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3-(Arylthiomethyl)isoxazole-4,5-dicarboxamides: Chemoselective Nucleophilic Chemistry and Insecticidal Activity

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Abstract

A collection of ninety-one 3-(arylthiomethyl)isoxazole-4,5-dicarboxamides were prepared starting from dimethyl 3-(chloromethyl)isoxazole-4,5-dicarboxylate. The thioether moieties in these compounds were subsequently oxidized to give the corresponding 3-(arylsulfonylmethyl)isoxazole-4,5-dicarboxamides. By carefully controlling stoichiometry and reaction conditions, the C4 and C5 carbomethoxy groups could be differentially derivatized to carboxamides. A total of 182 trisubstituted isoxazoles are reported and deposited in the National Institutes of Health Molecular Repository; an 80 compound subset was evaluated for insecticidal activity.

Keywords

isoxazole; insecticidal activity; nucleophilic selectivity

Introduction

The 5-membered isoxazole provides a valuable scaffold in medicinal chemistry as well as a useful synthon in organic synthesis.¹ In addition, the aromatic isoxazole displays wide ranging biological activities, including pharmacological applications such as hypoglycemic, analgesic, antiinflammatory, antibacterial, and HIV-inhibitory activity as well as agrochemical applications spanning herbicidal, fungicidal, and insecticidal activities.² As part of collaboration with Dow AgroSciences, lead generation libraries are designed and biologically evaluated for new chemistry as well as product pipeline potential. Indeed, there are several reports of combinatorial libraries as discovery tools for agrochemicals and these have provided numerous hits and leads³. These libraries serve to both produce molecules with activity and, simultaneously, provide valuable information to facilitate optimization. 3,4,5-Trisubstituted isoxazoles were recently found to have novel PPAR δ agonist's properties with good in vivo pharmacokinetics.⁴ The antiepileptic and antiobesity drug zonisamide⁵ (Figure 1) piqued our interest in sulfide/sulfone substituents – functionalities which also have important pharmaceutical applications⁶ – tethered to the isoxazole heterocycle. We previously reported that the three electrophilic centers of dimethyl 3-chloromethylisoxazole-4,5-dicarboxylate (**1**) are available for diversification and reported the elaboration to a library of 5-

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Supporting Information Available: ¹H-NMR and ¹³C-NMR and LCMS spectral data for representative library members and crystallographic data of **9**{1,1} and CIF file are available. This material is available free of charge via the Internet at <http://pubs.acs.org>.

alkylcarbamoyl-3-arylsulfanylmethylisoxazole-4-carboxylic acids (e.g., **2**).⁷ Herein, we report the elaboration of **1** to chemsets of 3-(arylthiomethyl)isoxazole-4,5-dicarboxamides (**6** and **9**) and 3-(arylsulfonylmethyl)isoxazole-4,5-dicarboxamides (**7** and **10**).

Materials and Methods

General: All chemicals were purchased from commercial suppliers and used without further purification. Analytical TLC was carried out on pre-coated plates (silica gel 60, F254) and visualized with UV light. Flash chromatography was performed with silica gel 60 (230-400 mesh). NMR spectra (¹H at 300 MHz, 400 MHz, 600MHz, ¹³C at 75 MHz, 100 MHz, 150MHz) were measured in Acetone-d₆ and CDCl₃ as solvents indicated individually at specific experimental section and chemical shifts are reported in parts per million (ppm) related to internal duterated solvents or TMS. The LC/MS analyses were performed on a Waters 2690 with electrospray (+) ionization, mass range 100-1500 Da, 23-V cone voltage, and Xterra® MS C₁₈ column (2.1 mm × 50 mm × 3.5 μm).

Preparation of Dimethyl 3-Chloromethylisoxazole-4,5-dicarboxylate (1**):**⁷ adopted from literature; IR, ¹H-NMR and ¹³C-NMR matched literature data.

NOTE: the intermediate oxime was not purified by distillation which was reported to lead to a violent explosion. In addition, this oxime was reported to irritate the eyes and the mucous membrane of the nose as well as blister the skin. Following the literature routes as well as the protocol outlined in Scheme 1, we had no exposure problems.

General procedure for the preparation of sulfide ether: Dimethyl 3-(phenylthiomethyl)isoxazole-4,5-dicarboxylate (**4**{**1**})

To a DMF (18 mL) solution of **1** (1.21 g, 5.19 mmol) under N₂ gas was added thiophenol (**3**{**1**}: 0.629 g, 5.71 mmol) and triethylamine (0.577 g, 5.71 mmol). The resulting solution was stirred at room temperature for 10 min, at which time TLC analysis (hexane:ethyl acetate = 4:1) indicated that the reaction had gone to completion. The reaction mixture was diluted with water (200 mL) and extracted with ethyl acetate (2×50mL). The combined organic extracts were washed with 5% aq. NaOH (2×50mL) and brine (1×100mL), dried over anhydrous Na₂SO₄, filtered, and the solvent removed *in vacuo*. The resulting yellow oil was purified by flash column chromatography (SiO₂/hexane:ethyl acetate = 4:1) to give **4**{**1**} (1.54g, 97%). ¹H-NMR (300MHz, CDCl₃) δ 7.35-7.23 (m, 5H, C₆H₅), 4.26 (s, 2H, CH₂), 3.98 (s, 3H, CH₃), 3.90 (s, 3H, CH₃).

Following this procedure, also delivered **4**{**2-7**}: (90% - 95%).

General Procedure for the Preparation of homo-bisamides: 3-(Phenylthiomethyl)-N⁴,N⁵-dipropylisoxazole-4,5-dicarboxamide **6**{**1**,**1**}

Propylamine (**5**{**1**}: 303 mg, 5.12 mmol) was added to a methanol (1 mL) solution of crude **4**{**1**} (157 mg, 0.512 mmol). The resulting solution was stirred at room temperature overnight or 40 °C for 2 h at which time TLC analysis (hexane:ethyl acetate = 4:1) indicated that the reaction had gone to completion. The reaction mixture was cooled with ice-water for 15 min and the resulting white precipitate was collected by filtration and washed with cold methanol. Alternatively, methanol can be evaporated from the reaction mixture to give **6**{**1**,**1**} (141 mg, 85%) as a white paste, mp 102-103°C. ¹H-NMR: (400MHz, (CD₃)₂CO) δ 10.04 (br s, 1H, N-H), 8.62 (br s, 1H, N-H), 7.42-7.19 (m, 5H, phenyl), 4.59(s, 2H, S-CH₂), 3.43 (apparent q, *J* = 8Hz, 2H, N-CH₂), 3.31 (apparent q, *J* = 8Hz, 2H, N-CH₂), 1.72-1.55 (m, 4H, 2C-CH₂), 1.00-0.94 (m, 6H, 2C-CH₃). ¹³C-NMR (100MHz, (CD₃)₂CO) δ 163.6, 159.4, 159.2, 157.6,

136.0, 130.0, 129.1, 126.7, 115.5, 41.6, 41.0, 28.6, 22.6, 22.3, 11.2, 10.9. Following this procedure, also delivered **6**{1-7, 1-7}.

General Procedure for the Preparation of mixed-bisamides: N⁵-Benzyl-3-(phenylthiomethyl)-N⁴-propylisoxazole-4,5-dicarboxamide (9**{1,1})**

Benzylamine (**5**{7}: 307 mg, 2.87 mmol) was added to a methanol (10 mL) solution of crude **4**{1} (881 mg, 2.87 mmol) and the resulting solution was stirred at room temperature for 4 h at which time a white precipitate had formed. This precipitate was collected by filtration and washed with cold methanol to yield **8**{1} methyl 5-(benzylcarbamoyl)-3-(phenylthiomethyl)isoxazole-4-carboxylate (601 mg, 55%) as a white solid, mp 92-93°C. ¹H-NMR: (600 MHz, CDCl₃): δ 7.37-7.23 (m, 10H, phenyl C-H), 4.66 (d, *J* = 5.4 Hz, 2H, N-CH₂), 4.26 (s, 2H, S-CH₂), 3.90 (s, 3H, O-CH₃). ¹³C-NMR (150 MHz, CDCl₃): δ 166.0, 163.8, 161.8, 137.8, 134.2, 131.8, 128.7, 128.6, 128.2, 128.1, 128.0, 110.0, 53.8, 44.0, 30.2.

Without further purification, **8**{1} (68 mg, 0.178 mmol) was suspended in methanol (1 mL) and *n*-propylamine (**5**{1}: 105 mg, 1.78 mmol) was added. The resulting suspension was stirred at room temperature and the reaction was monitored by TLC analysis (hexane:ethyl acetate = 4:1) After 6 h, TLC analysis indicated that the reaction had gone to completion. The reaction mixture was concentrated (condensed air evaporation) to give **9**{1,1} (64.8 mg, 89%) as a white powder, mp 93-94 °C. ¹H-NMR (400 MHz, (CD₃)₂CO) δ 9.96 (br s, 1H, N-H), 9.14 (br s, 1H, N-H), 7.42-7.18 (m, 10H, phenyl C-H), 4.67 (d, *J* = 4.4 Hz, N-CH₂), 4.54 (s, 2H, S-CH₂), 3.31 (apparent q, 2H, *J* = 8 Hz, N-CH₂), 1.63-1.54 (m, 2H, C-CH₂), 0.98-0.95 (t, 3H, *J* = 7.4 Hz, C-CH₃). ¹³C-NMR (100 MHz, (CD₃)₂CO) δ 163.6, 159.2, 157.7, 157.6, 138.1, 136.0, 130.1, 129.9, 129.2, 129.0, 128.8, 128.6, 128.1, 127.9, 127.5, 126.8, 115.8, 43.4, 43.3, 41.1, 22.7, 11.3, 11.2. Following this procedure, also chemset **9**{1-7,1-6} were delivered.

General Procedure for the Preparation of homo-bisamides sulfones: 3-(pyridine-2-ylsulfonylmethyl)-N⁴,N⁵-dibenzylisoxazole-4,5-dicarboxamide **7{5,7}**

Hydrogen peroxide (30%; 39 µL, 0.382 mmol) and catalysts (including Aliquat®336, Na₂WO₄•2H₂O and C₆H₅PO₃H; 0.038 mmol each) were added to an acetic acid (2 mL) and EtOAc (2 mL) solution of **6**{5,7} (70 mg, 0.153 mmol). The resulting mixture was stirred at room temperature and monitored by TLC analysis (hexane:ethyl acetate = 1:1). After 12 h, TLC analysis indicated the reaction was complete. The reaction mixture was diluted with 5% NaOH (10 mL) and extracted with ethyl acetate (10mL × 2). The organic layer was collected and dried over anhydrous Na₂SO₄, filtered and concentrated onto a small amount of silica gel for dry loading flash column. A short column (hexane:ethyl acetate = 1:1) was preceded to remove biphasic catalyst to yield **7**{5,7} (60mg, 80%) as a white solid, mp 129-130 °C. Following this procedure, **7**{1-7, 1-7} as well as the mixed bisamides **10**{1-7, 1-6} were delivered.

General procedure for bioassays: insecticidal activity was evaluated as described previously.⁸ Briefly, the primary screen used two 96 well-based high throughput insect assays, one for beet armyworm (*Spodoptera exigua*: Lepidoptera) larvae and another for yellow fever mosquito (*Aedes aegypti*: Diptera). Artificial diet (100 µl/well, 96-well microtiter plate) that had been pretreated with test compounds (12 µg dissolved in 30 µl of DMSO-acetone-water (2:1:7) mixture, and then dried for several hours) was seeded with eggs of *S. exigua*. Infested plates were then covered, held in the dark (29°C), and the mortality recoded 6 days post-treatment. The *A. aegypti* assay used one-day old larvae pipetted into each well of pre-treated (6 µg/well, dissolved in 15 µl of DMSO-acetone-water (1:1:8) mixture, then allowed to dry) 96-well microtiter plate. The plates were covered with a lid held at room temperature, and then graded for mortality three days post-treatment. There were six replicates per treatment for each assay. Compounds active in the primary screen (67%) were further evaluated by means of a

larger format (3 mL, 128-well diet trays containing 1 mL of diet and selected dosages of the test compound) diet-based bioassay using second instar of *S. exigua* or *Helicoverpa zea* (corn earworm: Lepidoptera) larvae. The wells (eight per treatment) were covered with clear plastic and percent mortality (average of the eight wells) was recorded for each treatment five days after the assay was initiated. Approximate LC₅₀s (lethal concentration for 50% of the population) were estimated using probit analysis.

Results and Discussion

In our earlier work, we established that the C5 carbomethoxy of **1** was more reactive than the C4 carbomethoxy and, by exploiting this reactivity difference, we were able to elaborate isoxazole **1** to a 5-alkylcarbamoyl-3-arylsulfanylmethylisoxazole-4-carboxylic acid (**2**) library.⁷ Two additional enabling discoveries are reported here (Figure 2). The first is that thiolate nucleophiles chemoselectively engage the C3 chloromethyl electrophile. This observation suggested that isoxazole **1** might lead to homo bisamide **6** in two simple transformations: thiolate S_N2 displacement of chloride followed by concomitant C4/C5 ester → amide transformation. In addition, sulfone **7** could potentially be derived from **6** by S-oxidation.

Dimethyl 3-chloromethylisoxazole-4,5-dicarboxylate (**1**), prepared as previously described,⁷ reacts rapidly in the aprotic solvent DMF with aryl thiols **3**{1-7} in the presence of triethylamine to give the corresponding thioethers in quantitative yield **4**{1-7}; Scheme 1). No evidence for involvement of either ester is detected and the crude product of this reaction is obtained in such high purity that it can be employed in subsequent reactions without purification.

Treating a methanolic solution of crude bis-ester **4**{1-7} with an excess (10 eq.) of various primary amines **5**{1-7} at 40 °C for 30 min delivered novel homo bisamides **6**{1-7, 1-7} in 85-90% overall yield from chlorodiester **1**. Under these conditions no mixed ester/amide products were detected upon work-up, but TLC monitoring of this reaction did reveal the appearance of the presumed C5-amide/C4-ester intermediate which, in the presence of excess amine, then proceeds on to bisamide **6**.

The presumed intermediacy of a C5-amide/C4-ester led us to treat a methanol solution of crude bis-esters **4**{1-7} with primary amine **5**{7} at near stoichiometric levels and at room temperature (instead of 40 °C). Under these conditions, the reaction required 4-12 h for completion, but cleanly delivered the C5-amide/C4-ester. When TLC indicated complete consumption of bis-ester **4**{1-7}, an excess (10 eq.) of primary amine **5**{1-6} was added and stirring was continued for an additional 6-12 h. This protocol delivered forty-two mixed bisamides of general structure **8**{1-7} in 75-80% overall yield from chlorodiester **1**. Interestingly, the mixed bisamide **9**{2,5} has very low yield.

Two surprises accompanied this **8** → **9** transformation. First, allowing a methanolic solution of mono amide-mono ester **8** and excess (10 eq.) amine to stir at room temperature for multiple days led cleanly to the homo bisamide product **6** instead of the mixed bisamide **9**. That is, transamination of the C5 amide occurs under extended reaction times; even at room temperature. This transamination process can be expedited by warming the methanolic reaction mixture to 40 °C (homo bisamide obtained in 12 h). Second, and related to the first, concentration of the crude mono amide-mono ester **8** plus excess amine reaction mixture must be effected at room temperature; otherwise, a mixture (sometimes only pure bisamide **6**) of homo bisamide **6** and mixed bisamide **9** is obtained.

The regioselectivity of these mixed bisamide products **9** was, based on our previous results with **1**,⁷ presumed to derive from the first amine reacting at the C5 ester and the second amine

reacting at the C4 ester. To verify this, crystalline mixed bisamide **9**{1,1}, prepared by treatment first with benzyl amine (1.1 eq.) and subsequently with propyl amine (10 eq.), was evaluated by X-ray crystallographic analysis. As depicted in Figure 3, the first amine reacted at the C5 ester and the second amine reacted at the C4 ester.

The thioether moieties in homo bisamides **6**{1 - 7, 1 - 7} and mixed bisamides **9**{1 - 7, 1 - 6} were oxidized to the corresponding sulfones. While a number of reagents are effective for this transformation, green chemistry consideration led us to select a recently reported tungsten-mediated procedure which employs hydrogen peroxide as the stoichiometric oxidant. This procedure also employs [CH₃(n-C₈H₁₇)₃N]HSO₄ as a phase-transfer catalyst and C₆H₅P(=O)(OH)₂ as a phosphonic acid promoter.⁹ With this protocol, we were able to use an ethyl acetate/acidic acid solvent system instead of the more typical chlorohydrocarbon solvent. With catalytic Na₂WO₄/C₆H₅P(=O)(OH)₂/[CH₃(n-C₈H₁₇)₃N]HSO₄, (physiologically harmless), these oxidation reactions generally went to completion in 12 h at room temperature. TLC analysis indicated the presence of the sulfoxide intermediate and, in cases where sulfones/sulfoxide mixtures were obtained within 12 h, separation of the sulfoxide from the sulfone was accomplished by silica gel chromatography. In those cases where an allyl amide was present, ¹H-NMR analysis indicated that the C,C-double bond remained unaffected.

Finally, we attempted a one-pot conversion of 3-(chloromethyl)isoxazole-4,5-dicarboxylate **1** to mixed bisamide **9** by treating **1** sequentially with thiolate **3**{1}, benzylamine **5**{7} (1.1 eq.), and propan-2-amine **5**{5} in methanol. Various procedural modifications (equivalency, reaction temperature, reaction time, microwave vs. conventional heating, etc.) generally led to a mixture of homo and mixed bisamides which, due to quite similar R_f values, proved difficult to separate. Consequently, we found it to be more practical to effect **1** → **9** as a three-pot/no intermediate purification procedure.

Eighty of the compounds synthesized as part of this study were evaluated for insecticidal activity. The initial assays were high throughput screening (HTS) assays utilizing larvae of *Spodoptera exigua* (beet armyworm) and *Aedes aegypti* (yellow fever mosquito). None of compounds prepared via Scheme 1 were active against *A. aegypti* larvae. In contrast, more than half (68.8%) of the compounds tested exhibited >67% mortality in the *S. exigua* HTS assay (Tables 1-4) and nearly a fifth (18.8%) of the compounds tested exhibited 100% mortality. Further evaluation of the hits (>67% mortality) from the *S. exigua* HTS assay involved testing in a larger format assay against two lepidopteran species: *S. exigua* and *Helicoverpa zea* (corn earworm). Although none of the *S. exigua* HTS hits exhibited activity against *H. zea* larvae, five of the 44 hits (11.4%) exhibited some level of activity against *S. exigua* larvae in the follow-up assay (Table 1 entry 38; Table 2 entries 1 and 8; Table 3 entry 7, and Table 4 entry 5). Although the activity for all five compounds never exceeded 75% mortality at the 50 µg/cm² dose, two of the compounds (Table 2 entry 1 and 8) exhibited LC₅₀s (lethal concentration for 50% of the population) of approximately 30 and 19 µg/cm², respectively. Some structure activity relationship trends can be gained from these data. In general, it appears that the sulfones are more efficacious than the corresponding thioethers (Table 1, chemset **6** vs. Table 2 chemset **7**). One potential explanation for this observation could be that the thioether moiety is not oxidized to the corresponding sulfone by the insect larvae and/or that other parts of the molecules [i.e. amide linkages] are metabolized before thio-oxidation occurs. An electron withdrawing substituent on the S-aryl ring (in both the thioether and the sulfone series) appears to be advantageous for delivering secondary assay insecticidal activity (Table 1 entry 38; Table 4 entry 5). Although bisamide sulfones exhibited some of the best biological activity, it is interesting that, in general, there seems to be little insecticidal difference between the homo bisamide sulfone (Table 2, chemset **7**) and the mixed bisamide sulfone (Table 4 chemset **10**) series. Thus, there appears to be a degree of chemical flexibility in this particular bioactive scaffold.

While significantly less active than commercial standards such as spinosadTM ($LC_{50} = 0.06 \mu\text{g}/\text{cm}^2$),¹⁰ the compounds described herein did exhibit a hit rate that was far higher than typically seen in the random screening of diverse chemsets (~6%, Sparks and Lorschbach, unpublished data). However, the above normal hit rate in the HTS assay did not translate to high potency in the more demanding secondary assays. One reason for the lack of translation to secondary assays may be related to the non-aglike physical properties of these compounds. Future efforts around this series of compounds will expand the SAR trends, address potential metabolic handles in the analogs, and include inputs that lead to more aglike targets with less lipophilicity.

In summary, we have systematically exploited the three electrophilic centers in dimethyl 3-(chloromethyl)isoxazole-4,5-dicarboxylate to prepare 3-(arylthiomethyl)- and 3-(arylsulfonylmethyl)isoxazole-4,5-dicarboxamides. Eighty compounds from this library were evaluated for insecticidal activity and many of them exhibited HTS activity against *S. exigua*. Despite the fact that insecticidal activity diminished in secondary assays, second generation libraries will focus on improving the physical properties of the compounds by incorporating aglike features.¹¹ The HTS activity observed confirms that 3,4,5-trisubstituted isoxazoles present a bioactive scaffold that can be utilized to design novel insecticides. Moreover, as a lead generation effort, this library achieved its goal of producing actionable starting points for further exploitation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Zonisamide – an antiepileptic and antiobesity drug; 3-chloromethylisoxazole-4,5-dicarboxylate as a discovery platform.

Figure 2.
3-(Arylthiomethyl)isoxazole- and 3-(arylsulfonylmethyl)-isoxazole-4,5-dicarboxamides.

Figure 3. The X-ray crystallography-determined structure of **9** {1,1} [N⁵-benzyl-3-(phenylthiomethyl)-N⁴-propylisoxazole-4,5-dicarboxamide].

Scheme 1.

Reagents and conditions: (a) NH₂OH·HCl, water, RT, 30 min; not isolated. (b) DMAD, NaOCl, THF; 70%. (c) ArSH **3**{1-7}, Et₃N, DMF, 10 min; 95%. (d) RNH₂ **5**{1-7}; 10 eq., MeOH, 40 °C, 2 to 4 h; 85-90%. (e) C₆H₅CH₂NH₂, **5**{7}; 1.1 eq., MeOH, RT, 4-5 h; (f) RNH₂ **5**{1-6}; 10 eq., MeOH, RT, 12 h; 75-80%. (g) H₂O₂, Q⁺HSO₄⁻ (PTC phase-transfer-catalyst), Na₂WO₄·2H₂O, C₆H₅PO₃H, EtOAc, HOAc, RT, 1 h.

Table 1

Biological activity against *Spodoptera exigua* (beet armyworm) for homo bisamide thioether derivative (chemset 6).

Entry	Ar	R	% mortality against <i>Spodoptera exigua</i> in HTS	% mortality against <i>Spodoptera exigua</i> in secondary assay
1	C ₆ H ₅	CH ₃ CH ₂ CH ₂	50	NT
2	4-Cl-C ₆ H ₄	CH ₃ CH ₂ CH ₂	50	NT
3	4-F-C ₆ H ₄	CH ₃ CH ₂ CH ₂	33	NT
4	3,5-(Me) ₂ C ₆ H ₃	CH ₃ CH ₂ CH ₂	50	NT
5	2-pyridine	CH ₃ CH ₂ CH ₂	50	NT
6	3-OMeC ₆ H ₄	CH ₃ CH ₂ CH ₂	50	NT
7	4-pyridine	CH ₃ CH ₂ CH ₂	33	NT
8	C ₆ H ₅	CH ₂ =CHCH ₂	33	NT
9	4-Cl-C ₆ H ₄	CH ₂ =CHCH ₂	17	NT
10	4-F-C ₆ H ₄	CH ₂ =CHCH ₂	67	0
11	3,5-(Me) ₂ C ₆ H ₃	CH ₂ =CHCH ₂	17	NT
12	2-pyridine	CH ₂ =CHCH ₂	17	NT
13	3-OMeC ₆ H ₄	CH ₂ =CHCH ₂	67	0
14	4-pyridine	CH ₂ =CHCH ₂	17	NT
15	C ₆ H ₅	CH ₃ OCH ₂ CH ₂	83	0
16	4-Cl-C ₆ H ₄	CH ₃ OCH ₂ CH ₂	83	0
17	4-F-C ₆ H ₄	CH ₃ OCH ₂ CH ₂	67	0
18	3,5-(Me) ₂ C ₆ H ₃	CH ₃ OCH ₂ CH ₂	NT	NT
19	2-pyridine	CH ₃ OCH ₂ CH ₂	17	NT
20	3-OMeC ₆ H ₄	CH ₃ OCH ₂ CH ₂	67	0
21	4-pyridine	CH ₃ OCH ₂ CH ₂	50	NT
22	C ₆ H ₅	CH ₃ CH ₂ CH ₂ CH ₂	NT	NT
23	4-Cl-C ₆ H ₄	CH ₃ CH ₂ CH ₂ CH ₂	33	NT
24	4-F-C ₆ H ₄	CH ₃ CH ₂ CH ₂ CH ₂	50	NT
25	3,5-(Me) ₂ C ₆ H ₃	CH ₃ CH ₂ CH ₂ CH ₂	NT	NT
26	2-pyridine	CH ₃ CH ₂ CH ₂ CH ₂	NT	NT
27	3-OMeC ₆ H ₄	CH ₃ CH ₂ CH ₂ CH ₂	NT	NT
28	4-pyridine	CH ₃ CH ₂ CH ₂ CH ₂	67	0
29	C ₆ H ₅	(CH ₃) ₂ CH	67	0
30	4-Cl-C ₆ H ₄	(CH ₃) ₂ CH	83	0
31	4-F-C ₆ H ₄	(CH ₃) ₂ CH	50	NT
32	3,5-(Me) ₂ C ₆ H ₃	(CH ₃) ₂ CH	NT	NT
33	2-pyridine	(CH ₃) ₂ CH	50	NT
34	3-OMeC ₆ H ₄	(CH ₃) ₂ CH	0	NT
35	4-pyridine	(CH ₃) ₂ CH	NT	NT

Entry	Ar	R	% mortality against <i>Spodoptera exigua</i> in HTS	% mortality against <i>Spodoptera exigua</i> in secondary assay
36	C ₆ H ₅	(CH ₃) ₂ CH ₂ CH ₂	33	NT
37	4-Cl-C ₆ H ₄	(CH ₃) ₂ CH ₂ CH ₂	100	0
38	4-F-C ₆ H ₄	(CH ₃) ₂ CH ₂ CH ₂	100	38
39	3,5-(Me) ₂ C ₆ H ₃	(CH ₃) ₂ CH ₂ CH ₂	NT	NT
40	2-pyridine	(CH ₃) ₂ CH ₂ CH ₂	NT	NT
41	3-OMeC ₆ H ₄	(CH ₃) ₂ CH ₂ CH ₂	NT	NT
42	4-pyridine	(CH ₃) ₂ CH ₂ CH ₂	83	0
43	C ₆ H ₅	C ₆ H ₅ CH ₂	67	NT
44	4-Cl-C ₆ H ₄	C ₆ H ₅ CH ₂	67	0
45	4-F-C ₆ H ₄	C ₆ H ₅ CH ₂	67	0
46	3,5-(Me) ₂ C ₆ H ₃	C ₆ H ₅ CH ₂	83	0
47	2-pyridine	C ₆ H ₅ CH ₂	67	0
48	3-OMeC ₆ H ₄	C ₆ H ₅ CH ₂	50	NT
49	4-pyridine	C ₆ H ₅ CH ₂	NT	NT

NT = not tested

Table 2

Biological activity against *Spodoptera exigua* (beet armyworm) for homo bisamide sulfone derivative (chemset 7).

Entry	Ar	R	% mortality against <i>Spodoptera exigua</i> in HTS	% mortality against <i>Spodoptera exigua</i> in secondary assay
1	C ₆ H ₅	CH ₃ CH ₂ CH ₂ CH ₂	100	75
2	C ₆ H ₅	(CH ₃) ₂ CH	100	0
3	C ₆ H ₅	CH ₃ CH ₂ CH ₂	100	0
4	C ₆ H ₅	CH ₂ =CHCH ₂	100	0
5	4-Cl-C ₆ H ₄	CH ₃ CH ₂ CH ₂ CH ₂	100	0
6	4-Cl-C ₆ H ₄	CH ₃ OCH ₂ CH ₂	100	0
7	4-Cl-C ₆ H ₄	CH ₂ =CHCH ₂	100	0
8	C ₆ H ₅	CH ₃ OCH ₂ CH ₂	83	75
9	4-Cl-C ₆ H ₄	CH ₃ CH ₂ CH ₂	83	0
10	4-Cl-C ₆ H ₄	(CH ₃) ₂ CH	97	0

Table 3

Biological activity against *Spodoptera exigua* (beet armyworm) for mixed bisamide thioether derivatives (chemset **9**).

Entry	Ar	R	% mortality against <i>Spodoptera exigua</i> in HTS	% mortality against <i>Spodoptera exigua</i> in secondary assay
1	4-Cl-C ₆ H ₄	(CH ₃) ₂ CH	100	0
2	4-Cl-C ₆ H ₄	CH ₃ CH ₂ CH ₂	100	0
3	C ₆ H ₅	CH ₃ CH ₂ CH ₂ CH ₂	100	0
4	4-Cl-C ₆ H ₄	CH ₃ CH ₂ CH ₂ CH ₂	83	0
5	4-Cl-C ₆ H ₄	CH ₂ =CHCH ₂	83	0
6	C ₆ H ₅	(CH ₃) ₂ CH	83	0
7	C ₆ H ₅	CH ₃ CH ₂ CH ₂	83	38
8	4-Cl-C ₆ H ₄	(CH ₃) ₂ CH ₂ CH ₂	67	0
9	C ₆ H ₅	(CH ₃) ₂ CH ₂ CH ₂	67	0
10	C ₆ H ₅	CH ₃ OCH ₂ CH ₂	17	NT
11	4-Cl-C ₆ H ₄	CH ₃ OCH ₂ CH ₂	17	NT
12	C ₆ H ₅	CH ₂ =CHCH ₂	0	NT

NT = not tested

Table 4

Biological activity against *Spodoptera exigua* (beet armyworm) for mixed bisamide sulfone derivatives (chemset 10).

Entry	Ar	R	% mortality against <i>beet armyworm</i> in HTS	% mortality against <i>beet armyworm</i> in secondary assay
1	C ₆ H ₅	CH ₃ OCH ₂ CH ₂	100	NT
2	C ₆ H ₅	CH ₂ =CHCH ₂	100	0
3	C ₆ H ₅	CH ₃ CH ₂ CH ₂	100	0
4	4-Cl-C ₆ H ₄	CH ₃ OCH ₂ CH ₂	100	0
5	4-Cl-C ₆ H ₄	CH ₂ =CHCH ₂	100	38
6	4-Cl-C ₆ H ₄	CH ₃ CH ₂ CH ₂	100	0
7	4-Cl-C ₆ H ₄	CH ₃ CH ₂ CH ₂ CH ₂	83	0
8	C ₆ H ₅	CH ₃ CH ₂ CH ₂ CH ₂	67	0
9	4-Cl-C ₆ H ₄	(CH ₃) ₂ CH	NT	NT

NT = not tested