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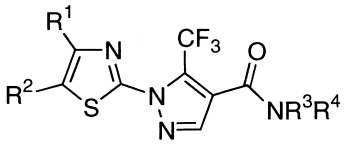
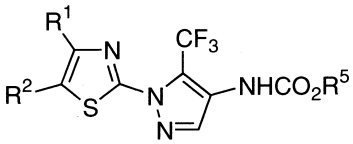


11 422-member library



16 108 member library

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Design, Synthesis, and Biological Evaluation of a Library of 1-(2-Thiazolyl)-5-(trifluoromethyl)pyrazole-4-carboxamides

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A library of 422 1-(2-thiazolyl)-5-(trifluoromethyl)pyrazole-4-carboxamides was prepared in five steps using solution-phase chemistry. The first step in the synthesis was the reaction of ethyl 2-ethoxymethylene-3-oxo-4,4,4-trifluorobutanoate with thiosemicarbazide, which is reported in the literature to afford a 1:1 mixture of ethyl 1-thiocarbamoyl-5-(trifluoromethyl)pyrazole-4-carboxylate and ethyl 1-thiocarbamoyl-3-(trifluoromethyl)pyrazole-4-carboxylate. We reassigned the structure of the product to be a single compound, ethyl 5-hydroxy-1-thiocarbamoyl-5-(trifluoromethyl)-4,5-dihydro-1*H*-pyrazole-4-carboxylate. This common intermediate was diversified by reaction with 17 α-bromoketones affording, in two steps, 17 1-(2-thiazolyl)-5-(trifluoromethyl)pyrazole-4-carboxylic acids. Scavenger resins were used to facilitate formation and purification of up to 27 amides from each of these acids in the last step. In addition, the Curtius reaction was applied to 12 of the acids followed by quenching with alcohols to afford a 108-member carbamate library. Certain compounds in the two libraries were toxic to *C. elegans*.

Introduction

Fluorinated compounds in general, and fluorinated heterocycles in particular, continue to play an increasingly important role as agrochemicals[1] and pharmaceuticals.[2] Ethyl 3-oxo-4,4,4-trifluorobutanoate (**1**, Figure 1) and its derivatives ethyl 2-chloro-3-oxo-4,4,4-trifluorobutanoate (**2**), ethyl 2-ethoxymethylene-3-oxo-4,4,4-trifluorobutanoate (**3**), and ethyl 3-amino-4,4,4-trifluorocrotonate (**4**) have proved to be versatile building blocks for the construction of a wide variety of trifluoromethyl-substituted heterocycles.[3−24] These include pyrazoles,[3−6] isoxazoles,[7,8] thiazoles,[9] pyridines,[10−14] pyrimidines,[15−19] and pyrones.[20,21] The resulting compounds have been reported to possess biological activity as herbicides,[16,22,23] fungicides,[24] inhibitors of platelet aggregation,[6] androgen receptor agonists and antagonists[13,14,20] and hypoglycemics.[25]

Our attention was drawn to building blocks **1**−**4** as attractive starting points for the production of a number of small libraries (100−500 members each), based on various trifluoromethyl-substituted heterocyclic scaffolds, for agrochemical lead discovery. In this context we became interested in a literature report[6] on certain amides of general structure **11** (Scheme 1, R^1 = aryl, R^2 = H, R^3 = aminoalkyl, R^4 = H) synthesized as inhibitors of fibrinogen-mediated platelet aggregation. There appeared to be significant scope to produce a library of compounds based on this chemistry but with greater diversity than those reported to date by using a more diverse set of α-bromoketones **7** in the second step, leading to additional variations in R^1 and R^2, and a more diverse set of amines **10** in the final step, leading to additional variations in R^3 and R^4. Furthermore, we anticipated that the previously unreported Curtius rearrangement of acids **9** would afford new aminopyrazole scaffolds that would form the basis of a second library. This article describes the design, solution-phase synthesis, and screening against *C. elegans* of two libraries of 1-(2-thiazolyl)-5-(trifluoromethyl)pyrazoles.

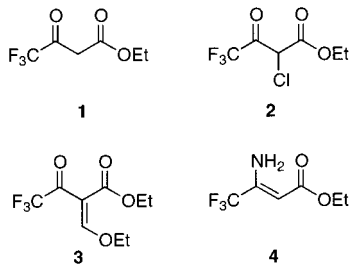

Figure 1. Ethyl 3-oxo-4,4,4-trifluorobutanoate and its derivatives.

Library Design

Our library design goals were twofold. We wanted to maximize the diversity of the library; however, we wanted the majority of the library members to be compliant with Lipinski's rule of 5[26] and similar rules developed for agrochemicals.[27] The molecular weight of the scaffold is 264, which limits the combined molecular weights of substituents

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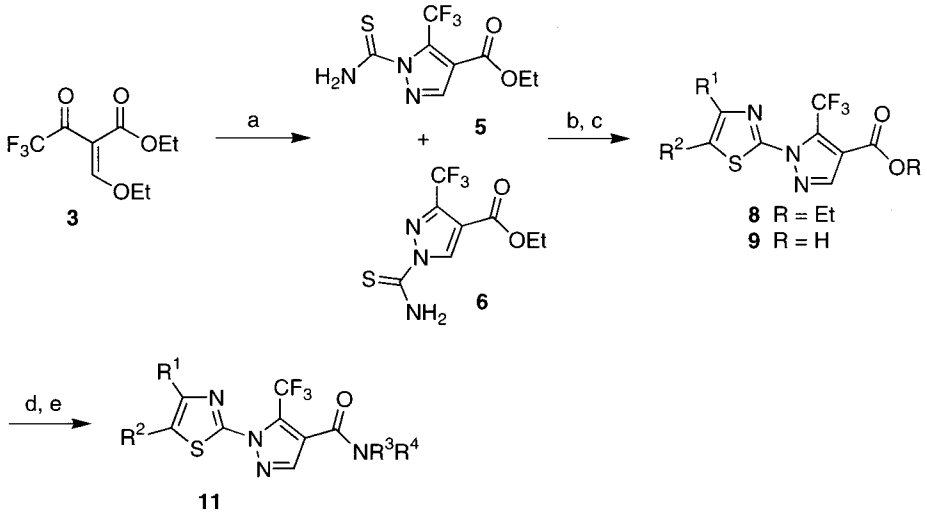
Scheme 1. Literature Route to 1-(2-Thiazolyl)-5-(trifluoromethyl)pyrazole-4-carboxamides[a]



[a] (a) $H_2NC(=S)NHNH_2$, EtOH, −15 °C to room temperature; (b) $R^1C(=O)CHR^2Br$ (**7**), EtOH, reflux; (c) KOH, EtOH, reflux; (d) carbonyl diimidazole, DMF; (e) $R^3R^4NH_2$ (**10**).

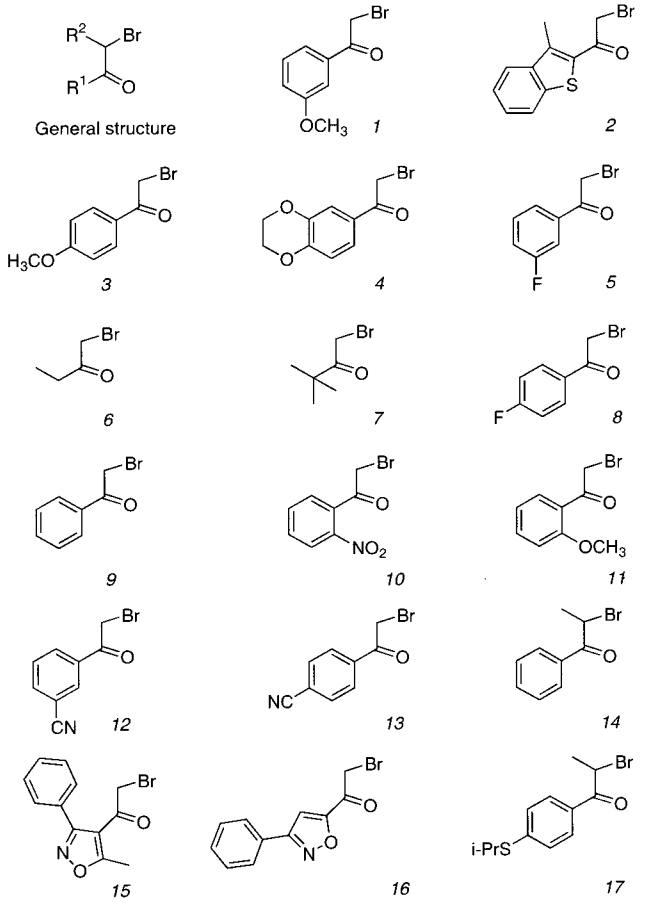


Figure 2. α-Bromoketones **7** used for library production.

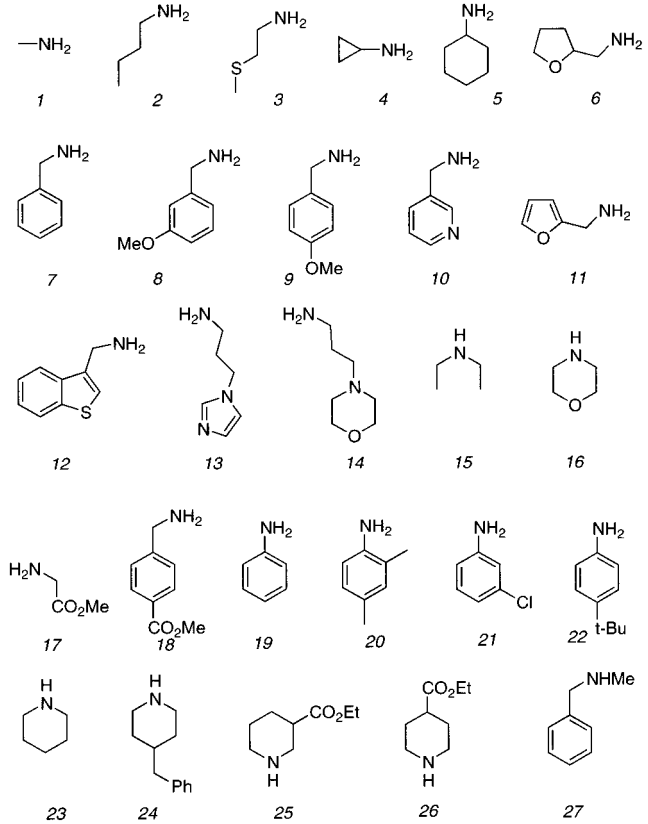


Figure 3. Amines **10** used for library production.

R^1-R^4 to be ≤236, if the molecular weight limit of Lipinski's rule of 5 (≤500) is to be met. On the other hand the scaffold is rich in nitrogen and oxygen atoms, which allows R^1-R^4 to be hydrophobic substituents while still meeting the Lipinski rule clogP limit for the molecule. Hydrophobic α-bromoketone (**7**) and amine (**10**) building blocks are readily available. A total of 17 commercially available α-bromoketones **7**{*1*−*17*} (Figure 2) and 27 amines **10**{*1*−*27*} (Figure 3) were selected on the basis of diversity and price. Preference was given to building blocks containing polar functional groups that would provide additional pharmacophoric elements beyond those present in the scaffold. The α-bromoketone set is heavily dominated by phenacyl bromides (**10**, R^1 = substituted-Ph, R^2 = H). The amine set contains both primary and secondary amines and includes anilines as well as alkylamines and benzylamines.

The 2D diversity of the virtual libraries built from these building blocks was unimpressive because of the large size of the scaffold; however, as stated in the Introduction, our ultimate intent was to achieve diversity by preparing several modest-sized (100−500-member) libraries with different

heterocyclic scaffolds, all prepared from ethyl 3-oxo-4,4,4-trifluorobutanoate **1** and its derivatives **2**−**4** rather than from a single very large library. Thus, the overall diversity of the entire collection of compounds ultimately produced would depend significantly on the use of several different scaffolds, as well as on the substituents appended to the scaffolds. The two libraries described in this paper are the first phase of this larger design.

The distributions of molecular weight, clogP, hydrogen bond acceptors, and rotatable bonds for the planned synthesis library derived from **7**{*1*−*17*} and **10**{*1*−*27*} are shown in Figure 4. About a quarter of the library exceeds the Lipinski molecular weight limit of 500, but none of the library members exceed 600. Three-quarters of the library members have clogP values below 5. None of the library members have more than 10 hydrogen bond acceptors, and the maximum number of rotatable bonds is also 10. The 340 library members derived from primary amines **10**{*1*−*14,17*−*22*} possess one hydrogen bond donor, while the 119 members derived from secondary amines possess no hydrogen bond donors.

Chemistry

Initially we contemplated solid-phase synthesis of the library of amides **11**. The synthetic sequence in Scheme 1 might be adapted to solid phase by replacing the ethyl ester in **3** with an analogous resin-bound ester (Scheme 2), and in fact the preparation of solid-supported analogues of compound **3** has been reported in the literature.[28,29] The ester linkage to the resin would need to withstand thiosemicarbazide but react with amine **10** to afford the desired amides **11**. These constraints could probably be met with an ester safety catch linker (Scheme 2, reaction 1)[30] or by susbstituting the ester with an acylsulfonamide linker (Scheme 2, reaction 2).[31] Alternatively, **3** might be attached as a more stable amide to an N-alkylated Rink resin and cleaved at the end of the sequence by acid treatment.[32] In this case R^4 would necessarily be H and R^3 would be limited to groups that could be alkylated onto Rink resin. Of greater concern for a solid-phase approach was the literature report that condensation of **3** with thiosemicarbazide afforded a 1:1 mixture of **5** and its regioisomer **6** (Scheme 1) and, somewhat surprisingly, that isomer **6** did not react with α-bromoketones **7**.[6] While it was possible that this reaction would lead to a different, and perhaps more favorable, ratio of the resin bound analogues of **5** and **6** when implemented on a polymer support, the pollution of the final products by undesired products derived from unreacted **6** was seen as a serious problem with the sequence because each product would require purification. Finally, it was unclear to us whether the effort to develop a multistep solid-phase synthetic sequence was warranted given that, at least initially, we intended to prepare a library of only a few hundred compounds based on this heterocyclic core. The lack of regioselectivity in the preparation of **5** is much less problematic in a solution-phase approach because it occurs prior to the introduction of diversity. In principle, only a single large-scale separation of **5** from **6** would be required to allow library production. Thus, we embarked upon a solution-phase approach.

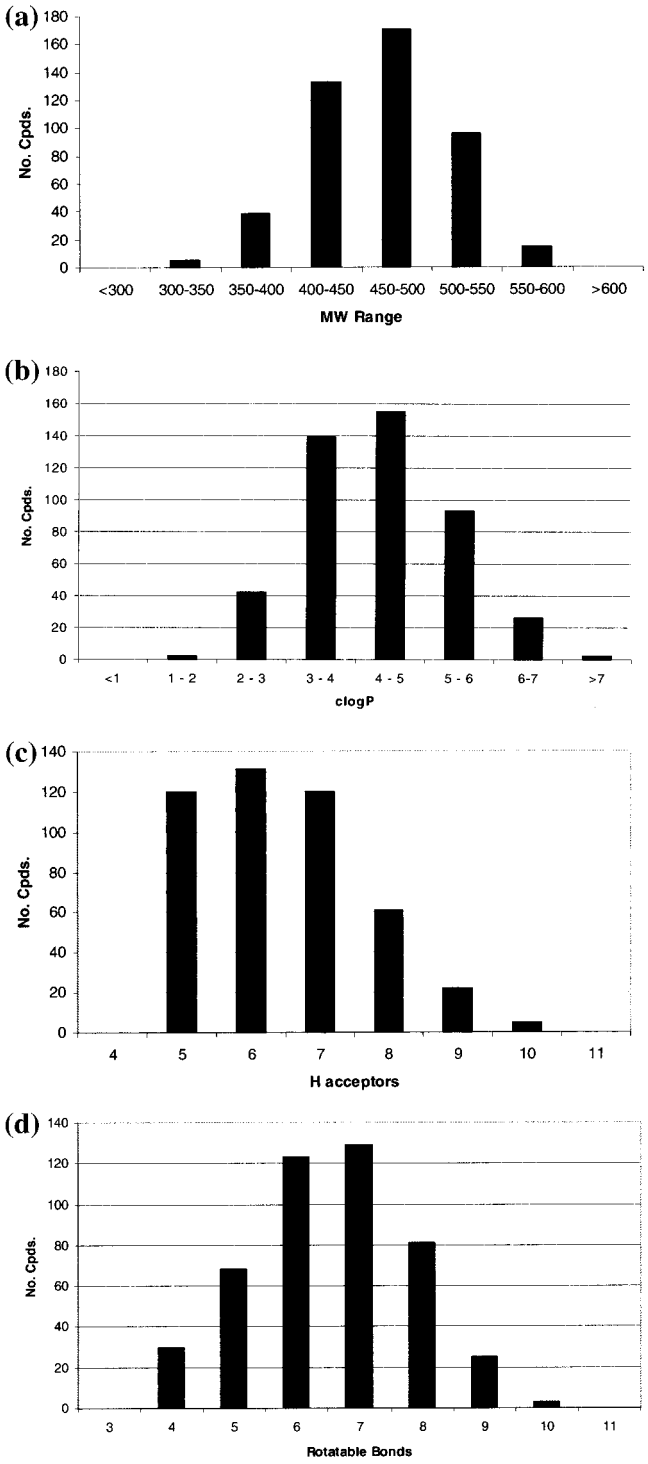
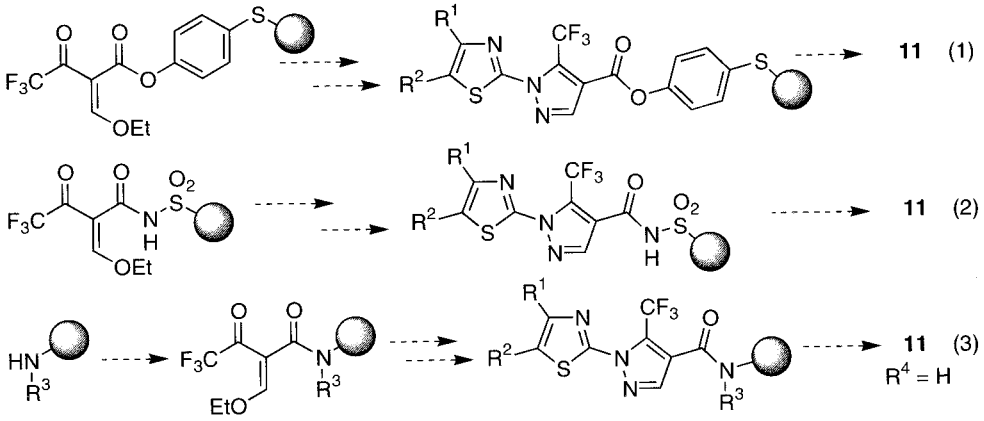


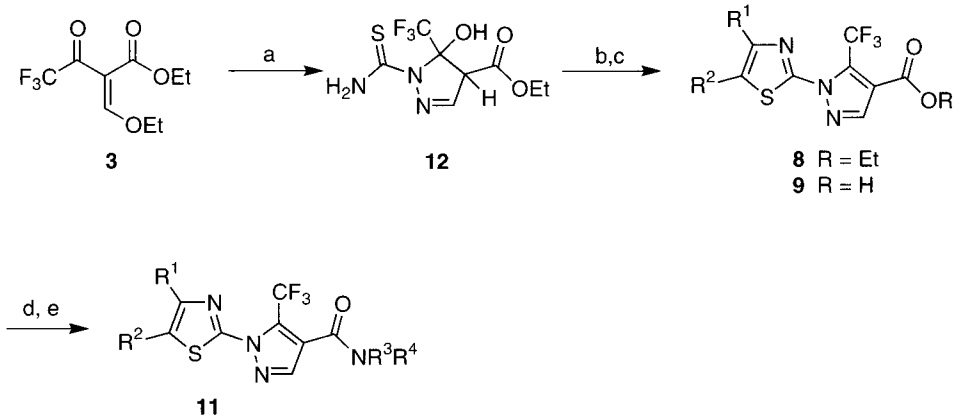
Figure 4. Property distributions of library members: (a) molecular weight; (b) clogP; (c) hydrogen bond acceptors; (d) rotatable bonds.

As a first step, we set out to reproduce the literature preparation of ethyl 1-thiocarbamoyl-5-trifluoromethyl-1*H*-pyrazole-4-carboxylate **5** (Scheme 1).[6] Ethyl 2-ethoxymethylene-3-oxo-4,4,4-trifluorobutanoate (**3**) was condensed with thiosemicarbazide, using the reported conditions.[6] Contrary to the literature, we obtained only a single product and its ^{1}H NMR, ^{13}C NMR, and IR spectra were consistent with one of the diastereomers corresponding to structure **12** (Scheme 3) rather than with a mixture of **5** and **6** (Scheme 1). Thus, the ^{13}C NMR spectrum of the product has only eight peaks as expected for a single compound. If the product

Scheme 2. Possible Solid-Phase Approaches to 1-(2-Thiazolyl)-5-(trifluoromethyl)pyrazole-4-carboxamides



Scheme 3. Solution-Phase 1-(2-Thiazolyl)-5-(trifluoromethyl)pyrazole-4-carboxamide Library Production Route[a]



[a] (a) $H_2NC(=S)NHNH_2$, EtOH, −15 °C to room temperature; (b) $R^1C(=O)CHR^2Br$ (**7**), EtOH, reflux; (c) KOH, EtOH, reflux; (d) $(COCl)_2$, DMF, CH_2Cl_2; (e) (i) R^3R^4NH (**10**), PS-morpholine, CH_2Cl_2, (ii) PS-isocyanate.

were a mixture of **5** and **6**, up to 16 peaks would be expected. Furthermore, the presence of the resonances at 92.95, which we assigned to be the quaternary carbon bearing the OH and CF_3 groups in **12**, and at 60.98, which we assigned to be the carbon bearing the ethoxycarbonyl group, is difficult to rationalize on the basis of structure **5** or **6**. The ^1H NMR spectrum shows a singlet at 8.9 ppm and two broad peaks at 8.2 and 8.3 ppm, all of which exchange with D_2O, consistent with the OH and NH_2 protons in structure **12**. A 2D HMQC NMR spectrum confirmed that none of these three protons was attached to a carbon atom. The remaining four peaks in the ^1H NMR spectrum consisted of two singlets at 7.4 and 4.5 ppm, integrating for 1 hydrogen each, which we assigned to be C_3-H and C_4-H, respectively, and the characteristic ethyl ester quartet, integrating for two hydrogens at 4.25 ppm, and the corresponding triplet at 1.30 ppm, integrating for three hydrogens. Furthermore, the elemental analysis of the product was consistent with the formula of **12**. A literature search uncovered a number of precedents for structure **12**.[33,34] Closer examination of the paper describing the preparation of **5** revealed a discrepancy between the description of the chemistry in the text and the experimental section.[6] In the text of the article **3** and thiosemicarbazide are reported to afford a 1:1 mixture of **5** and **6** and it is stated that **6** does not react with phenacyl bromides **7**. However, in the experimental section an unseparated 1:1 mixture of **5** and **6** is reported to react with 3-(trifluoromethyl)phenacyl bromide to afford an 82% yield of **8** (R^1 = 3-CF_3−Ph, R^2 = H). In our hands several attempts to convert **12** to **5** using thermal and acidic conditions afforded either recovered starting material or unidentified decomposition products that did not have spectroscopic features consistent with structure **5**. The stereochemistry of **12** was not determined.

Notwithstanding our reassignment of the structure of the adduct of thiosemicarbazide and **3**, we proceeded to react **12** with bromomethyl ethyl ketone **7**{*6*} in refluxing ethanol and obtained the desired product **8**{*6*} in 59% yield (Scheme 3). Water was eliminated from the hydroxypyrazole ring under the conditions of this reaction, presumably after reaction of **12** with **7**. Following the literature procedure, ester **8**{*6*} was saponified with KOH in ethanol at reflux to afford acid **9**{*6*} in quantitative yield. To make the chemistry more amenable to automation, we chose to activate **9**{*6*} as its acid chloride by treatment with oxalyl chloride rather than as its acyl imidazole derivative as reported in the literature. The acid chloride of **9**{*6*} reacted smoothly with benzylamine **10**{*7*} to give the desired product **11**{*6,7*} in good yield and >95% purity based on evaporative light scattering.

For library production batches of acids **8**{*1*−*17*} were prepared by standard solution chemistry. The 17 α-bromoketones **7**{*1*−*17*} all reacted sufficiently well with **12** to afford useable quantities of esters **8**. However, α-bromoketones **7**{*14,17*} that have a secondary bromide and **7**{*6,7*} with aliphatic R^1 groups generally gave poorer yields than

	α-Bromoketone (7)																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Amine (10)																	
1	++	++	++	+	+	++	+	+	++	++	++	++	++	++	+	+	
2	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	
3	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
4	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
5	++	++	++	++	++	++	++	++	++	--	++	++	++	++	++	++	
6	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	+	
7	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
8	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	
9	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	
10	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
11	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	
12	-	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	
13	++	++	++	++	++	++	++	+	++	+	+	+	+	+	+	+	+
14	++	++	++	++	++	++	++	++	++	+	+	++	++	++	++	++	++
15	++	++	++	++	++	++	++	++	++	++	++	++	++		++	-	
16	++	++	++	++	++	++	++	++	++	++	++	++	++		++	++	++
17	+	++	+	++	++	+	+	++	+	+	++	+	+		++	++	++
18	++	-	++	-	-	++	++	-	+	++	++	+	+		++	++	
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25	++	++	++	++	++	++	++	++	++	++	++	++	++		++	++	
26	++	++	++	++	++	++	++	++	++	++	++	++	++		++	++	
27	++	++	++	++	++	+	++	++	++	++	++	++	++		++	++	

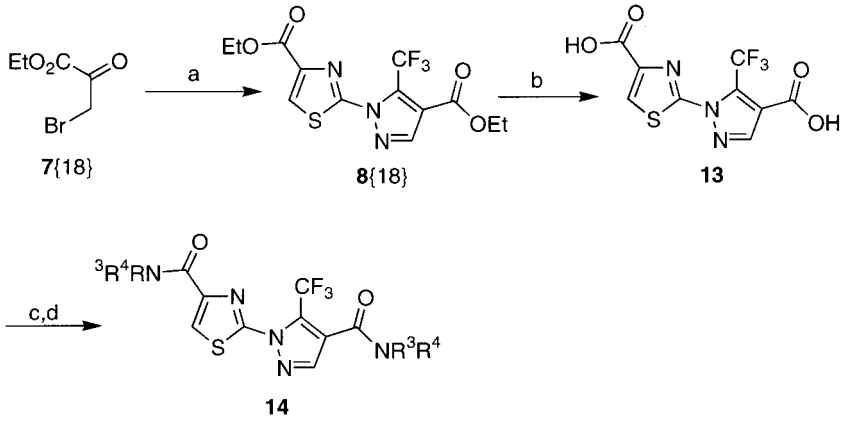
Figure 5. Purity and biological activity of library of amides **11**. The purity was determined on the basis of evaporative light-scattering detection and is indicated as follows: 80−100% = ++, 40−80% = +, 0−40% = − (compound not tested). Blank cells represent reagent combinations that were not attempted. Compounds active against *C. elegans* are indicated with a gray background.

those with primary bromides and aromatic R^1 groups. The very hindered adamantyl bromomethyl ketone failed to give any of the desired product. To increase throughput in the final amide-forming step, the reactions were run in arrays of polypropylene cartridges using a slight excess of amine **10** in the presence of morpholinomethylpolystyrene as base. At the end of the reactions excess amine was scavenged using polymer-bound isocyanate.[35,36] The entire library of amides **11** was characterized by LC−MS with combined UV and evaporative light-scattering detection (ELSD). Purities were assigned on the basis of ELSD. In addition, a random sample of compounds representing 5% of the library was characterized by ^{1}H NMR. A total of 422 of the 459 possible library members were produced, and over 90% of them were formed in >80% purity (Figure 5). Thirty-six library members were 40−80% pure, and in six cases either the desired amide **11** was not formed or the purity was <40% and the product was discarded. Because of limitations on the quantities of acids **9**{*14,17*}, these acids were reacted only with certain members of the panel of amines **10**. Overall, amines **10**{*1,13,17,18*} gave the poorest results in terms of product purity. The volatility of methylamine **10**{*1*} may have led to some loss from the reaction mixture, while aminoesters **10**{*17,18*} are less nucleophilic than typical primary amines and thus less reactive both with acid chlorides and with the isocyanate scavenger resin.

A small sublibrary of 18 diamides **14** (Scheme 4) deserves comment. Use of ethyl bromopyruvate **7**{*18*} afforded the expected diester **8**{*18*}. Saponification gave the diacid **13**, which was converted to diamides **14** by applying the same conditions used to convert **9** to **11** except that double the amounts of oxalyl chloride, amines **10**, and the scavenger resins were used. This procedure afforded the 17 diamides **14**{*1−11,14−16,19,23,27*} in >80% purity. The diamide **14**{*17*}derived from glycine methyl ester **10**{*17*} was the only compound of low purity (∼45%). As noted above **10**{*17*} often afforded products of low purity.

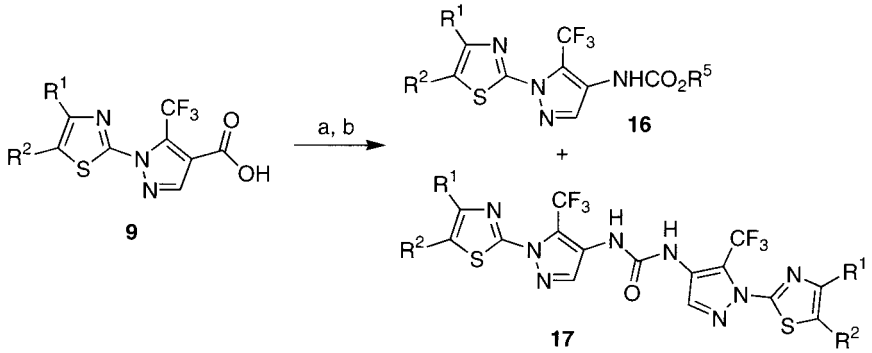
We next attempted the Curtius reaction of acids **9**.[37] In an initial experiment **9**{*5*} was refluxed with diphenylphosphoryl azide in benzene in the presence of triethylamine and quenched by addition of ethanol to afford not only the desired ethyl carbamate **16**{*5,1*} but also the symmetrical urea **17**{*5*} (Scheme 5). Running the reaction in the presence of ethanol, rather than adding it at the end of the reaction, substantially decreased the amount of **17**{*5*} formed and afforded **16**{*5,1*} in acceptable purity. On the basis of this chemistry, a library of 108 carbamates **16** was prepared using acids **9**{*1−5,7−13*} and the alcohols **15**{*1−10*} depicted in Figure 6. The

Scheme 4. Diamide Sublibrary[a]



[a] (a) **12**, EtOH, reflux; (b) KOH, EtOH, reflux; (c) $(COCl)_2$, DMF, CH_2Cl_2; (d) (i) R^3R^4NH (**10**), PS-morpholine, CH_2Cl_2, (ii) PS-isocyanate.

Scheme 5. Curtius Reaction of Acids **9**[a]



[a] (a) $(PhO)_2P(=O)N_3$, Et_3N, C_6H_6, reflux; (b) R^5OH (**15**).

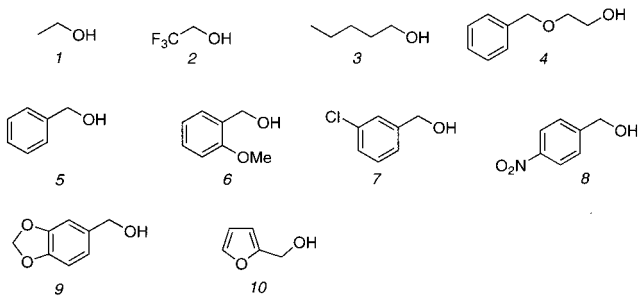


Figure 6. Alcohols **15** used for carbamate library production.

purities of the members of this library are summarized in Figure 7.

Screening Results

The libraries of amides **11** and carbamates **16** were screened in a number of whole-organism agrochemical bioassays, including one utilizing *C. elegans*. The nematode *C. elegans* has been used as an indicator organism for insecticidal activity, pharmacological activity, and environmental toxicity.[38−40] It is an attractive organism for screening because its genome has been sequenced and its biology is well understood.[41]

Fifteen members of the library of 1-(2-thiazolyl)-5-(trifluoromethyl)pyrazole-4-carboxamides **11** were active in the *C. elegans* bioassay (Figure 5). The α-bromoketone building blocks that appeared most frequently in active compounds were **7**{*8,9*}, which occurred three times, and **7**{*13*}, which appeared twice, while amine building block **10**{*27*} occurred four times, **10**{*20*} three times, and **10**{*14*} twice. Notably, however, the library members formed by combining the most frequently occurring building blocks **7**{*8,9*} and **10**{*27*} were not active, suggesting that more than one island of activity may be present in the library. A number of strategies could be adopted to design followup libraries. For example, the activity of **11**{*7,20*}, **11**{*8,19*}, **11**{*8,20*}, and **11**{*9,20*} suggests that a followup library based on additional para-substituted phenacyl bromides **7** and anilines **10** might be of interest. Interestingly, although the majority of the active compounds were within the Lipinski's rule of 5[26] limits for molecular weight, hydrogen bond donors, and hydrogen bond acceptors, over half had clogP above 5. In the library of carbamates **16**, activity was confined to carbamates derived from the aliphatic alcohols **15**{*1*} and **15**{*3*}, suggesting that a followup library incorporating additional alcohols of this type would be desirable. In the event, none of the hits in the *C. elegans* bioassay were active in subsequent testing against an agriculturally important nematode or against any insect species tested, and no followup synthesis was performed.

Conclusions

Application of standard solution-phase chemistry allowed us to produce 17 acids **9**{*1*−*17*} in gram quantities. These acids were efficiently diversified by amide formation with up to 27 amines, using scavenger resin technology to afford a library of 422 amides **11**. In addition, 12 of the acids **9** were subjected to Curtius rearrangement and the resulting isocyanates were intercepted with 10 alcohols to afford a

				α-Bromoketone (7)								
	1	2	3	4	5	7	8	9	10	11	12	13
Alcohol (15)												
1	++	++	++	++	++	++	++	++	++	++	+	++
2	++	++	++	++	++	++	++	++	++	++	+	++
3	++	++	+	++	++	+	++	++	++	++	++	+
4	++	++	+	++	++	-	++	++	++	++	++	++
5	++	++	+	++	++	+	++	++	-	++	++	+
6	++	-	++	++	++	+	++	++	++	++	++	++
7	++	-	+	+	+	+	++	++	++	+	++	+
8	-	-	+	+	++	+	++	++	++	++	-	-
9	++	-	+	++	++	++	++	++	+	++	++	++
10	++	+	++	++	++	++	++	-	++	-	-	++

Figure 7. Purity and biological activity of library of carbamates **16**. The purity was determined on the basis of evaporative light-scattering detection and is indicated as follows: 80−100% = ++, 40−80% = +, 0−40% = − (compound not tested). Blank cells represent reagent combinations that were not attempted. Compounds active against *C. elegans* are indicated with a gray background.

library of 108 carbamates **16**. Most of the library members lie within druglike space as defined by Lipinski's rule of 5. Certain members of these libraries were toxic to *C. elegans*.

Experimental Procedures

General. Unless otherwise stated, all reagents were purchased from commercial sources and used without further purification. Resins were purchased from Novabiochem. Melting points were obtained on a Perkin-Elmer Pyris I differential scanning calorimeter. ^{1}H NMR spectra were acquired at 400 MHz on a Bruker DMX400 or at 300 MHz on a Bruker DPX300. ^{13}C NMR spectra were recorded at 100 MHz on a Bruker DMX400 or at 75 MHz on a Bruker DPX300. ^{19}F NMR spectra were recorded on a Bruker DPX300 at 282 MHz. Infrared spectra were recorded on a Perkin-Elmer Spectrum 1000 with Golden Gate. LC−MS experiments were run on a Hewlett-Packard 1100 series liquid chromatography system equipped with diode array detection, a SEDEX 55 evaporative light-scattering (ELS) detector and a Micromass platform LCZ. The LC conditions were as follows: a Waters Symmetry C_8 3.5 μm, 5 cm × 0.46 cm column was used, and it was eluted with a gradient made up of two solvent mixtures. Solvent A consists of water and 0.1% formic acid. Solvent B consists of acetonitrile and 0.1% formic acid. The gradient was run as follows: 95% of solvent A and 5% of solvent B for 0.75 min, followed by ramping to 100% of solvent B at 4 min. Compound purities were assigned on the basis of ELS data.

Synthesis of Ethyl 5-Hydroxy-1-thiocarbamoyl-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazole-4-carboxylate (12). Thiosemicarbazide (5.63 g, 61.8 mmol, 1 equiv) was dissolved in ethanol (80 mL), and the mixture was stirred under nitrogen at −15 to −20 °C. Ethyl 2-ethoxymethylene-3-oxo-4,4,4-trifluorobutanoate (**3**, 14.85 g, 61.8 mmol, 1 equiv) was added slowly over 20 min. The reaction mixture was stirred at −15 °C for 1 h, then allowed to warm slowly to room temperature and stirred for 2 h. The solvent was removed by evaporation to give an oily solid. Hydrochloric acid (1 M, 80 mL) was added, and the oil was triturated until a pale-yellow solid was formed. Filtration, washing with ice−water, and drying overnight at 40 °C under vacuum yielded ethyl 5-hydroxy-1-thiocarbamoyl-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazole-4-carboxylate (**12**) as a pale-yellow solid (14.9 g, 90%), mp 113−116 °C. ^{1}H NMR (acetone-d_6): δ 1.30 (m, 3H), 4.25 (m, 2H), 4.50 (s, 1H), 7.41 (s, 1H), 8.10−8.40 (broad d, 2H, exchanged with D_2O), 8.90 (s, 1H, exchanged with D_2O). ^{13}C NMR (acetone-d_6): δ 14.75, 60.98, 63.16, 92.95 (q), 124.56 (q), 145.20, 164.80, 179.49. IR (KBr): 3440, 3310, 2985, 1737, 1590, 1451 cm^{-1}. Anal. Calcd for $C_8H_{10}F_3N_3O_3S$: C, 33.69; H, 3.53; N, 14.73; S, 11.24. Found: C, 33.34; H, 3.28; N, 14.89; S, 11.10.

Preparation of Ethyl 1-(4-Phenyl-2-thiazolyl)-5-(trifluoromethyl)pyrazole-4-carboxylate (8{*9*}). Hydroxypyrazole **12** (360 mg, 1.35 mmol, 1 equiv) and 2-bromoacetophenone (**7**{*9*}, 268 mg, 1.35 mmol, 1 equiv) were dissolved in ethanol (6 mL), and the mixture was refluxed under nitrogen for 3 h. The solvent was removed under reduced pressure, and the residue was triturated with methanol. Filtration, washing of the precipitate with cold methanol, and drying under vacuum yielded **8**{*9*} (250 mg, 50%) as an off-white solid. Purity, >95%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (t, J = 7.1 Hz, 3H), 4.40 (q, J = 7.1 Hz, 2H), 7.40 (d, 1H), 7.50 (m, 2H), 7.60 (s, 1H), 7.90 (d, 2H), 8.15 (s, 1H). MS (ESI, +ve ion): 368 $(M + H)^+$.

The same experimental procedure was followed replacing 2-bromoacetophenone with other α-bromoketones. The products were purified by recrystallization or by flash chromatography. The following analytical data are representative.

Ethyl 1-(4-(3-Methoxyphenyl)-2-thiazolyl)-5-(trifluoromethyl)pyrazole-4-carboxylate 8{*1*}. Purity, >95%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (t, J = 7.1 Hz, 3H), 3.90 (s, 3H), 4.40 (q, J = 7.1 Hz, 2H), 6.95 (m, 1H), 7.40 (m, 1H), 7.50−7.60 (m, 3H), 8.10 (s, 1H). MS (ESI, +ve ion): 398 $(M + H)^+$.

Ethyl 1-(4-(3-Methyl-2-benzothienyl)-2-thiazolyl)-5-(trifluoromethyl)pyrazole-4-carboxylate 8{*2*}. Purity, >95%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (t, J = 7.1 Hz, 3H), 2.65 (s, 3H), 4.35 (q, J = 7.1 Hz, 2H), 7.25−7.35 (m, 2H), 7.40 (s, 1H), 7.70−7.80 (m, 2H), 8.10 (s, 1H). MS (ESI, +ve ion): 438 $(M + H)^+$.

Ethyl 1-(4-(4-Methoxyphenyl)-2-thiazolyl)-5-(trifluoromethyl)pyrazole-4-carboxylate 8{*3*}. Purity, >95%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (t, J = 7.1 Hz, 3H), 3.90

(s, 3H), 4.40 (q, J = 7.1 Hz, 2H), 6.95 (m, 2H), 7.40 (s, 1H), 7.85 (m, 2H), 8.10 (s, 1H). MS (ESI, +ve ion): 398 $(M + H)^+$.

Ethyl 1-(4-(3,4-Ethylenedioxyphenyl)-2-thiazolyl)-5-(trifluoromethyl)pyrazole-4-carboxylate 8{*4*}. Purity, >95%. ^{1}HNMR (400 MHz, CDCl3): δ 1.40 (t, 3H), 4.30 (s, 4H), 4.40 (q, J = 7.1 Hz, 2H), 6.95 (m, 1H), 7.40 (s, 1H), 7.40−7.50 (m, 2H), 8.10 (s, 1H). MS (ESI, +ve ion): 426 $(M + H)^+$.

Ethyl 1-(4-(3-Fluorophenyl)-2-thiazolyl)-5-(trifluoromethyl)pyrazole-4-carboxylate 8{*5*}. Purity, >95%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (t, J = 7.1 Hz, 3H), 4.35 (q, 2H), 7.00−7.60 (5H), 8.05 (s, 1H). MS (ESI, +ve ion): 386 $(M + H)^+$.

Ethyl 1-(4-Ethyl-2-thiazolyl)-5-(trifluoromethyl)pyrazole-4-carboxylate 8{*6*}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20−1.45 (m, 6H), 2.80−2.90 (m, 2H), 4.35−4.45 (m, 2H), 7.00 (s, 1H), 8.10 (s, 1H).

Ethyl 1-(4-(1,1-Dimethylethyl)-2-thiazolyl)-5-(trifluoromethyl)pyrazole-4-carboxylate 8{*7*}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (s, 9H), 1.35 (t, J = 7.1 Hz, 3H), 4.30 (q, J = 7.1 Hz, 2H), 6.90 (s, 1H), 8.0 (s, 1H).

Ethyl 1-(4-(4-Fluorophenyl)-2-thiazolyl)-5-(trifluoromethyl)pyrazole-4-carboxylate 8{*8*}. Purity, >95%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (t, J = 7.1 Hz, 3H), 4.40 (q, J = 7.1 Hz, 2H), 7.20 (t, J = 8.7 Hz, 2H), 7.44 (s, 1H), 7.90 (m, 2H), 8.10 (s, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −57.1. MS (ESI, +ve ion): 386 $(M + H)^+$.

Preparation of 1-(4-Ethyl-2-thiazolyl)-5-(trifluoromethyl)pyrazole-4-carboxylic Acid (9{*6*}). Ester **8**{*6*} (600 mg, 1.88 mmol, 1 equiv) was dissolved in ethanol (9 mL), solid KOH (158 mg, 28.2 mmol, 1.5 equiv) was added to the flask, and the reaction mixture was refluxed for 3 h. The solvent was removed under vacuum, and the resulting oil was dissolved in water. A 12 N HCl solution was added to adjust the pH to 1, and the resulting precipitate was filtered, washed with ice-cold water, and dried under vacuum at 40 °C for 2 days to yield **9**{*6*} (550 mg, 100%) as an off-white solid. Purity, >95%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 1.30 (t, J = 7.5 Hz, 3H), 2.80 (q, J = 7.5 Hz, 2H), 7.30 (s, 1H), 8.20 (s, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −56.9, −113.7. ^{13}C NMR (75 MHz, $CDCl_3$): δ 112.4, 115.8 (d), 118.9 (q), 119.7, 127.9 (d), 129.7, 132.1 (q), 143.6, 151.9, 157.9, 162.3, 162.5 (d). MS (ESI, −ve ion): 290 $(M - H)^-$.

1-(4-(3-Fluorophenyl)-2-thiazolyl)-5-(trifluoromethyl)-pyrazolecarboxylic Acid 9{*5*}. Purity, >95%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.07 (m, 1H), 7.43 (m, 1H), 7.56 (s, 1H), 7.63 (m, 2H), 8.22 (s, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −56.8, −112.8. MS (ESI, −ve ion): 358 $(M - H)^-$.

1-(4-Phenyl-2-thiazolyl)-5-(trifluoromethyl)pyrazolecarboxylic Acid 9{*9*}. Purity, >95%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 7.30−7.45 (m, 3H), 7.90−8.0 (m, 3H), 8.20 (s, 1H). MS (ESI, −ve ion): 338 $(M - H)^-$.

Production of Library Amides 11{*x,y*}. The following procedure is illustrative. Acid **9**{6} (100 mg, 0.34 mmol) was dissolved in CH_2Cl_2 (3 mL) and placed under nitrogen. Oxalyl chloride (45 μL, 0.52 mmol) was added followed by DMF (~20 μL). After the mixture was stirred for 3 h at room temperature, the solvent was removed under reduced pressure and the resulting oil was placed under vacuum for 1 h. A 0.1 M stock solution of acid chloride was prepared by redissolving the oil in CH_2Cl_2 (3 mL).

A suspension of morpholinomethylpolystyrene resin (~70 mg, ~0.2 mmol) in CH_2Cl_2 (1 mL) was placed in a polypropylene solid-phase extraction cartridge, and 3-aminomethylpyridine (**10**{*10*}, 14 μL, 0.13 mmol) was added, followed by the acid chloride stock solution (1 mL, 0.11 mmol). The reaction mixture was shaken overnight at room temperature. Methyl isocyanate polystyrene resin (~100 mg, 1.22 mmol/g, 1.2 mmol) was added, and the reaction was shaken for 1 h. The reaction mixture was filtered, and the filtrate was concentrated in a Genevac HT8 evaporator to yield **11**{*6,10*}. Purity, 96%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (t, J = 7.5 Hz, 3H), 2.78 (q, J = 7.5 Hz, 2H), 4.65 (d, 2H, J = 5.9 Hz, 2H), 6.38 (br s, 1H), 6.90 (s, 1H), 7.33 (m, 1H), 7.72 (d, 1H, J = 7.7 Hz), 7.93 (s, 1H), 8.59 (m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −57.0. MS (ESI, +ve ion): 382 $(M + H)^+$.

The procedure above was followed using benzylamine (15 μL, 0.14 mmol) to afford **11**{*6,7*}. Purity, >95%. MS (ESI, +ve ion): 381 $(M + H)^+$. The procedure above was followed using 3-methoxybenzylamine (18 μL, 0.14 mmol) to afford **11**{*6,8*}. Purity, >95%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (t, J = 7.5 Hz, 3H), 2.78 (q, J = 7.5 Hz, 2H), 3.88 (s, 3H), 4.61 (d, J = 5.9 Hz, 2H), 6.40 (br s, 1H), 6.88 (s, 1H), 6.95 (m, 2H), 7.34 (m, 2H), 7.91 (s, 1H). MS (ESI, +ve ion): 411 $(M + H)^+$.

***O*-Pentyl-*N*-(4-(4-fluorophenyl)-2-thiazolyl)-5-(trifluoromethyl)-4-pyrazolyl)carbamate (16{*8,3*}).** Acid **9**{*8*} (30 mg, 0.085 mmol, 1 equiv) was dissolved in toluene (1 mL). Triethylamine (14 μL, 0.094 mmol, 1.1 equiv) and pentanol (18.5 μL, 0.17 mmol, 2 equiv) were added to the reaction followed by diphenylphosphoryl azide (20 μL, 0.094 mmol, 1.1 equiv). The reaction was heated at 80 °C for 3 h. The solvent was removed by evaporation, and the residue was loaded onto a prepacked 5 g FlashSi column (Isolute) and purified using a FlashMaster II (Jones Chromatography). The column was eluted with a gradient of 0−100% ethyl acetate in hexanes over 15 min to yield **16**{*8,3*} (26 mg, 70%). Purity, >95%. MS (ESI, +ve ion): 443 $(M + H)^+$.

***C. elegans* Bioassay.** Compounds were assayed in 48-well plates under sterile conditions. Each well of the plate was charged with *E. coli* nematode diet (650 μL), *C. elegans* culture (30 μL), and test compound (10.5 μg) in mixed solvent (57:24:14:5 acetone/2-propanol/water/DMSO, 20 μL). The plates were maintained in the dark at room temperature for 6 days. Compounds applied to wells in which all nematodes were dead after 6 days were considered active.

Supporting Information Available. NMR and LC−MS spectra for some members of libraries **8**, **9**, **11**, **12**, **14**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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