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Bioorganic & Medicinal Chemistry Letters 15 (2005) 5211–5217
Bioorganic & Medicinal Chemistry Letters

Synthesis and evaluation of thiazole carboxamides as vanilloid receptor 1 (TRPV1) antagonists

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Received 2 August 2005; accepted 18 August 2005
Available online 3 October 2005

Abstract—A thiazole derivative, 2-(2,6-dichlorobenzyl)-*N*-(4-isopropylphenyl) thiazole-4-carboxamide (**1**), was identified as a TRPV1 antagonist. We synthesized various thiazole analogs and evaluated them for their ability to block capsaicin- or acid-induced calcium influx in TRPV1-expressing CHO cells. The IC_{50} values of the most potent antagonists were ca. 0.050 μM in these assays.

The vanilloid receptor 1 (VR1 or TRPV1), a non-selective cation channel within the transient receptor potential (TRP) family, is highly expressed in sensory neurons located primarily in the dorsal root ganglia.[1] TRPV1 is activated by a variety of stimuli such as heat and acid, and exogenous chemical stimuli such as capsaicin (the pungent component found in chili peppers). Activation of TRPV1 induces the initial excitation of primary sensory neurons that often leads to a burning sensation. Prolonged stimulation with TRPV1 agonists can desensitize sensory nerves, making them less sensitive to subsequent painful stimuli. However, TRPV1 agonists are neurotoxic and cause initial excitatory effects on sensory neurons, making their use as analgesics limited.[2] TRPV1 receptor antagonists, on the other hand, inhibit the activation of the primary sensory neurons, so they should be devoid of the neurotoxicity associated with activation and desensitization of the nerve cell. Therefore, TRPV1 antagonists may serve as better analgesic agents than TRPV1 agonists.[3]

In our work toward the discovery of new analgesic agents, we identified a series of thiazole carboxamides as TRPV1 antagonists.[4] The initial lead compound, 2-(2,6-dichlorobenzyl)-*N*-(4-isopropylphenyl) thiazole-4-carboxamide (**1**), was discovered by high-throughput screening measuring Ca^{2+} influx in Chinese hamster ovary (CHO) cells.[5] For the purpose of our structure–activity relationship (SAR) study, we measured the inhibition of capsaicin (CAP) and acid (pH 5) induced influx of $^{45}Ca^{2+}$ into CHO cells that express rat–human chimera TRPV1.[6] Our goal was to improve the potency over compound **1** as well as to gain a better understanding of the pharmacophores required for activity at the TRPV1 receptor. Toward this end, we first optimized the left-side aryl amide portion followed by the central core and then the right-side aryl portion of compound **1** (Fig. 1).

We began our initial SAR studies by examining the effect of varying the left phenyl ring and prepared a

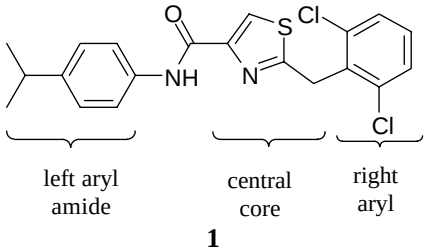

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Figure 1. 2-(2,6-Dichlorobenzyl)-*N*-(4-isopropylphenyl) thiazole-4-carboxamide (**1**) identified as a TRPV1 antagonist through high-throughput screening.

Keywords: Vanilloid receptor 1 (TRPV1); Antagonists; Thiazole carboxamides.
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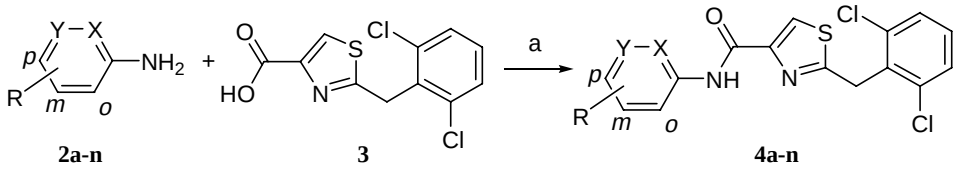
doi:10.1016/j.bmcl.2005.08.100



Scheme 1. Reagents and conditions: (a) HATU, DMF, 0–23 °C, 70–95% yield.

series of substituted aryl amides. As illustrated in Scheme 1, compounds **4a**–**n** were synthesized by the condensation of substituted anilines **2a**–**n** with commercially available 2-(2,6-dichlorobenzyl) thiazole-4-carboxylic acid (**3**) in the presence of HATU.[7] The assay results for these aryl amides are reported in Table 1.

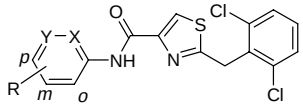
We found that the potency at TRPV1 was sensitive to the substitution on the aryl amides. For example, the larger *tert*-butyl homolog (**4a**) and the truncated 4-ethyl analog (**4b**) were 1.5- to 2-fold less potent than **1** in the CAP-mediated assay. The decrease in activity for the unsubstituted phenyl analog (**4c**) was greater than 10-fold. Compounds possessing a strongly electron-donating *para*-substituent, such as *p*-NMe_2 (**4d**) and *p*-OMe (**4e**), also showed significantly lower potencies (IC_{50} values >4 μM in both CAP- and acid-mediated assays). In contrast, electron-withdrawing *para*-substituents improved activity at the TRPV1 receptor. For example, the *p*-Br analog (**4f**) had an IC_{50} = 0.40 μM in the CAP-mediated assay, making it >10-fold more potent than the *p*-OMe analog (**4e**) and 1.5-fold more potent than the *p*-Et analog (**4b**). These results suggest that it is the electronic effects of bromide that cause the activity enhancement, since bromide has similar size to those of OMe and Et groups, as measured by molecular refractivity, MR.[8]

Accordingly, we prepared more electronegative aryl amide analogs, **4g**–**j**. The *p*-CN substituted phenyl amide (**4g**) was comparable in potency to both compound **1** and the *p*-Br analog (**4f**). The most potent analog was the *p*-CF_3 analog **4h** with IC_{50} values of 0.14 and 0.09 μM in the CAP- and acid-mediated assays, respectively. The larger homolog (*p*-CF_2CF_3, **4i**), however, was slightly less potent in these assays (IC_{50} = 0.29 in the CAP assay and 0.35 μM in the acid assay). The trends in potencies observed for the substituted 3-pyridyl analogs (**4j**,**k**) were similar to their phenyl counterparts (**4h**,**e**). For example, the *p*-CF_3-pyridyl (**4j**) was as potent as the *p*-CF_3-phenyl analog (**4h**), whereas the *p*-OMe-pyridyl (**4k**) had IC_{50} values >4 μM in both assays, as was also observed for the corresponding *p*-OMe-phenyl (**4e**). In contrast, shifting the pyridyl nitrogen from the 3- to the 2-position caused a reduction in potency (i.e., **4l** vs **f**).

Finally, the position of the substituent was important for TRPV1 activity. For example, moving the bromine substituent from the *para*-position (**4f**) to the *ortho*- or *meta*-positions (**4m**,**n**) resulted in a decrease in potency to >4 μM.

In the next phase of our investigation, we kept the most potent left aryl amide (*p*-CF_3-phenyl, **4h**) and modified the central core (Table 2, compounds **25a**–**i**). A thiazole regioisomer and a substituted thiazole analog were

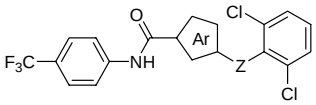
Table 1. Structures and assay results of thiazole analogs with variations at the left phenyl amide portion

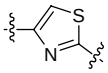
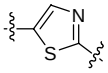
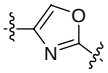
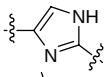
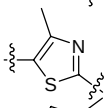
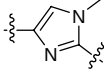
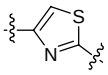
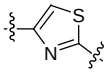
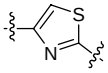
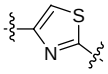


Compound	R	X	Y	CAP[a] IC_{50} ± SEM (μM)	Acid[a] IC_{50} ± SEM (μM)
1	*p*-Pr^i	CH	CH	0.37 ± 0.19	0.52 ± 0.30
4a	*p*-Bu^t	CH	CH	0.57 ± 0.24	0.30 ± 0.05
4b	*p*-Et	CH	CH	0.81 ± 0.13	1.45 ± 0.86
4c	H	CH	CH	>4	>4
4d	*p*-NMe_2	CH	CH	>4	1.27 ± 0.49
4e	*p*-OMe	CH	CH	>4	>4
4f	*p*-Br	CH	CH	0.40 ± 0.09	0.46 ± 0.11
4g	*p*-CN	CH	CH	0.45 ± 0.06	0.72 ± 0.20
4h	*p*-CF_3	CH	CH	0.14 ± 0.03	0.088 ± 0.019
4i	*p*-CF_2CF_3	CH	CH	0.29 ± 0.03	0.35 ± 0.16
4j	*p*-CF_3	CH	N	0.11 ± 0.04	0.13 ± 0.01
4k	*p*-OMe	CH	N	>4	>4
4l	*p*-Br	N	CH	>4	>4
4m	*o*-Br	CH	CH	>4	>4
4n	*m*-Br	CH	CH	>4	>4

[a] The activation assays were carried out in a rat–human chimera of the TRPV1 channel expressed in CHO cells. Results are the average of at least two independent experiments with three replicates at each concentration.

Table 2. Structures and assay results of TRPV1 antagonists with different central cores



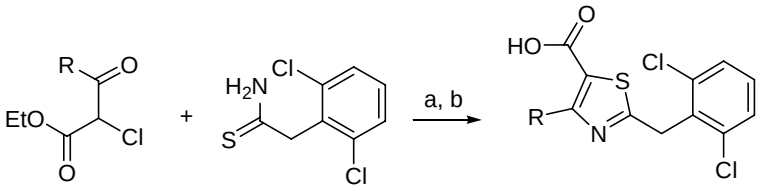
Compound	Ar	Z	CAP[a] IC_{50} ± SEM (μM)	Acid[a] IC_{50} ± SEM (μM)
4h		CH_2	0.14 ± 0.03	0.088 ± 0.019
25a		CH_2	0.79 ± 0.025	1.78 ± 0.55
25b		CH_2	0.062 ± 0.014	0.200 ± 0.008
25c		CH_2	0.23 ± 0.12	0.23 ± 0.11
25d		CH_2	3.42 ± 1.49	>4
25e		CH_2	1.01 ± 0.50	1.02 ± 0.32
25f		Bond	>4	>4
25g		CH_2CH_2	>4	>4
25h		O	0.87[b]	1.28 ± 0.86
25i		NH	0.051 ± 0.023	0.048 ± 0.009

[a] The activation assays were carried out in a rat–human chimera of the TRPV1 channel expressed in CHO cells. Results are the average of at least two independent experiments with three replicates at each concentration.
[b] Single experimental determination.

prepared and tested. In addition, the central core was replaced with two other five-membered heterocycles: oxazole and imidazole rings. As part of the central core modifications, the linker between the thiazole group and dichlorophenyl ring was also altered (e.g., CH_2, CH_2CH_2, O, and NH, or removed). The syntheses of these core analogs are shown in Schemes 2–6.

Schemes 2 and 3 illustrate the synthesis of the key intermediates containing the different core structures (i.e., compounds **8**, **9**, **15**, and **16**). Thiazole 5-carboxylic acids **8** and **9** were obtained in good yields by the condensation of α-chloro-β-ketoesters **5** and **6** with 2-(2,6-dichlorophenyl) ethanethioamide **7** in EtOH,[9] followed by a basic hydrolysis of the resulting esters. Oxazole acid **15**[10] and imidazole acid **16**[11] (Scheme 3) were prepared through the oxidation of the corresponding dihydro intermediates **13** and **14**. Cyclization of serine methyl ester **10** with acetimidate **12** afforded 4,5-dihydrooxazole **13**. Oxidation of **13** with $CuBr_2$ under basic conditions followed by ester hydrolysis with 1 N NaOH provided oxazole acid **15** in 15% overall yield. Similarly, 4,5-dihydro-*1H*-imidazole-4-ester **14** was obtained in 63% yield via the cyclization of **12** with 2,3-diamino propanoic ester **11**. Oxidation of **14** with MnO_2 in CH_2Cl_2 proceeded smoothly to yield the corresponding imidazole ester, which was hydrolyzed to give acid **16** in excellent yield.

Compounds with different linking groups between the thiazole and the dichlorophenyl (Scheme 4, compounds **19a**–**c**) were constructed through the condensation of thioamides **18a**,**b** and thiourea **18c** with ethyl bromopyruvate **17**.[12] Thioamide **18a** and thiourea **18c** were purchased from commercial sources, while 3-(2,6-dichlorophenyl) propanethioamide **18b** was prepared from 3-(2,6-dichlorophenyl) propanenitrile according to the method of Klimesova, et al.[13] Oxygen-linked thiazole analog **24** was synthesized using a copper-catalyzed procedure, as shown in Scheme 5.[14] Coupling of

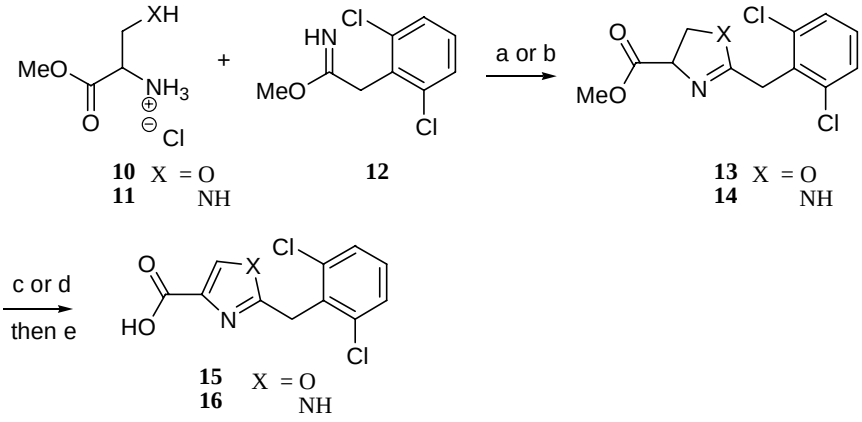


5 R = H
6 Me

7

8 R = H
9 Me

Scheme 2. Reagents and conditions: (a) EtOH, pyridine, reflux, R = H, 33% and R = Me, 80%; (b) 1 N NaOH, MeOH/THF, 75%.



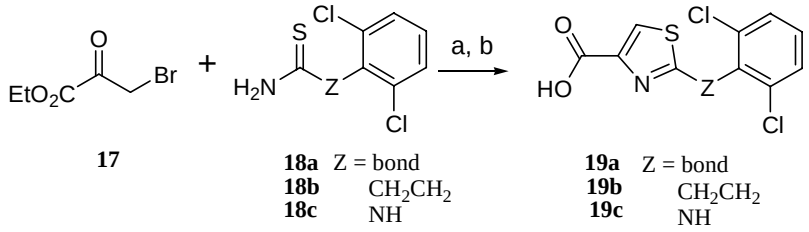
10 X = O
11 NH

12

13 X = O
14 NH

15 X = O
16 NH

Scheme 3. Reagents and conditions: (a) *i*-Pr_2NEt, CH_2Cl_2, rt, 51% for X = O; (b) Et_3N, MeOH, rt, 63%, $CuBr_2$, DBU, CH_2Cl_2, rt, 31% for X = NH; (c) $CuBr_2$, DBU, CH_2Cl_2, rt, 31% for X = O; (d) MnO_2, CH_2Cl_2, rt, 46% for X = NH; (e) 1 N NaOH, MeOH/THF, 70–86%.

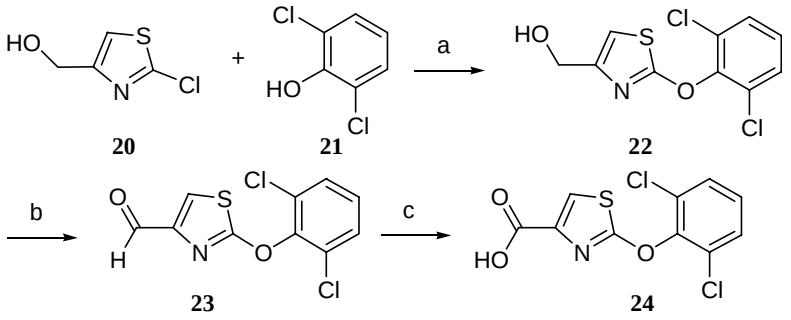


17

18a Z = bond
18b CH_2CH_2
18c NH

19a Z = bond
19b CH_2CH_2
19c NH

Scheme 4. Reagents and conditions: (a) EtOH, pyridine, reflux, >80%; (b) 1 N NaOH, MeOH/THF, 90%.



20

21

22

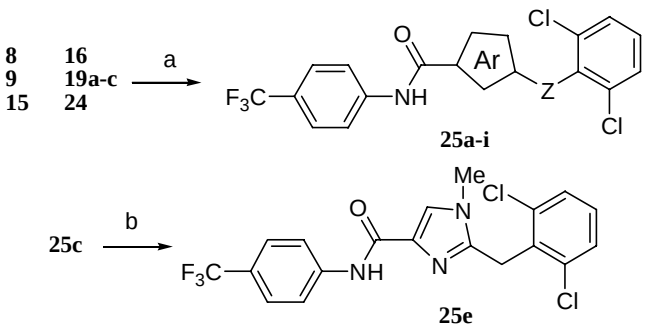
23

24

Scheme 5. Reagents and conditions: (a) CuI, K_2CO_3, DMF, microwave, 240 °C, 10 min, 24%; (b) MnO_2, CH_2Cl_2, rt, 86%; (c) SeO_2, H_2O_2, THF, room temperature, 82%.

2-chlorothiazole **20** with 2,6-dichlorophenol **21** with microwave heating in the presence of CuI afforded alcohol **22**. Oxidation of alcohol **22** with MnO_2 gave aldehyde **23**, which was then converted to acid **24** in excellent yield by oxidation with SeO_2/H_2O_2.

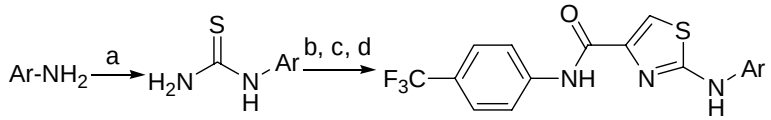
The final steps to prepare amides **25a**–**i** required the coupling of acids **8**, **9**, **15**, **16**, **19a**–**c**, and **24** with *p*-trifluoromethyl aniline, as illustrated in Scheme 6. Compound **25e** was obtained by *N*-methylation of the imidazole ring of **25c** with MeI under basic



Scheme 6. Reagents and conditions: (a) *p*-trifluoromethyl aniline, HATU, *i*-Pr_2NEt, DMF, rt, 41–90%; (b) MeI, K_2CO_3, DMF, rt, 34%.

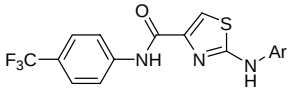
conditions, and the position of the methyl group was unambiguously confirmed by NMR spectroscopic methods.[15]

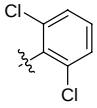
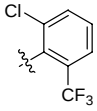
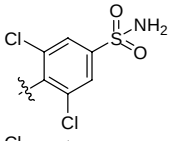
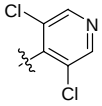
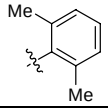
Changes to the central core significantly influenced potency, as demonstrated by the assay data summarized in Table 2. For example, shifting the carboxamide group from the 4-position (e.g., **4h**) to the 5-position (e.g., **25a**) resulted in a 5-fold decrease in potency in the CAP-mediated assay and 20-fold decrease in potency in the acid-mediated assay. The effects of replacing the sulfur atom in thiazole **4h** with either oxygen or nitrogen are illustrated by oxazole **25b** or imidazole **25c**. Oxazole **25b** showed an $IC_{50} = 0.062\ \mu M$ in the CAP-mediated assay, which was about 2-fold more potent than **4h**. In the acid-mediated assay, however, **25b** was 2-fold less potent than **4h**. Imidazole **25c** displayed IC_{50} values of 0.23 μM in both the CAP- and acid-mediated assays. Introducing a methyl group to the central core was poorly tolerated, as shown by 4-methyl 5-carboxamide **25d** ($IC_{50} > 3\ \mu M$ in both the CAP- and acid-mediated assays). Similarly, the methylated



Scheme 7. Reagents and conditions: (a) benzoyl isothiocyanate, THF, then 1 N NaOH, 90%; (b) ethyl bromopyruvate, EtOH, pyridine, reflux, >80%; (c) 1 N NaOH, MeOH/THF, 90%; (d) *p*-trifluoromethyl aniline, HATU, *i*-Pr_2NEt, DMF, rt, 70–90%.

Table 3. Structures and assay results of thiazole analogs with variations at the right phenyl portion



Compound	Ar	CAP[a] IC_{50} ± SEM (μM)	Acid[a] IC_{50} ± SEM (μM)
25i		0.051 ± 0.023	0.048 ± 0.009
28a		>4	>4
28b		1.75 ± 0.71	1.41 ± 0.02
28c		1.78 ± 0.37	1.74 ± 0.07
28d		0.36 ± 0.03	0.88 ± 0.03
28e		0.090 ± 0.006	0.082 ± 0.014

[a] The activation assays were carried out in a rat–human chimera of the TRPV1 channel expressed in CHO cells. Results are the average of at least two independent experiments with three replicates at each concentration.

imidazole **25e** was >15-fold less potent than imidazole **25c**.

Altering the linker between the thiazole and the right dichlorophenyl moiety afforded compounds **25f–i**. Compounds with either shorter (no spacer, **25f**) or longer linker (–CH_2CH_2–, **25g**) were less potent in both the CAP- and acid-mediated assays (IC_{50}s > 4 μM). Changing the –CH_2– linker to an oxygen atom did not improve activity (e.g., **25h**). In contrast, the NH-linked derivative **25i** had significantly improved TRPV1 potency (IC_{50} = 0.051 μM in the CAP assay and 0.048 μM in the acid assay), which was about 2-fold more potent than compound **4h**.

Finally, we investigated the substituent effect of the right-side aromatic ring based on modifications to compound **25i**. Scheme 7 shows the synthesis of compounds **28a–e** (Table 3). The thioureas **27a–e** were obtained by one-pot reactions involving the condensation of anilines **26a–e** with benzoyl isothiocyanate followed by a basic hydrolysis to remove the benzoyl group.[16] The resulting thioureas were condensed with bromopyruvate followed by the hydrolysis of ester and coupling with *p*-trifluoromethyl aniline to provide the target compounds **28a–e**.

Small structural changes in this area had a significant impact on potency. For example, changing one of the chlorine atoms on the phenyl moiety to a CF_3 group (e.g., **28a**) resulted in a reduction in potency (IC_{50}s > 4 μM in both the CAP- and acid-mediated assays). Deletion of one chlorine atom also caused a reduction in activity, as observed with compound **28b** (IC_{50}s > 1 μM in both assays). Substitution on the *para*-position was also unfavourable. For example, *para*-sulfonamide analog **28c** had IC_{50} values of ~1.7 μM in both the CAP- and acid-mediated assays.

Pyridyl analog **28d** was much less potent than the corresponding phenyl counterpart **28i**, with an IC_{50} = 0.36 μM in the CAP assay, and 0.88 μM in the acid assay. Changing both chloride atoms to –CH_3 groups furnished a potent TRPV1 antagonist **28e** with IC_{50} values of ~0.09 μM in both assays.

In conclusion, through SAR studies based on compound **1**, we designed several novel thiazole analogs that are potent TRPV1 receptor antagonists. In addition, we found that compounds with a strong electron-withdrawing *para*-substituent on the left phenyl amide portion were more potent than the analogs with electron-donating *para*-substituents (e.g., **4h**,**i** vs **4d**,**e**). Excellent antagonistic potencies were also observed for the oxazole analog **25b**. The NH-linked analog **25i** was the most potent TRPV1 receptor antagonist in this series with IC_{50} values of 0.050 μM for both the CAP- and acid-mediated assays. Finally, we found that variations at the right phenyl ring were less tolerated, and most changes in this region led to a drop in potency at TRPV1 receptor.

Acknowledgment

We thank Duncan Smith for carrying out NMR spectroscopic studies to confirm the structure of compound **24e**.

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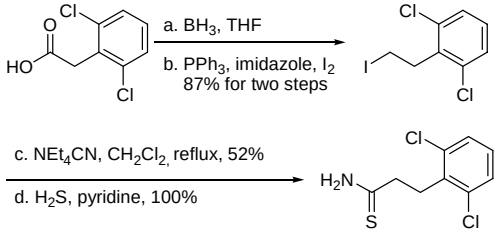
13. Thioamide **15b** was prepared using the following method:



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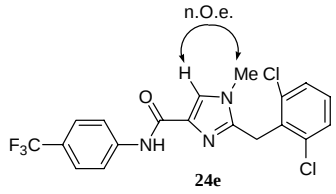
15. NMR spectroscopic methods including 2D NOESY, $^{1}H/^{13}C$ HSQC, and HMBC were used to confirm the structure of compound **24e**. A strong NOE was observed between the *N*-methyl and the imidazole C–H:



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