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Direct Amidation of Carboxylic Acids through an Active α-Acyl Enol Ester Intermediate

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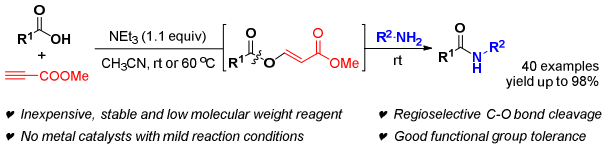


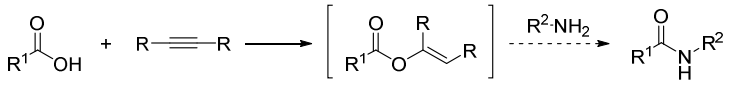
ABSTRACT

The development of a highly efficient and simple protocol for the direct amidation of carboxylic acids is described employing ynoates as novel coupling reagents. The transformation proceeds in good to excellent yields via *in situ* α-acyl enol ester intermediates formation under mild reaction conditions. This useful method has been demonstrated for a range of substrates to provide a succinct access to structurally diverse amides, including key intermediates of glibenclamide, tiapride hydrochloride and nateglinide, and can be conducted on a mole scale.

INTRODUCTION

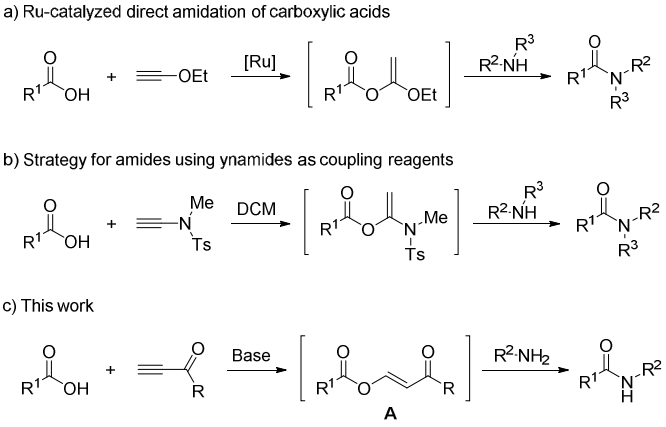
Amides represent an important functional group frequently found in numerous compounds of relevance to natural products, medicinal chemistry, crop protection, material sciences and biological systems.[1] Among the myriad methods previously developed using boronic acid, borate ester, and metal as a catalyst,[2,3] aminolysis of activated carboxylic acid derivatives, such as acyl chlorides, anhydrides or activated esters, is one of the most commonly used approaches for construction of an amide bond. In these reactions, *in situ* generation of activated esters with carbodiimides or phosphonium/uronium/aminium salts is currently a highly efficient and versatile method.[4] However, a significant drawback of this strategy is the high molecular weight of the stoichiometric coupling reagents leading to poor overall atom economy. Therefore, the search for

highly efficient coupling reagents with "ideal" atom economy is a matter of concern.[5] Following our recent studies on the acetylene chemistry,[6] we would like to think about whether alkynes can serve as a coupling agent for the construction of amides through enol esters species (Scheme 1)?



Scheme 1. Envisioned Strategy for the Amide Synthesis

Recently, very nice examples of such transformation have appeared employing commercially unavailable or unstable alkynes. In 2016, the Gooβen group reported a novel protocol for the direct amidation of carboxylic acids using acetylene or ethoxyacetylene as an activating reagent and catalyzed by the ruthenium complex (Scheme 2a, ethoxyacetylene is high sensitivity, and expensive).[7] Moreover, through employing ynamides as novel coupling reagents, a one-pot, two-step tandem approach for amides and peptides was described by Zhao and co-workers (Scheme 2b, more than 2 steps required to obtain ynamides, and difficult handling).[8] Both methods involved in the hydrocarboxylation of alkynes to form electron-rich enol esters intermediate. Despite these significant advances, the direct amidation is still in its infancy.[9] Active α-acyl enol esters **A**, distinct structures containing multiple reactive sites, has been widely explored as building blocks in synthetic transformations.[10] However, to date, such electron-deficient enol esters have not previously been exploited as a source of acyl groups for amidation. Taking into account the potential of this transformation, we became interested in employing α-acyl enol esters **A** as acyl precursors. Herein, we report the first example of direct amidation of carboxylic acids using ynoates as novel coupling reagents (Scheme 2c).

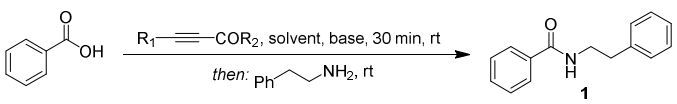


Scheme 2. Amide Bond Formation through Enol Esters Species

RESULTS AND DISCUSSION

To validate our hypothesis, the two-step, one-pot strategy was initially investigated by the treatment of phenylethylamine and α-acyl enol ester in situ generated from benzoic acid and ethyl propiolate via Michael-type addition reaction in the presence of pyridine in toluene at room temperature (Table 1).[11] To our delight, the desired product *N*-phenethylbenzamide **1** was isolated in 47% yield (entry 1). Encouraged by these preliminary outcomes, we examined a range of reaction parameters, including the solvent, base, coupling agent, and concentration. Among the evaluation of solvents, acetonitrile was found to be the best solvent (entry 5), whereas dichloromethane, 1,2-dichloroethane (DCE), and tetrahydrofuran also gave good yields of the corresponding product (entries 2−4). Other solvents such as methanol, and DMSO just provided the amine **1** in 41% and 40% yields, respectively (entries 6 and 7). However, for water, only a trace amount of product **1** was detected due to the procedure for the generation of key intermediate α-acyl enol ester **A** is being blocked (entry 8). A subsequent investigation of bases showed that both NEt_3 and *N,N,N',N'*-tetramethylethane-1,2-diamine (TMEDA) retain top status (entries 9−11). Interestingly, DMAP, which is commonly used in amidation, only afforded a low yield of the targeted product along with unidentified byproducts (entry 12). Under identical conditions, strong inorganic base KO*t*-Bu had a slight impact for this activator (entry 13). Further optimization of regarding coupling agents illustrated that R_1 substituent adversely affect the yield (entries 17 and 18). Meanwhile, R_2 groups also played an essential role on the reaction efficiency (entries 14−16). Among them, methyl propiolate and ethyl propiolate were found to be the more effective for this novel transformation (entries 9 and 14). Considering the cost and atom economy of the reaction, methyl propiolate should be the most suitable in this case. It is noteworthy that the acid-to-amine ratio exerts a substantial effect on the product yield (entry 19). Intriguingly, lower loading of NEt_3 is also remarkable but longer reaction time (entries 20 and 21) and a higher reaction temperature (entry 22) for the formation of α-acyl enol ester intermediate is required.

Table 1. Optimization of the One-Pot Synthesis of Amide[a]



Entry	Coupling agent	Solvent	Base [equiv]	Yield [%][b]
1	R_1 = H, R_2 = OEt	toluene	pyridine [2.2]	47

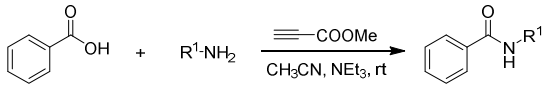
2	R_1 = H, R_2 = OEt	DCM	pyridine [2.2]	77
3	R_1 = H, R_2 = OEt	DCE	pyridine [2.2]	75
4	R_1 = H, R_2 = OEt	THF	pyridine [2.2]	82
5	R_1 = H, R_2 = OEt	acetonitrile	pyridine [2.2]	97
6	R_1 = H, R_2 = OEt	methanol	pyridine [2.2]	41
7	R_1 = H, R_2 = OEt	DMSO	pyridine [2.2]	40
8	R_1 = H, R_2 = OEt	water	pyridine [2.2]	trace
9	R_1 = H, R_2 = OEt	CH_3CN	NEt_3 [2.2]	98
10	R_1 = H, R_2 = OEt	CH_3CN	DABCO [2.2]	59
11	R_1 = H, R_2 = OEt	CH_3CN	TMEDA [2.2]	97
12	R_1 = H, R_2 = OEt	CH_3CN	DMAP [2.2]	18
13	R_1 = H, R_2 = OEt	CH_3CN	KO*t*-Bu [2.2]	21
14	R_1 = H, R_2 = OMe	CH_3CN	NEt_3 [2.2]	98
15	R_1 = H, R_2 = Me	CH_3CN	NEt_3 [2.2]	87
16	R_1 = H, R_2 = O*t*-Bu	CH_3CN	NEt_3 [2.2]	78
17	R_1 = Me, R_2 = OEt	CH_3CN	NEt_3 [2.2]	n.d.
18	R_1 = CO_2Et, R_2 = OEt	CH_3CN	NEt_3 [2.2]	n.d.
19[c]	R_1 = H, R_2 = OMe	CH_3CN	NEt_3 [2.2]	79
20	R_1 = H, R_2 = OMe	CH_3CN	NEt_3 [1.1]	98
21[d]	R_1 = H, R_2 = OMe	CH_3CN	NEt_3 [0.5]	97
22[e]	R_1 = H, R_2 = OMe	CH_3CN	NEt_3 [0.3]	97

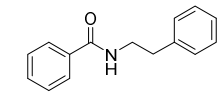
[a]Reactions were performed by using benzoic acid (0.5 mmol), coupling agent (0.55 mmol), and base in solvent (3.0 mL) for 30 min at room temperature; then phenylethylamine (1.0 mmol) was added. [b]Isolated yield, n.d. = not determined. [c]Phenylethylamine (0.55 mmol) was used. [d]6 h for the first step. [e]14 h for the first step, and reaction temperature: 60 °C.

With the optimized reaction conditions in hand the scope of this one-pot method was evaluated with a wide range of amine derivatives (Table 2). Under the standard reaction conditions (Table 1, entry 20), various phenylethylamines bearing electron-withdrawing as well as electron-donating substituent underwent smooth to afford the corresponding amides (**2**−**6**) in good to excellent yields. Notably, the 1,2-amino alcohol was also found to be applicable for this approach to access the desired product (**7**) tolerated free OH group. Similarly, a series of benzylamines provided the expected amides (**8**−**11**) in excellent yields, surprisingly, the use of aniline didn't generate the desired amidation product (**12**), and the exact cause is unclear. In the cases of aliphatic amines, the

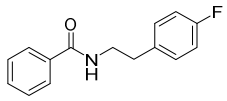
corresponding products (**13**−**17**) were achieved in excellent yields for all these examples. Also, sterically hindered α-amino ester could be successfully applied to this protocol resulting in good yield (**18**). However, the second amines such as diethylamine, morpholine, diallylamine, and *N*-methylbenzylamine is not compatible, and only the pyrrolidine would participate in the amidation and furnished the target products (**19**) in 79% yield**.** Gratifyingly, our method also tolerates ammonium hydroxide to produce the benzamide (**20**) in high yield.

Table 2. Substrate Scope for Various Amines[a]

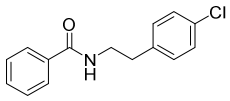




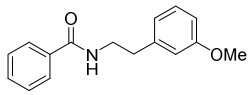
1, 98%, 30 min/10 min



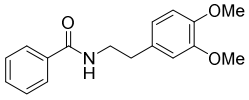
2, 96%, 30 min/15 min



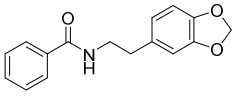
3, 86%, 30 min/15 min



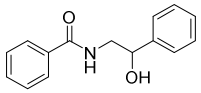
4, 86%, 30 min/10 min



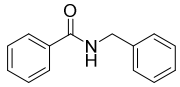
5, 71%, 30 min/10 min



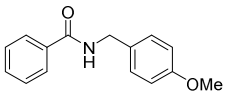
6, 91%, 30 min/10 min



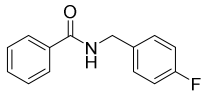
7, 98%, 30 min/40 min



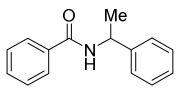
8, 96%, 30 min/30 min



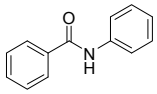
9, 92%, 30 min/25 min



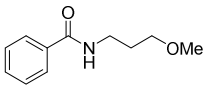
10, 97%, 30 min/20 min



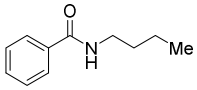
11, 96%, 30 min/40 min



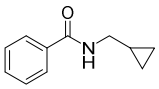
12, n.d.



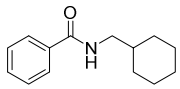
13, 91%, 30 min/10 min



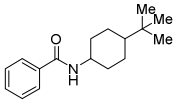
14, 91%, 30 min/10 min



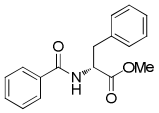
15, 93%, 30 min/10 min



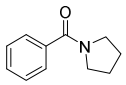
16, 98%, 30 min/10 min



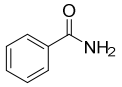
17, 93%, 30 min/10 min



18, 64%, 30 min/15 min



19, 79%, 30 min/10 min



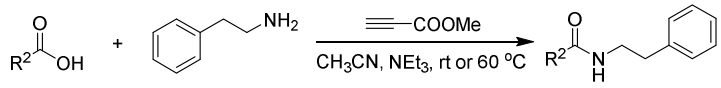
20, 81%, 30 min/20 min

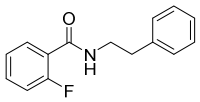
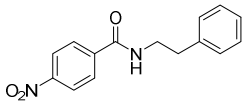
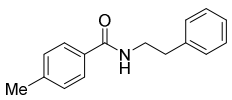
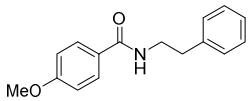
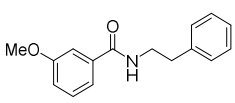
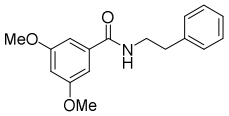
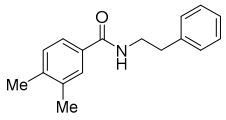
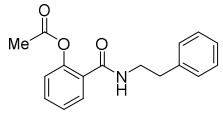
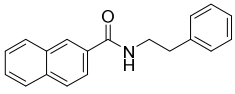
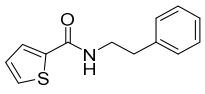
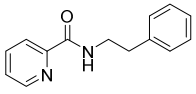
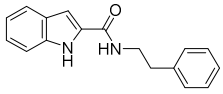
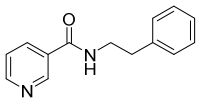
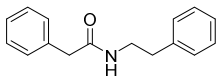
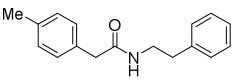
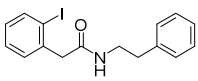
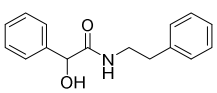
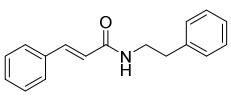
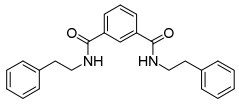
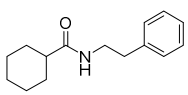
[a]Reaction conditions: benzoic acid (0.5 mmol), amine (1.0 mmol), methyl propiolate (0.55 mmol), triethylamine (0.55 mmol), in CH_3CN (3.0 mL) at room temperature; The reaction times of the first step and the second step, respectively; isolated yield; n.d. = not determined.

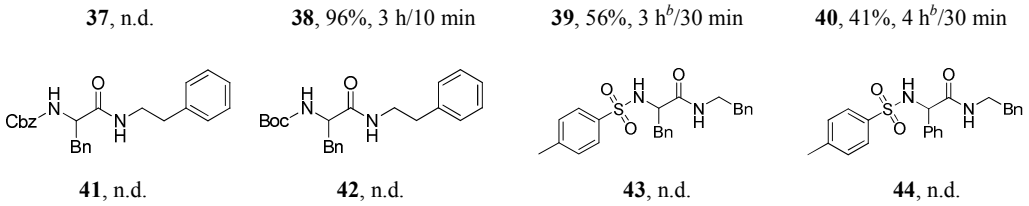
To further explore the utility of this strategy, the scope of the reaction with respect to the carboxylic acids was then tested, and it was found that this direct transformation is versatile and robust (Table 3). Treatment of the benzoic acids, tolerating fluoro, nitro, methyl, and methoxy substituents in different positions, with phenylethylamine led to the expected amides (**21**–**27**) in good to excellent yields. Pleasingly, large steric hindrance group did not inhibit product formation,

and successfully afforded **28** in slightly decreased yield (57%). In addition, not only a naphthalene ring but also heterocyclic substrates, such as thiophene, pyridine, and indole could be employed without any difficulties (**29**−**32,** 75−90% yield). However, when nicotinic acid was present, the amidation did not occur (**33**). Next, we turned our attention to phenylacetic acids reacted smoothly to produce the corresponding products (**34**−**36**) in 67−82% yield. Unexpectedly, no desired product (**37**) was obtained with unknown side reactions when 2-hydroxy-2-phenylacetic acid was used. Highly efficient reaction was gained in the case of cinnamic acid delivered the desired product (**38**) in excellent yield. Interestingly, isophthalic acid could also be successfully engaged in this reaction providing the diamide (**39**) in 56% yield. A moderate yield (**40**, 41%) was observed when cyclohexanecarboxylic acid was introduced as the starting material. Unfortunately, the target products (**41**, **42**, **43**) were not obtained using N-Boc, Cbz, or Tos protected phenylalanines. Moreover, the product (**44)** was not observed when a 2-((4-methylphenyl)sulfonamido)-2-phenylacetic acid was employed. In these unsuccessful examples, the acids were unable to react with methyl propiolate to form α-acyl enol ester intermediates.

Table 3. Reaction Scope of Carboxylic Acids [a]

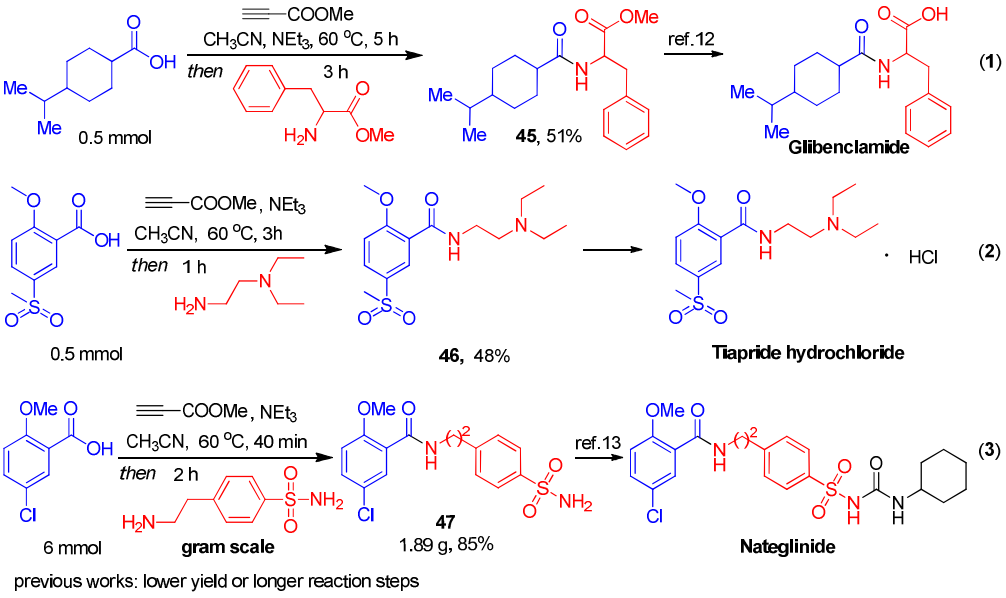


			
21, 96%, 2 h[b]/30 min	**22**, 65%, 4 h/10 min	**23**, 80%, 1 h/20 min	**24**, 94%, 30 min/10 min
			
25, 90%, 30 min/10 min	**26**, 68%, 50 min/20 min	**27**, 94%, 50 min/20 min	**28**, 57%, 2 h/20 min
			
29, 75%, 30 min/10 min	**30**, 96%, 2 h/10 min	**31**, 75%, 2 h/30 min	**32**, 90%, 3 h/30 min
			
33, n.d.	**34**, 73%, 4 h[b]/30 min	**35**, 82%, 2 h/30 min	**36**, 67%, 2 h/10 min
			



[a]Reaction conditions: carboxylic acid (0.5 mmol), phenylethylamine (1.0 mmol), methyl propiolate (0.55 mmol), and triethylamine (0.55 mmol), in CH_3CN (3.0 mL) at room temperature; reaction times for the first and second steps, respectively; isolated yield. [b]Reaction temperature: 60 °C.

Then, the synthetic value of this novel coupling reagent was emphasized by the construction of the important amide frameworks (Scheme 3). As showed in (1), the reaction of less active aliphatic acid with α-amino ester produced a 51% yield of amide **45** under modified reaction conditions, which is a key intermediate for the synthesis of the drug glibenclamide.[12] We also directly synthesized an antipsychotic drug tiapride hydrochloride **46** in 48% yield (2). Meanwhile, this coupling reagent was demonstrated in a gram scale amidation of 5-chloro-2-methoxybenzoic acid. In this case, we obtained 1.89 grams of **47** in 85% yields with high chemoselectivity (3). In the meantime, the product, could be readily converted into the drug molecule nateglinide,[13] was isolated without running a column chromatography paved the way for practical application.



Scheme 3. Synthetic Application.

CONCLUSIONS

In summary, we have described a new coupling reagent that is not only highly efficient but is also

the "ideal" atom economic (mol wt = 84.07) for the direct synthesis of amides from various carboxylic acids and amines. This reaction can be understood in one pot via *in situ* generation of α-acyl enol esters. Excellent functional group tolerance, simple experimental operation, good to excellent yields, and mild reaction conditions may make this transformation more attractive for an easy access to the key intermediate of drug molecules. Research on further applications for this novel coupling reagent is currently in progress in our laboratory.

EXPERIMENTAL SECTION

General information. All of the chemicals were purchased and used as received unless otherwise mentioned. Reactions were carried out in air using glassware and solvent that had not been pre-dried. Analytical thin-layer chromatography (TLC) was performed and visualization of the compounds was accomplished with UV light (254 nm) or iodine. Flash chromatography was performed using 100–200 mesh silica gel with the indicated solvent system.

All ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker Avance III instrument (400 MHz and 100 MHz, respectively). Chemical shifts (δ) are reported in ppm relative to the tetramethylsilane (TMS) signal or residual protio solvent signal. Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br = broad singlet, coupling constant(s) in Hz, integration). Data for ^{13}C NMR and ^{19}F NMR is reported in terms of chemical shift (δ, ppm).

General procedure for the synthesis of N-substituted benzamides. To a 10 mL reaction tube were added benzoic acid (0.50 mmol), methyl acetylenate (0.55 mmol), and triethylamine (1.10 mmol) in CH_3CN (3 mL) under air. The tube was sealed and stirred at room temperature for 30 min. Subsequently, amines (1.10 mmol) were added to the stirring solution, and the resulting mixture was stirred at room temperature for another 10−30 min, monitoring with TLC. Then 1N HCl solution (3 mL) was added into the mixture and extracted three times with ethyl acetate. The combined organic layers were dried with anhydrous sodium sulfate and filtered. The solvent was evaporated under reduced pressure and the residue was purified by silica gel flash column chromatography (10−25% ethyl acetate in petroleum ether) to afford the desired product 1−20 as a white solid.

*N-phenethylbenzamide **(1).*** The product **1** (110.4 mg, 98% yield) was obtained as a white solid:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.4 Hz, 2H), 7.46 (t, J = 7.4 Hz, 1H), 7.38 (t, J = 7.5 Hz, 2H), 7.31 (t, J = 7.3 Hz, 2H), 7.23 (t, J = 8.4 Hz, 3H), 6.40 (s, 1H), 3.69 (m, 6.9 Hz, 2H), 2.91 (t, J = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, CDCl3) δ 167.6, 138.9, 134.6, 131.4, 128.8, 128.7, 128.5, 126.9, 126.5, 77.4, 77.1, 76.8, 41.2, 35.7.

N-(4-fluorophenethyl)benzamide ***(2).*** The product **2** (116.3 mg, 96% yield) was obtained as a white solid: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.56 (s, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.49 (m, 3H), 7.38–7.21 (m, 2H), 7.12 (t, J = 8.9 Hz, 2H), 3.49 (m, 2H), 2.85 (t, J = 7.3 Hz, 2H); ^{19}F NMR (471 MHz, DMSO-*d6*) δ -117.17 (s).^{13}C NMR (100 MHz, DMSO-d6) δ 166.6, 162.4, 160.0, 136.1, 136.1, 135.0, 131.5, 130.9, 130.8, 128.7, 127.5, 115.5, 115.3, 41.2, 40.6, 40.3, 40.1, 39.9, 39.7, 39.5, 39.3, 34.6.

N-(4-chlorophenethyl)benzamide ***(3).*** The product **3** (111.4 mg, 86% yield) was obtained as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.5 Hz, 2H), 7.48 (t, J = 7.4 Hz, 1H), 7.39 (t, J = 7.5 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 6.37 (s, 1H), 3.66 (m, 2H), 2.89 (t, J = 7.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 137.4, 134.5, 132.3, 131.5, 130.1, 128.7, 128.6, 126.8, 77.4, 77.0, 76.7, 41.1, 35.0.

N-(3-methoxyphenethyl)benzamide ***(4).*** The product **4** (108.8 mg, 86% yield) was obtained as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.62 (m, 2H), 7.46 (t, J = 7.4 Hz, 1H), 7.38 (t, J = 7.5 Hz, 2H), 7.24 (m, 1H), 6.80 (m, 3H), 6.36 (s, 1H), 3.77 (s, 3H), 3.69 (m, 2H), 2.90 (t, J = 7.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) 167.5, 159.9, 140.5, 134.6, 131.4, 129.6, 128.5, 126.8, 121.1, 114.4, 112.0, 77.4, 77.1, 76.7, 55.1, 41.1, 35.7.

N-(3,4-dimethoxyphenethyl)benzamide ***(5).*** The product **5** (100.7 mg, 71% yield) was obtained as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.5 Hz, 2H), 7.47 (t, J = 7.4 Hz, 1H), 7.39 (t, J = 7.5 Hz, 2H), 6.81 (d, J = 8.0 Hz, 1H), 6.75 (d, J = 11.2 Hz, 2H), 6.43 (s, 1H), 3.83 (d, J = 13.9 Hz, 6H), 3.68 (m, 2H), 2.87 (t, J = 7.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 149.0, 147.7, 134.6, 131.5, 131.3, 128.5, 126.8, 120.6, 112.0, 111.4, 77.5, 77.1, 76.8, 55.9, 55.8, 41.3, 35.2.

N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)benzamide ***(6).*** The product **6** (122.2 mg, 91% yield) was obtained as a white solid: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.54 (s, 1H), 7.91–7.63 (m, 2H), 7.51 (m, 1H), 7.45 (m, 2H), 6.82 (d, J = 8.0 Hz, 2H), 6.69 (d, J = 7.9 Hz, 1H), 5.97 (s, 2H), 3.46 (m,

2H), 2.78 (t, J = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-*d6*) δ 166.6, 147.6, 145.9, 135.1, 133.8, 131.5, 128.7, 127.5, 122.0, 109.4, 108.5, 101.1, 41.5, 40.6, 40.3, 40.1, 39.9, 39,7, 39.5, 39.3, 35.2.

N-(2-hydroxy-2-phenylethyl)benzamide ***(7).*** The product **7** (118.4 mg, 98% yield) was obtained as a white solid: ^{1}H NMR (400 MHz, DMSO-d6) δ 8.54 (s, 1H), 7.94–7.76 (m, 2H), 7.52 (t, J = 7.2 Hz, 1H), 7.46 (t, J = 7.9 Hz, 2H), 7.36 (m, 4H), 7.26 (t, J = 7.7 Hz, 1H), 5.56 (d, J = 4.1 Hz, 1H), 4.81 (m, 1H), 3.51 (m, 1H), 3.38–3.26 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d6) δ 166.9, 144.2, 135.0, 131.5, 128.6, 128.5, 127.6, 127.5, 126.4, 71.6, 48.1, 40.5, 40.3, 40.1, 39.9, 39.7, 39.5, 39.3.

N-benzylbenzamide ***(8).*** The product **8** (102.3 mg, 96% yield) was obtained as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87–7.69 (m, 2H), 7.46 (t, J = 7.4 Hz, 1H), 7.36 (t, J = 7.8 Hz, 2H), 7.30 (d, J = 4.1 Hz, 4H), 7.26 (m, 1H), 6.89 (s, 1H), 4.57 (d, J = 5.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 138.3, 134.3, 131.5, 128.7, 128.5, 127.8, 127.5, 127.0, 77.4, 77.1, 76.8, 44.0.

N-(4-methoxybenzyl)benzamide ***(9).*** The product **9** (110.7 mg, 92% yield) was obtained as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.5 Hz, 2H), 7.38 (t, J = 7.4 Hz, 1H), 7.29 (t, J = 7.5 Hz, 2H), 7.16 (d, J = 8.7 Hz, 2H), 6.76 (d, J = 8.6 Hz, 2H), 6.62 (s, 1H), 4.44 (d, J = 5.6 Hz, 2H), 3.68 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 159.0, 134.5, 131.4, 130.4, 129.2, 128.5, 127.0, 114.1, 77.4, 77.1, 76.8, 55.2, 43.5.

N-(4-fluorobenzyl)benzamide ***(10).*** The product **10** (110.5 mg, 97% yield) was obtained as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 7.3 Hz, 2H), 7.49 (t, J = 7.4 Hz, 1H), 7.38 (t, J = 7.6 Hz, 2H), 7.32–7.22 (m, 2H), 7.20 (s, 1H), 6.98 (t, J = 8.7 Hz, 2H), 4.53 (d, J = 5.1 Hz, 2H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -116.17 (s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 163.3, 160.9, 134.2, 131.5, 129.4, 129.3, 128.5, 127.0, 115.5, 115.3, 77.4, 77.1, 76.8, 43.2.

N-(1-phenylethyl)benzamide ***(11).*** The product **11** (107.5 mg, 96% yield) was obtained as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 7.1 Hz, 2H), 7.51 (t, J = 8.0 Hz, 1H), 7.40 (m, 6H), 7.34–7.27 (m, 1H), 6.52 (s, 1H), 5.36 (m, 1H), 1.62 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 143.2, 134.6, 131.4, 128.7, 128.5, 127.4, 126.9, 126.2, 77.3, 77.0, 76.7, 49.2, 21.7.

N-(3-methoxypropyl)benzamide ***(13).*** The product **13** (87.1 mg, 91% yield) was obtained as a oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.6 Hz, 2H), 7.46 (t, J = 6.7 Hz, 1H), 7.39 (t, J = 7.7 Hz, 2H), 7.21 (s, 1H), 3.54 (m, 4H), 3.35 (s, 3H), 1.95–1.79 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ

167.4, 134.7, 131.1, 128.3, 126.9, 77.5, 77.2, 76.9, 71.8, 58.7, 38.6, 28.9.

*N-butylbenzamide **(14).*** The product **14** (80 mg, 91% yield) was obtained as a oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88–7.68 (m, 2H), 7.46 (t, J = 7.3 Hz, 1H), 7.38 (t, J = 7.5 Hz, 2H), 6.62 (s, 1H), 3.42 (m, 2H), 1.64–1.51 (m, 2H), 1.38 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 134.7, 131.1, 128.3, 126.9, 77.5, 77.2, 76.9, 71.8, 58.7, 38.6, 28.9.

*N-(cyclopropylmethyl)benzamide **(15).*** The product **15** (81.2 mg, 93% yield) was obtained as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 7.3 Hz, 2H), 7.45 (t, J = 7.3 Hz, 1H), 7.37 (t, J = 7.6 Hz, 2H), 6.93 (s, 1H), 3.37–3.16 (m, 2H), 1.05 (m, 1H), 0.49 (m, 2H), 0.23 (d, J = 4.9 Hz, 2H). ^{13}C NMR (100 MHz, CDCl3) δ 167.6, 134.7, 131.2, 128.3, 127.0, 77.5, 77.1, 76.8, 44.8, 10.7, 3.4.

*N-(cyclohexylmethyl)benzamide **(16).*** The product **16** (106.3 mg, 98% yield) was obtained as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87–7.70 (m, 2H), 7.45 (t, J = 7.3 Hz, 1H), 7.37 (t, J = 7.5 Hz, 2H), 6.83 (s, 1H), 3.25 (t, J = 6.5 Hz, 2H), 1.71 (m, 5H), 1.60–1.49 (m, 1H), 1.30–1.07 (m, 3H), 0.94 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 134.9, 131.1, 128.4, 127.0, 77.5, 77.1, 76.8, 46.2, 37.9, 30.9, 26.4, 25.8.

*N-(4-(tert-butyl)cyclohexyl)benzamide **(17).*** The product **17** (120.8 mg, 93% yield) was obtained as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 7.1 Hz, 2H), 7.39 (t, J = 6.7 Hz, 1H), 7.32 (t, J = 7.4 Hz, 2H), 6.09 (s, 1H), 3.80 (s, 1H), 2.04 (d, J = 9.3 Hz, 2H), 1.74 (d, J = 10.7 Hz, 2H), 1.18–0.98 (m, 4H), 0.98–0.83 (m, 1H), 0.78 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 135.0, 131.1, 128.4, 126.9, 77.3, 77.0, 76.7, 49.3, 47.3, 33.6, 32.3, 27.5, 26.1.

*Methyl benzoylphenylalaninate **(18).*** The product **18** (90 mg, 64% yield) was obtained as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.4 Hz, 2H), 7.42 (t, J = 7.4 Hz, 1H), 7.34 (t, J = 7.5 Hz, 2H), 7.27–7.12 (m, 3H), 7.06 (d, J = 6.5 Hz, 2H), 6.55 (d, J = 7.1 Hz, 1H), 5.10–4.95 (m, 1H), 3.68 (s, 3H), 3.18 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 166.8, 135.9, 133.9, 131.7, 129.3, 128.6, 127.4, 127.0, 77.3, 77.0, 76.7, 53.5, 52.4, 37.9.

*Phenyl(pyrrolidin-1-yl)methanone **(19).*** The product **19** (69.1 mg, 79% yield) was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 2H), 7.31 (d, J = 4.8 Hz, 3H), 3.45 (s, 4H), 1.83 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 129.7, 128.1, 127.0, 77.4, 77.1, 76.8, 49.2, 46.5, 29.6, 25.4.

*Benzamide **(20).*** The product **20** (48.7 mg, 81% yield) was obtained as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.1 Hz, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 6.9 Hz, 2H), 6.40 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 133.4, 132.0, 128.6, 127.3, 77.3, 77.0, 76.7.

General procedure for the evaluation of carboxylic acids. To a 10 mL reaction tube were added carboxylic acid (0.50 mmol), methyl acetylenate (0.55 mmol), and triethylamine (1.10 mmol) in CH_3CN (3 mL) under air. The tube was sealed and stirred at room temperature or 60 ^{o}C for 30 min to 4 hours. After cooling to room temperature, the phenylethylamine (1.10 mmol) was added to the stirring solution, and the resulting mixture was stirred at room temperature for another 10−30 min, monitoring with TLC. Then 1N HCl solution (3 mL) was added into the mixture and extracted three times with ethyl acetate. The combined organic layers were dried with anhydrous sodium sulfate and filtered. The solvent was evaporated under reduced pressure and the residue was purified by silica gel flash column chromatography (10−25% ethyl acetate in petroleum ether) to afford the desired product **21**−**40** as a white solid.

*2-Fluoro-N-phenethylbenzamide **(21).*** The product **21** (116.4 mg, 96% yield) was obtained as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (t, *J* = 7.9 Hz, 1H), 7.42 (m, 1H), 7.35–7.27 (m, 2H), 7.22 (m, 4H), 7.10–6.99 (m, 1H), 6.82 (s, 1H), 3.83–3.67 (m, 2H), 2.93 (t, *J* = 7.1 Hz, 2H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -114.43 (s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 161.8, 159.3, 138.8, 133.1, 133.0, 131.9 128.7, 128.6, 126.5, 124.7, 116.0, 115.8, 77.4, 77.1, 76.8, 41.3, 35.6.

*4-Nitro-N-phenethylbenzamide **(22).*** The product **22** (77.2 mg, 65% yield) was obtained as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.9 Hz, 2H), 7.75 (d, *J* = 8.9 Hz, 2H), 7.25 (t, *J* = 7.2 Hz, 2H), 7.21–7.11 (m, 3H), 6.29 (s, 1H), 3.66 (m, 2H), 2.87 (t, *J* = 6.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 149.5, 140.2, 138.5, 128.8, 128.7, 128.0, 126.7, 123.7, 77.3, 77.0, 76.7, 41.4, 35.4.

*4-Methyl-N-phenethylbenzamide **(23).*** The product **23** (95.6 mg, 80% yield) was obtained as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.0 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 2H), 7.30–7.17 (m, 5H), 6.45 (s, 1H), 3.71 (m, 2H), 2.94 (t, *J* = 7.0 Hz, 2H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 141.8, 139.0, 131.7, 129.1, 128.8, 128.6, 126.9, 126.5, 77.4, 77.1, 76.7, 41.2, 35.7, 21.3.

*4-Methoxy-N-phenethylbenzamide **(24).*** The product **24** (120.1 mg, 94% yield) was obtained as a

white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.8 Hz, 2H), 7.37–7.27 (m, 2H), 7.23 (m, 3H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.71 (s, 1H), 3.81 (s, 3H), 3.74–3.59 (m, 2H), 2.92 (t, *J* = 7.1 Hz, 2H). ^{3}C NMR (100 MHz, $CDCl_3$) δ 167.2, 162.1, 139.1, 128.8, 128.7, 128.6, 126.8, 126.4, 113.7, 77.5, 77.1, 76.8, 55.3, 41.2, 35.8.

3-Methoxy-N-phenethylbenzamide ***(25).*** The product **25** (114.3 mg, 90% yield) was obtained as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.19 (m, 8H), 7.02 (d, *J* = 10.4 Hz, 1H), 6.59 (s, 1H), 3.81 (s, 3H), 3.75–3.63 (m, 2H), 2.93 (t, *J* = 7.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 159.8, 139.0, 136.2, 129.5, 128.7, 128.6, 126.4, 118.9, 117.5, 112.4, 77.6, 77.2, 76.9, 55.3, 41.3, 35.7.

3,5-Dimethoxy-N-phenethylbenzamide ***(26).*** The product **26** (97.0 mg, 68% yield) was obtained as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (t, *J* = 7.6 Hz, 2H), 7.14 (m, 3H), 6.74 (d, *J* = 2.2 Hz, 2H), 6.45 (t, *J* = 1.9 Hz, 1H), 6.34 (s, 1H), 3.68 (d, *J* = 1.4 Hz, 6H), 3.58 (m,2H), 2.82 (t, *J* = 7.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 160.8, 138.9, 136.8, 128.7, 128.6, 126.5, 104.9, 103.6, 77.5, 77.1, 76.8, 55.4, 41.3, 35.6.

3,4-Dimethyl-N-phenethylbenzamide ***(27).*** The product **27** (119.1 mg, 94% yield) was obtained as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.44 (d, *J* = 7.7 Hz, 1H), 7.34 (t, *J* = 7.2 Hz, 2H), 7.26 (t, *J* = 7.5 Hz, 3H), 7.16 (d, *J* = 7.8 Hz, 1H), 6.41 (s, 1H), 3.71 (m, 2H), 2.94 (t, *J* = 7.0 Hz, 2H), 2.29 (d, *J* = 4.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 140.3, 139.1, 136.7, 132.2, 129.6, 128.8, 128.6, 128.3, 126.4, 124.2, 77.5, 77.2, 76.9, 41.2, 35.8, 19.7, 19.6.

2-(Phenethylcarbamoyl)phenyl acetate ***(28).*** The product **28** (80.7 mg, 57% yield) was obtained as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.7 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.36–7.19 (m, 6H), 7.06 (d, *J* = 8.1 Hz, 1H), 6.37 (s, 1H), 3.70 (m, 2H), 2.91 (t, *J* = 6.8 Hz, 2H), 2.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 165.6, 147.9, 138.8, 131.7, 129.7, 128.7, 128.1, 126.6, 126.2, 123.1, 77.3, 77.0, 76.7, 41.0, 35.4, 20.7.

N-phenethyl-2-naphthamide ***(29).*** The product **29** (103.5 mg, 75% yield) was obtained as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (s, 1H), 7.05–6.91 (m, 3H), 6.87 (d, *J* = 8.6 Hz, 1H), 6.72–6.55 (m, 2H), 6.55–6.41 (m, 2H), 6.37 (d, *J* = 5.5 Hz, 3H), 5.50 (s, 1H), 2.88 (m, 2H), 2.09 (t, *J* = 6.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 138.9, 134.7, 132.6, 131.9, 128.9, 128.8, 128.7, 128.4, 127.7, 127.6, 127.3, 126.7, 126.6, 123.5, 77.3, 77.0, 76.7, 41.3, 35.7.

*N-phenethylthiophene-2-carboxamide **(30).*** The product **30** (110.5 mg, 96% yield) was obtained as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 1H), 7.34 (m,1H), 7.25 (t, *J* = 7.2 Hz, 2H), 7.16 (m, 3H), 7.02–6.90 (m, 1H), 6.04 (s, 1H), 3.61 (m, 2H), 2.84 (t, *J* = 7.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 139.0, 138.8, 129.7, 128.8, 128.7, 127.9, 127.5, 126.6, 77.3, 77.0, 76.7, 41.1, 35.7.

*N-phenethylpicolinamide **(31).*** The product **31** (85 mg, 75% yield) was obtained as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 4.2 Hz, 1H), 8.14 (d, *J* = 7.8 Hz, 2H), 7.79 (t, *J* = 8.5 Hz, 1H), 7.35 (m, 1H), 7.29–7.21 (m, 2H), 7.21–7.12 (m, 4H), 3.67 (m,2H), 2.88 (t, *J* = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 149.5, 147.4, 138.9, 137.9, 128.7, 128.6, 126.4, 126.2, 122.6, 77.3, 77.0, 76.7, 40.8, 35.8.

*N-phenethyl-1H-indole-2-carboxamide **(32).*** The product **32** (117.8 mg, 90% yield) was obtained as a white solid: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.56 (s, 1H), 8.58 (t, *J* = 5.6 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.2 Hz, 1H), 7.35–7.24 (m, 4H), 7.19 (m, 2H), 7.12 (s, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 3.55 (m, 2H), 2.89 (t, *J* = 7.4 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-*d6*) δ 161.5, 139.9, 136.8, 132.3, 129.1, 128.8, 127.5, 126.5, 123.6, 121.9, 120.1, 112.7, 102.7, 40.9, 40.4, 40.1, 39.9, 39.7, 39.4, 39.3, 35.7.

*N-phenethyl-2-phenylacetamide **(34).*** The product **34** (87.4 mg, 73% yield) was obtained as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.12 (m, 8H), 7.02 (d, *J* = 7.9 Hz, 2H), 5.44 (s, 1H), 3.51 (s, 2H), 3.45 (m, 2H), 2.72 (t, *J* = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 138.7, 134.8, 129.4, 128.9, 128.6, 128.5, 127.2, 126.4, 77.3, 77.0, 76.7, 43.8, 40.7, 35.5.

*N-phenethyl-2-(p-tolyl)acetamide **(35).*** The product **35** (103.4 mg, 82% yield) was obtained as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.14 (m, 3H), 7.11 (d, *J* = 7.8 Hz, 2H), 7.08–6.95 (m, 4H), 5.43 (s, 1H), 3.48 (s, 2H), 3.44 (m, 2H), 2.71 (t, *J* = 6.8 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 138.6, 136.9, 131.6, 129.7, 129.3, 128.7, 128.5, 126.4, 77.3, 77.0, 76.7, 43.3, 40.7, 35.4, 21.1.

*2-(2-iodophenyl)-N-phenethylacetamide **(36).*** The product **36** (121.3 mg, 67% yield) was obtained as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.7 Hz, 1H), 7.40–7.10 (m, 5H), 7.06 (d, *J* = 6.7 Hz, 2H), 6.96 (t, *J* = 8.5 Hz, 1H), 5.49 (s, 1H), 3.66 (s, 2H), 3.47 (m, 2H), 2.75 (t, *J* = 6.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 139.8, 138.6, 138.3, 130.8, 129.2, 128.8, 128.7,

128.6, 126.4, 101.2, 77.4, 77.1, 76.8 ,48.6, 40.7, 35.4.

N-phenethylcinnamamide ***(38).*** The product **38** (120.4 mg, 96% yield) was obtained as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 15.6 Hz, 1H), 7.49 (m, 2H), 7.38–7.28 (m, 5H), 7.24 (t, *J* = 8.2 Hz, 3H), 6.53 (d, *J* = 6.7 Hz, 1H), 6.50 (d, *J* = 15.7 Hz, 1H), 3.68 (m, 2H), 2.93 (t, *J* = 7.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 140.9, 138.9, 134.9, 129.6, 128.7, 128.6, 127.8, 126.5, 120.9, 77.4, 77.1, 76.8, 41.0, 35.7.

N^1,N^3-diphenethylisophthalamide ***(39).*** The product **39** (103.4 mg, 56% yield) was obtained as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.71 (d, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.25 (s, 4H), 7.15 (t, *J* = 8.5 Hz, 6H), 6.43 (s, 2H), 3.72–3.53 (m, 4H), 2.85 (t, *J* = 6.9 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 138.6, 134.7, 129.8, 128.9, 128.7, 128.7, 126.6, 125.5, 77.3, 77.0, 76.7, 41.4, 35.6.

N-phenethylcyclohexanecarboxamide ***(40).*** The product **40** (103.4 mg, 82% yield) was obtained as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.3 Hz, 2H), 7.27–7.14 (m, 3H), 5.60 (s, 1H), 3.49 (t, *J* = 9.9 Hz, 2H), 2.80 (t, *J* = 6.9 Hz, 2H), 2.01 (m, 1H), 1.78 (t, *J* = 13.8 Hz, 4H), 1.70–1.53 (m, 1H), 1.39 (m, 2H), 1.31–1.11 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 139.0, 128.7, 128.5, 126.4, 77.4, 77.0, 76.7, 45.5, 40.3, 35.7, 29.6, 25.7.

Preparation of compound 45. To a 10 mL reaction tube were added 4-isopropylcyclohexane-1-carboxylic acid (0.50 mmol), methyl acetylenate (0.55 mmol), and triethylamine (1.10 mmol) in CH_3CN (3 mL) under air. The tube was sealed and stirred at 60 ^{o}C for 5 hours. After cooling to room temperature, the methyl phenylalaninate (1.10 mmol) was added to the stirring solution, and the resulting mixture was stirred at room temperature for another 3 hours, monitoring with TLC. Then 1N HCl solution (3 mL) was added into the mixture and extracted three times with ethyl acetate. The combined organic layers were dried with anhydrous sodium sulfate and filtered. The solvent was evaporated under reduced pressure and the residue was purified by silica gel flash column chromatography (10−25% ethyl acetate in petroleum ether) to give methyl (4-isopropylcyclohexane-1-carbonyl) phenylalaninate **45** (83.9 mg, 51% yield) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.11 (m, 3H), 7.00 (d, *J* = 6.7 Hz, 2H), 5.88 (d, *J* = 7.4 Hz, 1H), 4.82 (m, 1H), 3.65 (s, 3H), 3.05 (m, 2H), 2.05–1.87 (m, 1H), 1.79 (t, *J* = 13.1 Hz, 2H), 1.70 (d, *J* = 12.1 Hz, 2H), 1.31 (m,3H), 0.93 (m, 3H), 0.77 (d, *J* = 6.8 Hz, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 172.2, 135.9, 129.3, 128.4, 127.0, 77.3, 77.0, 76.7, 52.7, 52.2, 45.4, 43.2, 37.8, 32.7, 29.7, 29.4, 29.0, 28.9, 19.7.

Preparation of compound 46. To a 10 mL reaction tube were added 2-methoxy-5-(methylsulfonyl)benzoic acid (0.50 mmol), methyl acetylenate (0.55 mmol), and triethylamine (1.10 mmol) in CH_3CN (3 mL) under air. The tube was sealed and stirred at 60 ^oC for 3 hours. Then, N^1,N^1-diethylethane-1,2-diamine (1.10 mmol) was added to the stirring solution, and the resulting mixture was stirred at 60 ^oC for another 2 hours, monitoring with TLC. Finally, the solvent was evaporated under reduced pressure and the residue was purified by silica gel flash column chromatography (5−10% methyl alcohol in dichloromethane) to give N-(2-(diethylamino)ethyl)-2-methoxy-5-(methylsulfonyl)benzamide **46** (78.2 mg, 48% yield) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.65 (s, 1H), 8.02 (d, *J* = 11.2 Hz, 1H), 7.13 (d, *J* = 8.8 Hz, 1H), 4.10 (s, 3H), 3.75 (m, 2H), 3.06 (s, 3H), 2.97 (t, *J* = 5.6 Hz, 2H), 2.88 (m, 4H), 1.24 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 161.3, 133.1, 131.9, 122.7, 112.0, 77.3, 77.0, 76.7, 56.6, 51.9, 47.6, 44.5, 36.9, 10.3.

Preparation of compound 47. To a 10 mL reaction tube were added 5-chloro-2-methoxybenzoic acid (0.50 mmol), methyl acetylenate (0.55 mmol), and triethylamine (1.10 mmol) in CH_3CN (3 mL) under air. The tube was sealed and stirred at 60 ^oC for 40 min. Subsequently, the 4-(2-aminoethyl)benzenesulfonamide (1.10 mmol) was added to the stirring solution, and the resulting mixture was stirred at 60 ^oC for another 2 hours, monitoring with TLC. Then the reaction was cooled to 0 ^oC using the ice water for 30 min, and a white solid 5-chloro-2-methoxy-*N*-(4-sulfamoylphenethyl)benzamide **47** (1.89 g, 85% yield) was obtained by the filtration: ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.27 (t, *J* = 5.5 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.64 (d, *J* = 2.8 Hz, 1H), 7.50 (d, *J* = 11.7 Hz, 1H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.31 (s, 2H), 7.16 (d, *J* = 8.9 Hz, 1H), 3.81 (s, 3H), 3.53 (m, 2H), 2.91 (t, *J* = 7.0 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-*d6*) δ 164.0, 156.1, 144.1, 142.6, 131.9, 129.9, 129.6, 126.1, 125.3, 124.8, 114.6, 56.7, 35.0.

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: .

NMR spectra for compounds **1**−**11**, **13**−**32**, **34**−**36**, **38**−**40**, **45**−**47** (PDF)

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