.85 (m, 4H, 2$CH_2$), 1.36 (s, 9H, *t*-Bu). The Boc group was then removed (HCl in MeOH) to provide ***N*-{6-[imidazo[1,2-*d*]-[1,2,4]thiadiazol-3-yl(methyl)amino]hexyl}-2-nitrobenzenesulfonamide (21):** yield 88%; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.08 (br t, $J \approx$ 5.4 Hz, 1H, N*H*), 7.92−7.99 (m, 3H), 7.82−7.86 (m, 2H), 7.35 (s, 1H), 3.45 (t, $J$ = 7.2 Hz, 2H, NC$H_2$), 3.11 (s, 3H, $NCH_3$), 2.94 (br q, $J \approx$ 6.4 Hz, 2H, NHC$H_2$CH$_2$), 1.57 (br quint, 2H), 1.44 (br quint, 2H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 158.6 (C), 147.6 (C), 146.5 (C), 137.3 (CH), 133.9 (CH), 132.8 (C), 132.6 (CH), 129.4 (CH), 124.3 (CH), 114.0 (CH), 50.6 (N*C*$H_2$), 42.4 (N*C*$H_2$), 37.3 ($CH_3$), 26.3 ($CH_2$), 24.0 ($CH_2$); MS *m/z* 411 [M + 1]$^+$, 313, 257; HRMS (ESI) calcd for [MH]$^+$ $C_{15}H_{19}N_6O_4S_2$ 411.0909, found 411.0922; HPLC purity analysis 97.0% by Method 1 and 97.7% by Method 2. Anal. Calcd for $C_{15}H_{18}N_6O_4S_2$: C, 43.89; H, 4.42; N, 20.47. Found: C, 44.02; H, 4.64; N, 20.07.

**{Imidazo[1,2-*d*][1,2,4]thiadiazol-3-yl-[6-(2-nitrobenzenesulfonylamino)hexyl]amino}acetic Acid Methyl Ester (22a).** A mixture of **10b** (0.14 g, 0.50 mmol) and **24a** (0.19 mg, 0.50 mmol) in DMSO (15 mL) was stirred at rt for 16 h. The reaction mixture was quenched with a saturated $NaHCO_3$ solution and extracted with EtOAc. The organic fraction was collected and was successively washed with water, a 10% citric acid solution and water. After usual workup ($CH_2Cl_2$/EtOAc, 1/1, v/v), **22a** was obtained as a light yellow oil (0.19 g, 75%). Spectral data were similar to those previously described.[17a]

**2-{Imidazo[1,2-*d*][1,2,4]thiadiazol-3-yl-[6-(2-nitrobenzenesulfonylamino)hexyl]amino}acetamide (22c).** Same procedure as described for **22a** above, except 1.1 equiv of **24b** was used and the eluant was $CH_2Cl_2$/MeOH (95/5, v/v). Yield of **22c**: 63%. Spectral data were similar to those previously described.[17a]

Alternatively, **22c** was prepared from **22a** in the following manner:

$NH_3$ gas was bubbled into an ice-cooled solution of **22a** (3.40 g, 6.85 mmol) for 1.5 h. The resulting mixture was allowed to warm to rt and then stirred for overnight. A sample was removed and analyzed by TLC (95/5 $CH_2Cl_2$/$CH_3OH$, v/v, as eluant, UV and 1.5% aq $KMnO_4$ stain). The reaction was not complete, as **22a** and **22c** were present in almost equal proportions (UV intensity). The reaction mixture was cooled in ice, and $NH_3$ gas was bubbled into the reaction mixture for 2 h. The resulting mixture was allowed to warm to rt and then stirred overnight. This time, analysis of the reaction mixture by TLC indicated the presence of a major spot (**22c**) and a trace amount of **22a**. The reaction mixture was evaporated to dryness, and the residue was dissolved in $CH_3OH$. Silica gel was added, and the mixture was again evaporated to dryness. The latter residue was then placed on top of a wet-packed silica gel column chromatography. The desired product was eluted with a solvent gradient (1/1 $CH_2Cl_2$/EtOAc, 95/5 $CH_2Cl_2$/$CH_3OH$, and 9/1 $CH_2Cl_2$/$CH_3OH$, v/v, as eluant). The title compound[17a] was obtained as a white solid (3.00 g, 91%).

Also, **22b** can be prepared from **22a** in the following manner:

To a solution of **22a** (2.49 g, 5.00 mmol) in $CH_3OH$ was added a 2 N NaOH solution (15 mL, 30 mmol) at rt. The resulting mixture was stirred for 16 h. Volatiles were then removed in vacuo, and the residue was dissolved in water (50 mL). The aqueous layer was washed with EtOAc (50 mL) and then was acidified with a 3 N HCl solution to pH about 2. The whole mixture was evaporated to dryness. The residue was taken up in acetone, and hexane was added to precipitate out the product as a light yellow mass. The mixture was again evaporated to dryness. The latter two steps were repeated three more times with vigorous stirring. The solid was then collected by suction filtration, and dried at 40 °C under vacuum for 3h. **22b** was obtained as a light yellow solid (1.91 g, 79%). Spectral data were similar to those previously described.[17a]

**[(6-Aminohexyl)imidazo[1,2-*d*][1,2,4]thiadiazol-3-ylamino]acetic Acid Methyl Ester (25).** Same procedure as described for **22a** above, except 1.2 equiv of **23a** and 2 equiv of $Et_3N$ were used, and the eluant was 100% $CH_2Cl_2$ followed by $CH_2Cl_2$/MeOH (95/5, v/v). The intermediate [(6-*tert*-butoxycarbonylaminohexyl)imidazo[1,2-*d*][1,2,4]thiadiazol-3-ylamino]-acetic acid methyl ester was obtained as a light brown oil: yield 49%; $^1$H NMR ($CDCl_3$) $\delta$ 7.47 (s, 1H), 7.43 (s, 1H), 4.22 (s, 2H, NC$H_2$CO), 3.81 (s, 3H, $CH_3$), 3.62 (t, $J$ = 7.9 Hz, 2H, NC$H_2$), 3.11−3.15 (m, 2H, NC$H_2$), 1.72−1.77 (m, 2H, $CH_2$), 1.50−1.54 (m, 2H, $CH_2$), 1.46 (s, 9H, *t*-Bu), 1.34−1.44 (m, 4H, 2$CH_2$); MS *m/z* 412 [M + 1]$^+$, 356 (100), 214.

To a solution of the intermediate obtained above (4.6 g, 11 mmol) in $CH_2Cl_2$ (110 mL) was added TFA (110 mL) slowly at rt, and the resulting mixture was stirred at rt for 16 h. The light yellow solution was evaporated to dryness, and the residue was purified by column chromatography on silica gel using a mixture of solvents ($CH_2Cl_2$/MeOH, 95/5, v/v, then $CH_2Cl_2$/MeOH/28% $NH_4OH$, 80/20/0.4, v/v/v) as eluant. Compound **25** was obtained as a yellow powder (1.9 g): yield 55%; $^1$H NMR (DMSO-$d_6$) $\delta$ 7.88 (s, 1H), 7.50−7.80 (br, 2H, N$H_2$), 7.37 (s, 1H), 4.42 (s, 2H, NC$H_2$CO), 3.70 (s, 3H, $CH_3$), 3.57 (t, $J$ = 5.5 Hz, 2H, NC$H_2$), 2.76 (t, $J$ = 5.4 Hz, 2H, NC$H_2$), 1.62−1.72 (m, 2H, $CH_2$), 1.55−1.60 (m, 2H, $CH_2$), 1.30−1.40 (m, 4H, 2$CH_2$); MS *m/z* 312 [M + 1]$^+$, 214 (100), 197.

**[6-(Carbamoylmethylimidazo[1,2-*d*][1,2,4]thiadiazol-3-ylamino)hexyl]carbamic Acid *tert*-Butyl Ester (26a).** Same procedure as described for **22a** above, except 1.2 equiv of **23b** and 2 equiv of $Et_3N$ were used. The eluant was $CH_2Cl_2$/MeOH (98/2 then 95/5, v/v): yield 42%; $^1$H NMR ($CDCl_3$) $\delta$ 7.52 (s, 1H), 7.43 (s, 1H), 6.77 (s, 1H), 5.78 (s, 1H), 4.59 (br s, 1H), 4.17 (s, 2H), 3.60 (t, $J$ = 8.1 Hz, 2H), 3.11−3.14 (m, 2H), 1.72−1.80 (m, 2H), 1.20−1.50 (m, 15H); MS *m/z* 397 [M + 1]$^+$, 341 (100), 297, 199.

**2-[(6-Aminohexyl)imidazo[1,2-*d*][1,2,4]thiadiazol-3-ylamino]acetamide (26).** Similar procedure as for preparation of **25** above. Eluant was $CH_2Cl_2$/MeOH/28% $NH_4OH$, 75/25/10, v/v/v). The mixture was then stirred in a mixture of EtOAc (75 mL) and $CH_2Cl_2$ (15 mL). The solid was collected and dried under vacuum at 40 °C for 3 h. Compound **26** was obtained as a beige solid: yield 97%; mp 132−133 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 7.80 (s, 1H), 7.30 (br, 2H), 7.57 (s, 1H), 7.35 (s, 1H), 7.57 (s, 1H), 7.18 (s, 1H), 4.15 (s, 2H, C$H_2$CO), 3.55 (t, $J$ = 7.2 Hz, 2H, NC$H_2$), 2.77 (t, $J$ = 6.5 Hz, 2H, NC$H_2$), 1.60−1.64 (m, 2H, C$H_2$), 1.51−1.55 (m, 2H, C$H_2$), 1.30−1.35 (m, 4H, 2C$H_2$); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 174.1 (CO), 162.1 (C), 147.6 (C), 137.9 (CH), 114.7 (CH), 53.5 (N$CH_2$), 52.4 (N$CH_2$), 40.7 (N$CH_2$), 29.0 ($CH_2$), 28.6 ($CH_2$), 27.3 ($CH_2$), 27.2 ($CH_2$); MS *m/z* 297 [M + 1]$^+$, 227, 199 (100), 129.

**4-[[6-(Imidazo[1,2-*d*][1,2,4]thiadiazol-3-ylamino)hexyl]-(naphthalene-1-sulfonyl)amino]butyric Acid (27b).** A mixture of **27a** (0.27 g, 0.50 mmol) and 2 N NaOH solution (2.0 mL, 4.0 mmol) in MeOH (15 mL) was stirred at rt for 16 h. Volatile materials were removed in vacuo. The residue was partitioned between water and EtOAc. The aqueous layer was collected, acidified with 1 N HCl solution, and extracted with EtOAc (3×). The combined organic fractions were dried, filtered, and evaporated to dryness. **27b** was obtained as a white solid (0.18 g): yield 68%; mp 119−122 °C; $^1$H NMR ($CD_3OD$) $\delta$ 8.59 (d, $J$ = 11.6 Hz, 1H), 8.16 (d, $J$ = 9.6 Hz, 1H), 8.12 (d, $J$ = 10.8 Hz, 1H), 7.95 (d, $J$ = 10.8 Hz, 1H), 7.72−7.80 (br, 1H), 7.64 (t, $J$ = 9.2 Hz, 1H), 7.54−7.60 (m, 2H), 7.28−7.38 (br, 1H), 3.36 (t, $J$ = 9.6 Hz, 2H, NC$H_2$), 3.24−3.31 (m, 4H, 2NC$H_2$), 2.22 (t, $J$ = 9.4 Hz, 2H, C$H_2$CO), 1.78 (br quint, 2H, $CH_2CH_2CH_2$), 1.40−1.52 (m, 4H, 2C$H_2$), 1.10−1.26 (m, 4H, 2C$H_2$); $^{13}$C NMR ($CD_3OD$) $\delta$ 175.0 (CO), 161.0 (C), 146.1 (C), 137.5 (CH), 136.5 (C), 136.1 (C), 135.6 (CH), 130.9 (CH), 130.3 (CH), 130.0, 129.2 (CH), 128.1 (CH), 126.2 (CH), 125.5 (CH), 111.5, 48.0 (N$CH_2$), 47.4 (N$CH_2$), 43.3 (N$CH_2$), 31.8, 30.0, 29.0, 27.4, 27.3, 24.7; MS *m/z* 516 [M + 1]$^+$, 400 (100), 210. Anal. Calcd for $C_{24}H_{29}N_5O_4S_2$: C, 55.90; H, 5.67; N, 13.58. Found: C, 55.89; H, 5.86; N, 13.02.

**4-[[6-(Imidazo[1,2-*d*][1,2,4]thiadiazol-3-ylamino)hexyl]-(naphthalene-1-sulfonyl)amino]butyramide (27c).** A mixture of **27a** (0.27 g, 0.50 mmol) and a 28% $NH_4OH$ solution (20 mL) in MeOH (30 mL) was stirred at rt for 2 days. Volatiles were removed in vacuo and the residue was purified by column chromatography on silica gel ($CH_2Cl_2$/MeOH, 9/1, v/v). Compound **27c** was obtained as a waxy white solid (0.15 g): yield 59%; $^1$H NMR ($CD_3OD$) $\delta$ 8.60 (d, $J$ = 11.2 Hz, 1H), 8.15 (d, $J$ = 10.0 Hz, 1H), 8.08 (d, $J$ = 10.8 Hz, 1H), 7.93 (d, $J$ = 10.8 Hz, 1H), 7.68 (s, 1H), 7.64 (dt, $J$ = 10.0 and 1.6 Hz, 1H), 7.51−7.60 (m, 2H), 7.30 (s, 1H), 3.35 (t, $J$ = 10.0 Hz, 2H, NC$H_2$), 3.22−3.28 (m, 4H, 2NC$H_2$), 2.17 (t, $J$ = 9.8 Hz, 2H, $CH_2$CO), 1.80 (br quint, 2H, $CH_2CH_2CH_2$), 1.36−1.48 (m, 4H, 2$CH_2$), 1.00−1.20 (m, 4H, 2$CH_2$); $^{13}$C NMR ($CD_3OD$) $\delta$ 178.0 (CO), 160.0, 146.0, 137.5 (CH), 136.4, 136.0, 135.4 (CH), 130.8 (CH), 130.2 (CH), 130.0, 129.1 (CH), 128.0 (CH), 126.2 (CH), 125.4 (CH), 112.0, 48.0 (N$CH_2$), 47.6 (N$CH_2$), 43.3 (N$CH_2$), 33.4 (C$H_2$-CO), 30.0, 28.9, 27.3, 27.2, 25.4; MS *m/z* 515 [M + 1]$^+$, 400 (100), 191.

**Reaction of Tricyclic THD Derivative 7f with Phenethyl Mercaptan.**[28] To a suspension of **7f** (26 mg, 0.09 mmol) in MeOH (10 mL) was added 2.5 equiv of phenethyl mercaptan (31 $\mu$L, 0.23 mmol) via syringe. The progress of the reaction was monitored by TLC ($CHCl_3$/MeOH, 100/2, v/v) and compared with authentic 2-mercaptobenzimidazole (Aldrich) as reference ($R_f$ of **7f** = 0.17; $R_f$ of 2-mercaptobenzimidazole = 0.69). After a period of ca. 3 days, **7f** was faintly detected by TLC, and the major component was 2-mercaptobenzimidazole. A sample was evaporated to dryness and analyzed by MS-EI, which showed [M] $^+$ at 151.

In another experiment, a suspension of **7f** (26 mg, 0.09 mmol) and 25 equiv of phenethyl mercaptan (0.32 mL, 2.4 mmol) in MeOH (10 mL) was stirred at rt. Compound **7f** was converted to 2-mercaptobenzimidazole over a period of 2−3 h, as monitored with authentic material by TLC.

**Reaction of Dimethylamino THD 11a with Phenethyl Mercaptan.** To a solution of dimethylamino THD derivative **11a** (23 mg, 0.11 mmol) in methanol (10 mL) was added 25 equiv of phenethyl mercaptan (0.36 mL, 2.7 mmol) via syringe. The progress of the reaction was monitored by TLC using a mixture of chloroform and methanol as eluant (10/1, v/v, $R_f$ of **11a** = 0.43, $R_f$ of **28a** = 0.60). After 1 min, all of **11a** was consumed. The solvent was evaporated and the crude material was washed with $CHCl_3$ to afford 2-mercapto-*N*,*N*-dimethylbenzoimidazole-1-carboxamidine (**28a**): yield 15 mg (65%); $^1$H NMR (DMSO-$d_6$) $\delta$ 7.3−7.0 (m, 4H, Ar), 3.35 (br m, 2H, N*H*, S*H*), 2.88 (s, 6H, 2 NC$H_3$); $^{13}$C NMR ($CDCl_3$) $\delta$ 167.2, 149.7, 132.3, 131.8, 123.4 (CH), 122.5 (CH), 110.2 (CH), 109.4 (CH), 37.7 ($CH_3$), 36.7 ($CH_3$); IR (KBr) $\nu$ 3210, 1641, 1475, 1452, 1407, 1319 cm$^{-1}$; MS (EI) *m/z* 220 (M$^+$), 150 (M$^+$ − $Me_2NC$═NH, 100), 71.

**Reaction of Methoxy THD (11d) with Phenethyl Mercaptan.**[18c] To a solution of 3-methoxy thiadiazole **11d** (23 mg, 0.11 mmol) in MeOH (10 mL) was added 25 equiv of phenethyl mercaptan (0.38 mL, 2.8 mmol). All the starting material was consumed in less than 1 min as monitored by TLC (eluant: $CHCl_3$/MeOH, 100/2, v/v, $R_f$ of **11d** = 0.19, $R_f$ of **28b** = 0.26). 2-Mercaptobenzoimidazole-1-carboximidic acid methyl ester (**28b**) was isolated and identified as the major product of the reaction: $^1$H NMR (DMSO-$d_6$) $\delta$ 13.45 (br s, 1H), 9.80 (s, 1H), 7.70 (d, $J$ = 8 Hz, 1H, 1 ArH), 7.20−7.35 (m, 3H, 3 ArH), 3.95 (s, 3H, OC$H_3$); $^{13}$C NMR (DMSO-$D_6$) $\delta$ 168.2, 151.3, 130.1, 129.8, 124.7, 123.2, 114.7, 110.0, 54.4; IR (KBr) $\nu$ 3437, 3095, 1679, 1450, 1440, 1376, 1193, 735 cm$^{-1}$; MS (EI) *m/z* 207 [M]$^+$, 150 (M$^+$ − MeOC═NH, 100), 122, 90. Anal. Calcd for $C_9H_9N_3OS$: C, 52.16; H, 4.38; N, 20.27. Found: C, 51.70; H, 4.03; N, 20.21.

In another experiment, the reaction mixture was allowed to stir at rt for another 2 h. The methyl ester derivative **28b** converted to 2-mercaptobenzimidazole over a period of 2−3 h, as monitored by TLC.

**Acid/Base Stability of Bicyclic Derivative 12a (pH = 2, 7, 9.8, and 13.7).** Four solutions of compound **12a** (10.0 mg, 0.023 mmol) were prepared in $CH_3CN$ (1 mL), and 4 mL of the appropriate pH buffer was added (pH 2, 7, 9.8, and 13.7 (2 N NaOH)), respectively. The mixtures were stirred at rt, and their stability in the different media was verified by TLC (eluant: $CH_2Cl_2$/MeOH, 95/5, v/v) and by HPLC (method 1). A HPLC calibration curve was constructed with different concentrations of **12a**. Samples for HPLC analyses were prepared accordingly: 5 $\mu$L of reaction sample was withdrawn by syringe and added to 2 mL of $NH_4OAc$ buffer solution at a pH of 5.5. After 20 h at rt, only the starting material **12a** was detected in the media at the pH of 2, 7, and 9.8. It was deduced from analysis of the HPLC spectra of **12a** in 2N NaOH solution that 95% remained after 2 h and 60% after 20 h.

**Stability of Bicyclic Compound 12a in the Presence of *n*-Butylamine.** A solution of bicyclic derivative **12a** (10 mg, 0.023 mmol) and 7.5 equiv of *n*-butylamine in $CH_2Cl_2$ was stirred at rt. After 20 h at rt, analysis of the HPLC spectrum (method 1) indicated presence of starting material **12a** only.

**Single-Crystal X-ray Structure of Thiadiazole Derivative (21).** A single crystal (size 0.24 × 0.14 × 0.06 $mm^3$) obtained as a white plate from 1/1 MeOH/THF with slow evaporation was used for X-ray diffraction measurements. Crystal data: $C_{15}H_{18}N_6O_4S_2$, orthorhombic, space group *Pbca* with $a$ = 8.2010(2) Å, $b$ = 12.2350(3) Å, C, = 35.1640(11) Å; α= 90°, $\beta$= 90°, $\gamma$ = 90°; $V$ = 3528.33(16) $Å^3$; $Z$ = 8; $d$ = 1.545 $Mg/m^3$; $R$ = 0.0743 for 3986 independent reflections ($I > 2\sigma(I)$; wR2 = 0.1079 ($F^2$, all data). The structure of compound **21** is depicted in Figure 3 in the text, and the CIF file is available as Supporting Information.

**Acknowledgment.** We thank Dr. Glenn Williams and Lei Shang for the crystal growth of **21**, Tullio Cappelletto for the synthesis of compounds **11a** and **11d**, and Sandra Agostino for proof-reading the manuscript.

**Supporting Information Available:** Detailed synthesis and spectral data of the intermediates and compounds. NMR spectra of the following compounds: **8**, **12d**,**k**,**l**, **13**, **15**, **23a**, **24a**,**b**, **25**, **26a**, **29**, **30a**,**d** ($^1$H); **26** ($^{13}$C); **11c**, **12c**, **27a**,**c**, **28a** ($^1$H, $^{13}$C); **18**, **19**, **20a** (2D-COSY, HSQC, HMBC). The crystallographic data on the single X-ray crystal structure of compound **21** are also provided (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

JO0507486