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Column Chromatography-Free Solution-Phase Synthesis of a Natural Piper-Amide-like Compound Library

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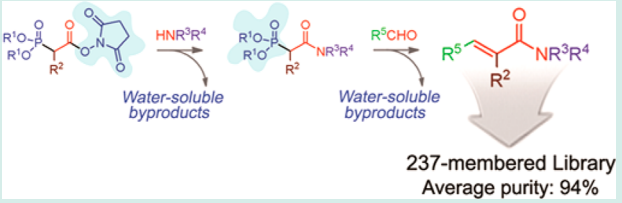
Supporting Information

ABSTRACT: We have achieved an efficient solution-phase parallel synthesis of a library of natural piper-amide-like compounds from the bifunctional β-phosphono-*N*-hydroxy-succinimidyl ester intermediate. The primary important feature in our study is the construction of natural-product-like molecules through the adaptation of sophisticated organic reactions that create water-soluble byproducts for a chromatography-free purification. This simple and efficient method rapidly provides a combinatorial library of high yield and purity. The library was evaluated against GPCR targets to demonstrate its potential use as a tool for drug discovery and in chemical biology.



KEYWORDS: *natural products, combinatorial chemistry, chromatography-free, solution-phase synthesis*

INTRODUCTION

Chemical libraries are important tools in the preliminary phase of drug discovery and chemical biology. Despite the advent of modern high-throughput synthetic technologies, the generation of chemical libraries still consumes considerable amounts of time and energy because of the inherently large number of synthetic operations required. Thus, the development of an efficient strategy for library synthesis is highly desirable to reduce the time and effort.

As part of our ongoing research focused into the synthesis of chemical libraries, we became interested in the structure of natural piper amides, the most common constituents of the genus *Piper*,[1] as a scaffold for these libraries. This became our focus because piper amides have a wide range of interesting biological activities including anti-inflammatory,[2] antifungal,[3] insecticidal,[4] analgesic,[5] antidepressant,[6] and antitumor activities.[7] Some representative natural piper amides are shown in Figure 1. Piper amides are structurally characterized by the presence of an α,β-unsaturated amide group. The α,β-unsaturated amide moiety is also found in many biologically active synthetic compounds and pharmaceuticals. For instance, AMG-9810 and SB-366791 (Figure 2) are very potent vanilloid receptor TRPV1 antagonists,[8] and tranilast is a clinical drug used in the treatment of allergic diseases and keloids.[9]

Because the α,β-unsaturated amide moiety is an attractive scaffold in medicinal chemistry and is found in natural products, a number of synthetic strategies for its assembly have been devised.[10] Most syntheses focus on the amidation of α,β-unsaturated carboxylic acid or on the olefination reaction for unsaturated double bonds. One notable strategy is the intermolecular three-component reaction between aldehydes, amines, and ketenylidenetriphenylphosphorane ($Ph_3P{=}C{=}C{=}O$).[11] However, this one-pot process suffers from low chemical yields and requires chromatographic purification, which render this process unsuitable for library generation. Another notable strategy is the solid-phase synthesis of *N*-(phenylalkyl)cinnamides via the formation of the polymer-bound Horner−Wadsworth−Emmons (HWE) reagent.[12] This method is suitable for generating a library, however only one point is available for structural diversification on the polymer-

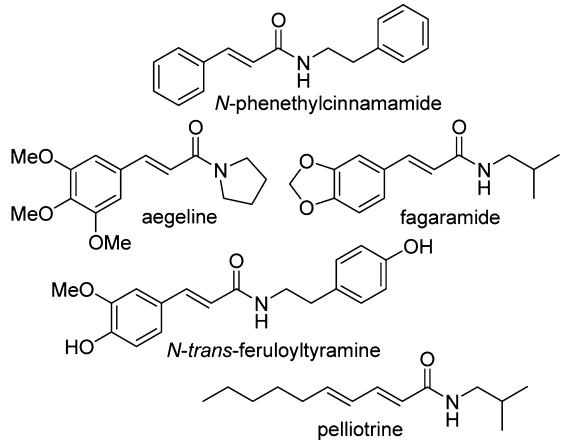


Figure 1. Structures of representative natural piper amides.

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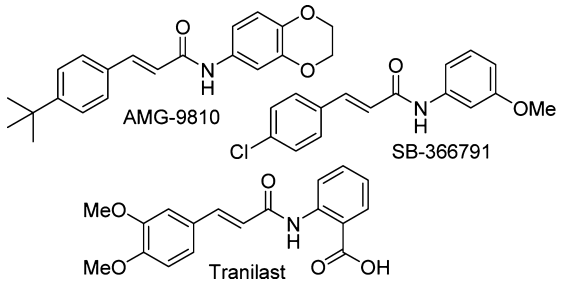


Figure 2. Structures of bioactive non-natural piper amides.

bound HWE reagent because the amine of the amide group is directly bound to the resin.

Piper amides are structurally simpler than other types of natural products and their syntheses require relatively fewer steps. We decided that the application of solid-phase synthetic techniques for generating a library of these natural-product-like compounds was not economically attractive because nearly half of the synthetic processes were wasted on linker manipulation, attachment to and detachment from the resin. Thus, we planned to generate the piper-amide-like library using solution-phase chemistry.

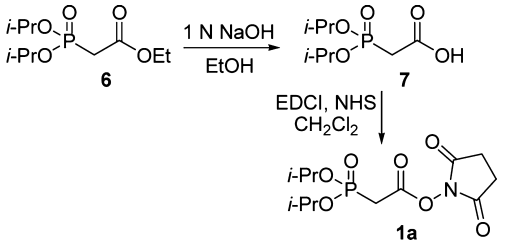
Herein, we wish to report an efficient solution-phase parallel synthesis of a combinatorial library of natural piper-amide-like compounds. Our strategy is characterized by the creation of water-soluble byproducts for chromatography-free purification of the reaction products. This approach offers the benefits of both time and cost savings in that the designed library was rapidly accessed without any laborious chromatographic separations or expensive solid-supported purification steps.

RESULTS AND DISCUSSION

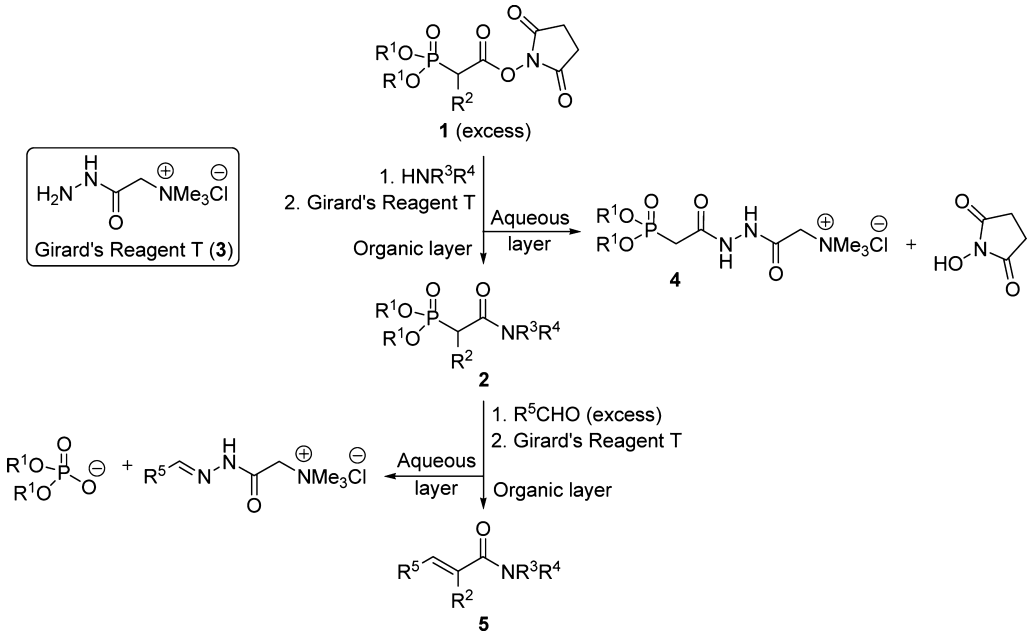
Our chromatography-free solution-phase synthetic strategy is shown in Scheme 1. The key intermediate in our synthetic sequence was bifunctional β-phosphono-*N*-hydroxysuccinimidyl ester **1**. The distinct feature of this intermediate is that, after the reaction, it releases the water-soluble byproducts *N*-hydroxysuccinimide (NHS) and dialkylphosphate salt, thus allowing for an aqueous workup purification. The reaction of **1** with a subequivalent amount of the amine would produce β-phosphono amide **2** and water-soluble *N*-hydroxysuccinimide. We expected that the remaining β-phosphono ester **1** could be removed from the reaction mixture as the water-soluble hydrazine derivative **4** by treatment with the carbonyl compound scavenger Girard's reagent T (**3**), followed by aqueous workup.[13,14] An HWE-type reaction between the obtained β-phosphono amide **2** and an excess of aldehyde would provide the desired α,β-unsaturated amide **5** with the release of water-soluble dialkylphosphate. We envisioned that the removal of the remaining aldehyde from the product could be achieved also by using Girard's reagent T as a scavenger.

As shown in Scheme 2, the requisite bifunctional intermediate **1a** was readily prepared in two steps from the commercially available β-phosphono ester **6** without chromatographic purification. It is notable that intermediate **1a** contains a bulky diisopropyl phosphonate group because the steric bulk of the phosphonate group is crucial for enhancing the *E*-alkene selectivity in the HWE reaction.[15] The hydrolysis of **6** in EtOH with NaOH gave phosphoryl acetic acid **7**. After aqueous workup without further purification, the obtained acid **7** was treated with EDCI and NHS in CH_2Cl_2 to give the active succinimidyl ester **1a**. The reaction mixture was purified only

Scheme 2. Synthesis of Bifunctional Intermediate 1a



Scheme 1. Outline of a Chromatography-Free Solution-Phase Piper-Amide-like Library Synthesis



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by aqueous extraction. The product thus obtained was essentially pure and could be used for further reactions.

The acquired bifunctional intermediate **1a** was coupled with a subequivalent amount (0.85 equiv) of eleven different amines **8**{*1*−*11*} in CH_2Cl_2 to give eleven amides **2** (Figure 3). The

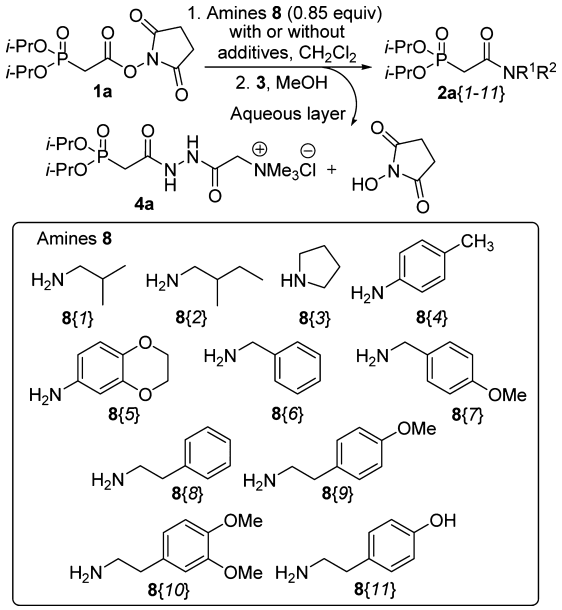

Figure 3. Synthesis of *β*-phosphono amide **2a** and structures of the employed amines **8**.

coupling reaction of **1a** with alkyl amines **8**{*1*−*3*} and **8**{*6*−*11*} was completed within 4 h at room temperature without any additives. However, reaction with the less nucleophilic aryl amines **8**{*4*} and **8**{*5*} required triethylamine and a catalytic amount of DMAP to be completed in the same amount of time and at the same temperature. Without base additives, the reaction with these aryl amines required a longer reaction time (12 h) and higher temperature (40 °C).[16] When complete consumption of amines **8** was observed by LC or TLC, the reaction mixture was treated with a solution of Girard's reagent T (**3**) in MeOH to convert the remaining succinimidyl ester **1a** to water-soluble derivative **4a**. The condensation reaction of Girard's reagent T with **1a** was somewhat slow, but the reaction was completed within 12 h at room temperature. After standard aqueous extractive workup, essentially pure *β*-phosphono amide **2a**{*1*−*11*} was obtained in high yield.[17]

The HWE reaction between *β*-phosphono amide **2a** and a moderate excess (1.5 equiv) of aldehyde was investigated (Figure 4). After considerable effort, it was recognized that *t*-BuOK was an appropriate base for this type of reaction.[18] Most aldehydes reacted with *β*-phosphono amide **2a** in the presence of *t*-BuOK in THF to give the desired *α*,*β*-unsaturated amide **5** in high yield with exclusive *E*-selectivity. However, in the case of hydroxy benzaldehyde, such as **9**{*9*}, NaH was a more appropriate reagent to complete the reaction.

The selected fourteen aldehydes **9**{*1*−*14*}, shown in Figure 4, were reacted with the obtained eleven *β*-phosphono amides **2a**{*1*−*11*} in a combinatorial manner. After completion of the reaction, excess aldehyde **9** was removed from the mixture by treatment with a solution of Girard's reagent T (**3**) in MeOH and a standard aqueous workup. Table 1 presents the obtained yields and purities. In all cases except one, the products could be obtained with an average HPLC purity of 95%. However, in

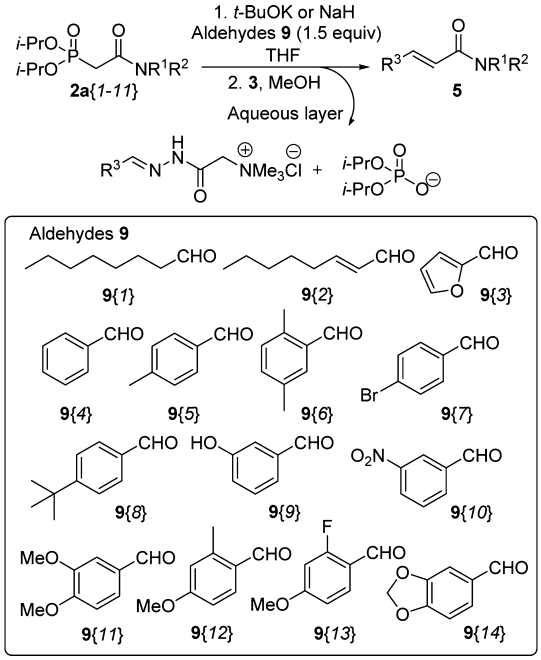

Figure 4. Synthesis of *α*,*β*-unsaturated amide **5** and structures of employed aldehydes **9**.

the case of library member **5**{*11*,*9*}, which has two phenolic hydroxyl groups, only starting *β*-phosphono amide was recovered without any desired condensation product. Therefore, we were able to obtain 153 natural piper-amide-like compounds stereoselectively out of the planned 154 (>99% success rate) with high purity by using only aqueous extractive workup.

To add an additional point of diversity on the piper amide scaffold, we also designed a bifunctional intermediate that contained the substituent at the *α*-position. *α*-Methyl *β*-phosphono-*N*-hydroxysuccinimidyl ester **1b** was chosen as an example of such a bifunctional intermediate (Scheme 3). Employing the same procedure as for the column chromatography-free preparation of **1a**, the *α*-branched intermediate **1b** was easily prepared from the known *α*-methyl *β*-phosphono ester **10**.[19] For the library reported here, a total of six amines (**8**{*1*}, **8**{*3*}, **8**{*5*}, **8**{*6*}, **8**{*8*}, and **8**{*10*}) were used to give six *β*-phosphono amides **2b** by reaction with **1b**. The selected fourteen aldehydes **9**{*1*−*14*} were condensed with **2b** in a combinatorial manner to give **11**.

As shown in Table 2, the planned 84 *α*-methyl piper amide compounds were successfully obtained. In most cases, the desired *α*,*β*-unsaturated amide was obtained in high yield with complete or very high *E*-selectivity. However, in the case of the HWE reaction of *β*-phosphono amide **2b**{3}, derived from the coupling of **1b** with the cyclic secondary amine pyrrolidine **8**{3}, the stereoselectivity was low or even reversed to afford a cis isomer as the major product. This low stereoselectivity of *β*-phosphono secondary amide **2b**{3} was somewhat surprising, and further studies were required to elucidate its origin. Although low stereoselectivity was found in some particular cases, the above results implied that our column chromatography-free protocol could be applicable to synthesizing a library of piper-amide-like compounds with a substituent at the *α*-position.

The resemblance to the natural products was one of the basic criteria in the selection of building blocks for the library. The

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Table 1. Library Data for α,β-Unsaturated Amides 5

entry	product **5** {amine **8**, aldehyde **9**}	yield (%)[a]	purity (%)[b]	entry	product **5** {amine **8**, aldehyde **9**}	yield (%)[a]	purity (%)[b]	entry	product **5** {amine **8**, aldehyde **9**}	yield (%)[a]	purity (%)[b]
1	**5**{*1,1*}	99	98	53	**5**{*4,11*}	81	92	105	**5**{*8,7*}	99	98
2	**5**{*1,2*}	99	99	54	**5**{*4,12*}	71	84	106	**5**{*8,8*}	100	97
3	**5**{*1,3*}	62	97	55	**5**{*4,13*}	57	89	107	**5**{*8,9*}	98	98
4	**5**{*1,4*}	98	100	56	**5**{*4,14*}	69	77	108	**5**{*8,10*}	99	93
5	**5**{*1,5*}	74	99	57	**5**{*5,1*}	89	90	109	**5**{*8,11*}	91	99
6	**5**{*1,6*}	80	99	58	**5**{*5,2*}	90	92	110	**5**{*8,12*}	100	88
7	**5**{*1,7*}	69	99	59	**5**{*5,3*}	70	95	111	**5**{*8,13*}	99	97
8	**5**{*1,8*}	94	100	60	**5**{*5,4*}	100	96	112	**5**{*8,14*}	100	99
9	**5**{*1,9*}	74	93	61	**5**{*5,5*}	99	83	113	**5**{*9,1*}	96	95
10	**5**{*1,10*}	62	96	62	**5**{*5,6*}	99	82	114	**5**{*9,2*}	98	100
11	**5**{*1,11*}	78	99	63	**5**{*5,7*}	100	89	115	**5**{*9,3*}	73	99
12	**5**{*1,12*}	71	92	64	**5**{*5,8*}	97	93	116	**5**{*9,4*}	99	96
13	**5**{*1,13*}	91	97	65	**5**{*5,9*}	58	99	117	**5**{*9,5*}	58	95
14	**5**{*1,14*}	99	99	66	**5**{*5,10*}	98	87	118	**5**{*9,6*}	76	99
15	**5**{*2,1*}	98	97	67	**5**{*5,11*}	77	99	119	**5**{*9,7*}	54	98
16	**5**{*2,2*}	98	98	68	**5**{*5,12*}	92	86	120	**5**{*9,8*}	100	95
17	**5**{*2,3*}	89	98	69	**5**{*5,13*}	100	85	121	**5**{*9,9*}	76	98
18	**5**{*2,4*}	98	97	70	**5**{*5,14*}	79	99	122	**5**{*9,10*}	82	90
19	**5**{*2,5*}	99	87	71	**5**{*6,1*}	95	98	123	**5**{*9,11*}	52	96
20	**5**{*2,6*}	99	98	72	**5**{*6,2*}	100	99	124	**5**{*9,12*}	74	91
21	**5**{*2,7*}	99	97	73	**5**{*6,3*}	85	97	125	**5**{*9,13*}	70	93
22	**5**{*2,8*}	98	99	74	**5**{*6,4*}	67	99	126	**5**{*9,14*}	75	99
23	**5**{*2,9*}	90	99	75	**5**{*6,5*}	75	94	127	**5**{*10,1*}	99	97
24	**5**{*2,10*}	96	93	76	**5**{*6,6*}	78	86	128	**5**{*10,2*}	91	99
25	**5**{*2,11*}	90	85	77	**5**{*6,7*}	82	100	129	**5**{*10,3*}	87	97
26	**5**{*2,12*}	100	97	78	**5**{*6,8*}	97	84	130	**5**{*10,4*}	96	98
27	**5**{*2,13*}	94	98	79	**5**{*6,9*}	75	99	131	**5**{*10,5*}	87	98
28	**5**{*2,14*}	99	82	80	**5**{*6,10*}	81	92	132	**5**{*10,6*}	90	98
29	**5**{*3,1*}	97	95	81	**5**{*6,11*}	82	83	133	**5**{*10,7*}	100	99
30	**5**{*3,2*}	98	97	82	**5**{*6,12*}	88	86	134	**5**{*10,8*}	96	98
31	**5**{*3,3*}	67	99	83	**5**{*6,13*}	87	99	135	**5**{*10,9*}	86	95
32	**5**{*3,4*}	99	97	84	**5**{*6,14*}	97	92	136	**5**{*10,10*}	85	92
33	**5**{*3,5*}	90	96	85	**5**{*7,1*}	93	98	137	**5**{*10,11*}	62	97
34	**5**{*3,6*}	97	99	86	**5**{*7,2*}	94	99	138	**5**{*10,12*}	92	95
35	**5**{*3,7*}	89	100	87	**5**{*7,3*}	66	99	139	**5**{*10,13*}	93	95
36	**5**{*3,8*}	99	99	88	**5**{*7,4*}	94	100	140	**5**{*10,14*}	94	97
37	**5**{*3,9*}	97	99	89	**5**{*7,5*}	83	88	141	**5**{*11,1*}	89	100
38	**5**{*3,10*}	58	98	90	**5**{*7,6*}	96	99	142	**5**{*11,2*}	87	99
39	**5**{*3,11*}	83	95	91	**5**{*7,7*}	90	99	143	**5**{*11,3*}	62	96
40	**5**{*3,12*}	89	92	92	**5**{*7,8*}	89	90	144	**5**{*11,4*}	57	95
41	**5**{*3,13*}	94	93	93	**5**{*7,9*}	78	100	145	**5**{*11,5*}	99	85
42	**5**{*3,14*}	100	95	94	**5**{*7,10*}	85	95	146	**5**{*11,6*}	68	91
43	**5**{*4,1*}	100	91	95	**5**{*7,11*}	69	95	147	**5**{*11,7*}	66	99
44	**5**{*4,2*}	99	81	96	**5**{*7,12*}	80	95	148	**5**{*11,8*}	99	99
45	**5**{*4,3*}	88	79	97	**5**{*7,13*}	78	97	149	**5**{*11,9*}[c]	-	-
46	**5**{*4,4*}	99	97	98	**5**{*7,14*}	78	96	150	**5**{*11,10*}	99	77
47	**5**{*4,5*}	76	88	99	**5**{*8,1*}	97	99	151	**5**{*11,11*}	60	95
48	**5**{*4,6*}	47	92	100	**5**{*8,2*}	68	99	152	**5**{*11,12*}	79	90
49	**5**{*4,7*}	62	82	101	**5**{*8,3*}	84	97	153	**5**{*11,13*}	79	93
50	**5**{*4,8*}	99	86	102	**5**{*8,4*}	93	100	154	**5**{*11,14*}	100	89
51	**5**{*4,9*}	96	85	103	**5**{*8,5*}	100	100				
52	**5**{*4,10*}	75	93	104	**5**{*8,6*}	88	99				

[a]Yields (%) were obtained after aqueous workup. [b]Purity was determined by HPLC (ZORBAX Eclipse plus C18 column, 4.6 mm × 150 mm, 5 μm; ultraviolet absorption detector at 250 nm; gradient, 20−100% MeOH/H_2O, 40 or 60 min). [c]No reaction. Recovered starting material.

other criterion was the drug-like properties. To verify the drug likeness, the structures of the library members were saved as SD file format and submitted to the analysis of Lipinski[20] and Veber rules.[21] According to the results, 96% of the library members passed the rules (see Table S2 in Supporting Information).[22] To assess and demonstrate the value of the piper amide library generated, 60 randomly selected library compounds were tested in a new drug screening program at LG Life Sciences. Many of the tested compounds showed moderate to good activity against the G-protein coupled receptor

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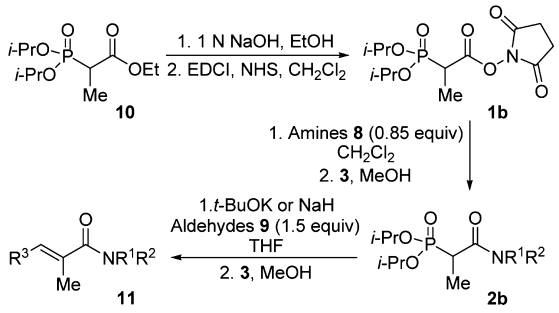
Scheme 3. Synthesis of α-Methyl Piper Amide 11



(GPCR) and kinase targets. Noteworthy test results showed that several compounds exhibited agonist activity toward recombinant bombesin receptor subtype-3 (BRS-3) expressed in CHO-K1 cells. These compounds had EC_{50} values in the nanomolar to micromolar range. Most of the active compounds had a phenethylamine group in common. The structures of three representatives and their EC_{50} values are shown in Figure 5.

BRS-3 is an orphan GPCR which is implicated in the regulation of energy homeostasis.[23] This receptor has been recently validated as a potential new target for treating obesity.[24] Recent extensive medicinal chemistry efforts have yielded several classes of nonpeptidic small-molecule BRS-3 agonists.[25] Our identified compounds are structurally distinct

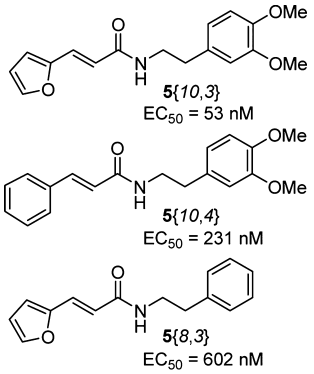


Figure 5. Structures of hit compounds and their EC_{50} values for the BRS-3 receptor.

from these small-molecules. Although a limited number of library members has been examined, the most potent hit compound exhibited an EC_{50} value of 53 nM, which is comparable to that of the leading small-molecule agonist.[26] These biological results have important implications in the potential use of a piper amide library in drug discovery and chemical biology.

Table 2. Library Data for α-Methyl Piper Amides 11

entry	product **11** {amine **8**, aldehyde **9**}	yield (%)[a]	purity (%)[b] (*E*:*Z*)[c]	entry	product **11** {amine **8**, aldehyde **9**}	yield (%)[a]	purity (%)[b] (*E*:*Z*)[c]	entry	product **11** {amine **8**, aldehyde **9**}	yield (%)[a]	purity (%)[b] (*E*:*Z*)[c]
1	**11**{*1,1*}	99	99	29	**11**{*5,1*}	99	80	57	**11**{*8,1*}	99	99 (9:1)
2	**11**{*1,2*}	93	93	30	**11**{*5,2*}	73	89	58	**11**{*8,2*}	99	97
3	**11**{*1,3*}	78	93	31	**11**{*5,3*}	89	77	59	**11**{*8,3*}	85	97
4	**11**{*1,4*}	83	99	32	**11**{*5,4*}	93	99 (7:1)	60	**11**{*8,4*}	90	99
5	**11**{*1,5*}	98	95	33	**11**{*5,5*}	84	96	61	**11**{*8,5*}	95	99
6	**11**{*1,6*}	82	96	34	**11**{*5,6*}	89	87	62	**11**{*8,6*}	80	99
7	**11**{*1,7*}	76	99	35	**11**{*5,7*}	84	98	63	**11**{*8,7*}	97	99
8	**11**{*1,8*}	93	98	36	**11**{*5,8*}	99	94	64	**11**{*8,8*}	98	96
9	**11**{*1,9*}	92	98	37	**11**{*5,9*}	79	95	65	**11**{*8,9*}	86	97
10	**11**{*1,10*}	99	65	38	**11**{*5,10*}	86	94	66	**11**{*8,10*}	99	68
11	**11**{*1,11*}	83	100	39	**11**{*5,11*}	94	90	67	**11**{*8,11*}	72	100
12	**11**{*1,12*}	87	93	40	**11**{*5,12*}	93	93	68	**11**{*8,12*}	86	99
13	**11**{*1,13*}	94	95	41	**11**{*5,13*}	99	89	69	**11**{*8,13*}	97	96
14	**11**{*1,14*}	93	98	42	**11**{*5,14*}	92	96	70	**11**{*8,14*}	92	96
15	**11**{*3,1*}	99	75 (3:1)	43	**11**{*6,1*}	99	88 (10:1)	71	**11**{*10,1*}	99	86 (8:1)
16	**11**{*3,2*}	99	85 (2:1)	44	**11**{*6,2*}	99	97	72	**11**{*10,2*}	99	99
17	**11**{*3,3*}	88	96 (2:1)	45	**11**{*6,3*}	97	80	73	**11**{*10,3*}	95	99
18	**11**{*3,4*}	87	99 (4:1)	46	**11**{*6,4*}	90	85	74	**11**{*10,4*}	84	100
19	**11**{*3,5*}	78	96 (1:2)	47	**11**{*6,5*}	90	96	75	**11**{*10,5*}	86	100
20	**11**{*3,6*}	96	99 (7:1)	48	**11**{*6,6*}	79	95	76	**11**{*10,6*}	96	99
21	**11**{*3,7*}	95	99 (1:1)	49	**11**{*6,7*}	99	97	77	**11**{*10,7*}	94	99 (9:1)
22	**11**{*3,8*}	98	97 (1:2)	50	**11**{*6,8*}	99	85	78	**11**{*10,8*}	96	97
23	**11**{*3,9*}	26	91 (1:49)	51	**11**{*6,9*}	95	99	79	**11**{*10,9*}	88	99
24	**11**{*3,10*}	85	90 (2:1)	52	**11**{*6,10*}	92	79	80	**11**{*10,10*}	77	84
25	**11**{*3,11*}	99	90 (1:3)	53	**11**{*6,11*}	66	91	81	**11**{*10,11*}	71	100
26	**11**{*3,12*}	93	97 (9:1)	54	**11**{*6,12*}	84	85	82	**11**{*10,12*}	92	90
27	**11**{*3,13*}	96	99 (7:1)	55	**11**{*6,13*}	99	81	83	**11**{*10,13*}	93	84
28	**11**{*3,14*}	80	94 (1:2)	56	**11**{*6,14*}	84	94	84	**11**{*10,14*}	76	99

[a]Yields (%) were obtained after aqueous workup. [b]Purity was determined by HPLC (ZORBAX Eclipse plus C18 column, 4.6 mm × 150 mm, 5 μm; ultraviolet absorption detector at 250 nm; gradient, 20−100% MeOH/H_2O, 40 or 60 min). [c]*E*/*Z* ratio was determined by HPLC and ^1H NMR spectroscopic analyses. Ratios above 10:1 were not included in this table. For detailed information, see Table S1 in Supporting Information.

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CONCLUSION

In summary, we have produced an α,β-unsaturated amide combinatorial library inspired by the structures and biological activities of natural piper amides. The library members exhibit three points of diversity. The scaffold was easily accessible in only two steps from the bifunctional β-phosphono-*N*-hydroxysuccinimidyl ester without chromatographic purification. The column chromatography-free and efficient nature of this library synthesis hinges, in part, on the creation of water-soluble byproducts. The key bifunctional intermediate released a water-soluble byproduct only after the reaction, and the excess reactants were removed from the product as the water-soluble hydrazone derivative. Because our approach employed aqueous workup for purification, there might be some limitations especially in the synthesis of highly water-soluble library members. However, the ease of operation and the excellent purity of the piper amide library obtained are important features of this protocol. The randomly selected library members were tested mainly against GPCR targets, resulting in the discovery of several compounds with BRS-3 agonist activity. Our biological results imply that the biological relevance of the library of natural piper-amide-like compounds is high and that such libraries is useful for discovering hits or probes for either unknown or discovered biological targets. Finally, we believe this study provides a novel direction for further preparation of a more diversified and expanded library.

EXPERIMENTAL PROCEDURES

General methods and additional experimental details are given in the Supporting Information.

General Procedure for the Synthesis of β-Phosphono Amides 2a and 2b. Amine **8** (4.25 mmol) was added to a solution of β-phosphono-*N*-hydroxysuccinimidyl ester **1a** or **1b** (5.00 mmol) in CH_2Cl_2. After stirring for 4 h at room temperature, a 1.0 M solution of Girard's reagent T (**3**) in MeOH (15 mL, 15.00 mmol) was added and stirred overnight. The reaction mixture was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, and then concentrated. Crude β-phosphono amide **2a** or **2b** was used without further purification in the HWE reaction.

General Procedure for the Synthesis of α,β-Unsaturated Amides 5 and 11.[27] A 1.0 M solution of *t*-BuOK in THF (0.3 mL, 0.30 mmol) was added to a solution of β-phosphono amide **2a** or **2b** (0.15 mmol) in dry THF (1.5 mL) at room temperature. After stirring for 5 min, the corresponding aldehyde **9** (0.23 mmol) was added. In the case of 3-hydroxybenzaldehyde **9**{9}, 95% NaH (12.6 mg, 0.50 mmol) was added instead of the *t*-BuOK solution. After the mixture was stirred for 6 h, a 1.0 M solution of Girard's reagent T (**3**) in MeOH (0.45 mL, 0.45 mmol) was added and stirred overnight. The reaction mixture was quenched with H_2O and extracted with EtOAc. The combined organic layers were washed with brine twice, dried over $MgSO_4$, and then concentrated. The resultant crude α,β-unsaturated amides **5** and **11** were checked by ^1H NMR and FAB-MS. Purities of all products were determined by HPLC peak area analysis.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental methods and full characterization for representative library compounds and ^1H and ^{13}C NMR spectra for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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