Synthesis L.-Y. Chen, M.-F. Wu Paper

An Efficient Catalytic Amidation of Esters Promoted by N-Heterocyclic Carbenes

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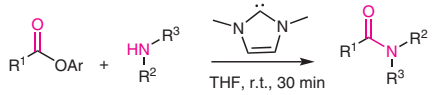

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Abstract An efficient NHC-catalyzed amidation between esters and amines or hydrazines is described. This strategy was tolerant for a wide scope of substrates, affording a series of amides (or hydrazides) in good to excellent yields (60–96%) under simple conditions. The approach was also used to synthesize the pharmaceutically relevant antidepressant moclobemide in 85% yield.

Key words N-heterocyclic carbenes, amidation, catalytic reaction, amides, nucleophilic addition

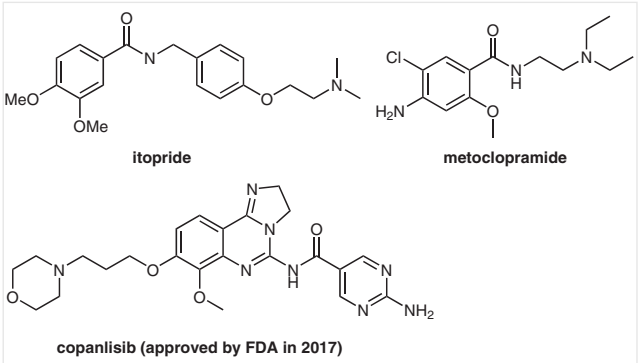


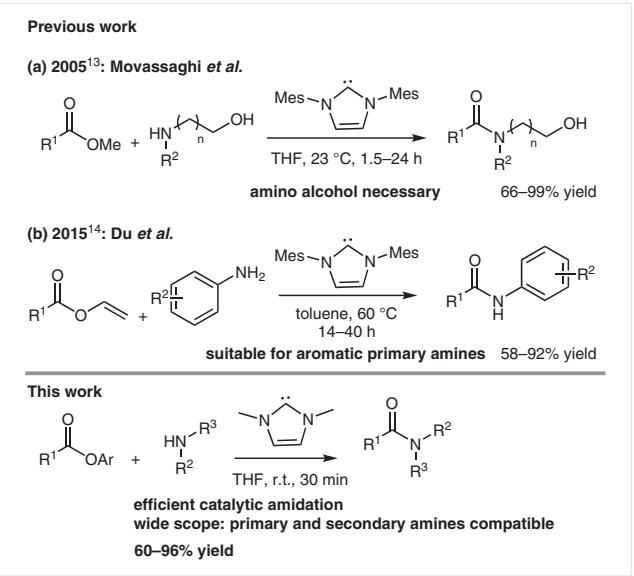
Figure 1 Selected examples of pharmaceutical products with amide bonds

Amidation is one of the most important transformations in organic synthesis, since amide compounds are abundantly found in biologically active compounds, pharmaceutical products, proteins, and natural products (Figure 1).[1–5] For example, itopride is indicated for the treatment of functional dyspepsia, metoclopramide is commonly used to treat and prevent nausea and vomiting, while copanlisib is a new drug approved by the U.S. Food and Drug Administration (FDA) in 2017 for the treatment of recurrent follicular lymphoma. Consequently, it is important to develop different methods for the synthesis of amide compounds.

The traditional methods for the synthesis of amides focus on the condensation between carboxylic acids and amines, using more reactive acyl chlorides or esters,[6,7] or using alternative intermediates without use of metals,[8a,b] followed by nucleophilic substitutions with amines, but they often need elevated temperatures in the absence of any catalyst, and the substrates could not completely be transformed even after long time. Therefore, it is highly desirable to seek suitable catalysts to facilitate faster amidation. Recently, enormous catalytical methods for preparing amides have been developed such as transition-metal-catalyzed[9] and N-heterocyclic carbenes (NHC)-catalyzed[8c–i] oxidative amidation, radical initiated amidation through the formation of activated intermediates,[10] and photocatalysis through radical process,[11] which even directly used aldehydes as the starting material instead of carboxylic acids or their derivatives. However, these direct oxidative amidation of aldehydes often need oxidants or other extra additives with obvious restrictions on substrate scope. Thus, transforming to acid derivatives still should be the major efficient and simple approach to produce the amide compounds if suitable catalysts are chosen.

In the past several decades, N-heterocyclic carbenes (NHCs) have emerged as efficient organocatalysts in organic synthesis.[12] In 2005, Movassaghi reported the amidation between unactivated esters and amino alcohol.[13] As the hydroxy group was necessary for the reaction, the reaction suffered from the limited substrate scope. Recently, Du and co-workers explored the amidation between vinyl ester and aromatic amines (Scheme 1). However, this method needed elevated temperature (60 °C), and did not mention the use

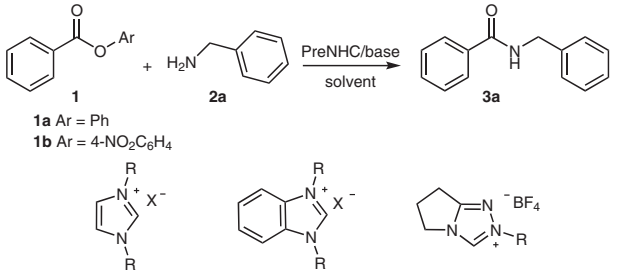
of secondary amines or aliphatic amines.[14] We envisioned whether the aliphatic amines (including secondary amines) or hydrazines could form the corresponding amides under mild conditions. As a result, we herein report an efficient approach for amidation between aryl esters and different amines or hydrazines promoted by NHCs, which is a useful supplementary method for preparing amide compounds (Scheme 1). Our approach was performed at room temperature in very short time, which is more efficient and easier to handle.



Scheme 1 NHC-catalyzed amidation of esters

According to NHC-catalyzed saturated ester process developed by Chi group,[15] our investigation started from the amidation between benzoate **1a** and benzylamine (**2a**) in CH_2Cl_2 at room temperature (Table 1). In the absence of catalyst, the reaction proceeded so slow that the yield was low even after 10 hours (Table 1, entry 1). As anticipated, when in the presence of 20% NHC precursor **4** and DBU, the reaction proceeded quickly, affording the desired amide in 68% yield in 1 hour (entry 2). When benzoate **1b** was used instead of **1a**, the yield rose to 93% (entry 3). Several other different NHC precursors **5**–**10** were also examined. The reaction showed strong dependence on the types of the catalysts or substituents on the catalysts (entries 3–10). For imidazole-based and benzimidazole-based NHC precursors, if the aromatic group was used instead of alkyl group, the yield decreased dramatically (entries 3–8). NHC precursor **8** even resulted only in trace amount of the product. For triazole-based NHC precursor, the yield was moderate (entries 9, 10). In order to further optimize the reaction, other parameters such as base and solvents were also screened. The results indicated that different bases had obvious effect on yields of the reaction. Importantly, DBU was proved to be the most efficient base providing the best result, while both Cs_2CO_3 and K_2CO_3 gave promising results as well (90% and 92%, respectively, entries 11 and 12). However, if other bases such as DMAP, Et_3N, *t*-BuOK, DABCO, and DIPEA were used, there was a significant decrease in yields (entries 10, 13–16). In addition, to our delight, when using THF instead of CH_2Cl_2 as the solvent, the desired amide was obtained in 97% yield in 30 minutes (entry 18). For other solvent such as toluene, methanol, acetonitrile, the yields were all poor

Table 1 Investigation of the Effects of Different NHC Precursors, Bases and Solvents on the Amidation Reaction[a]

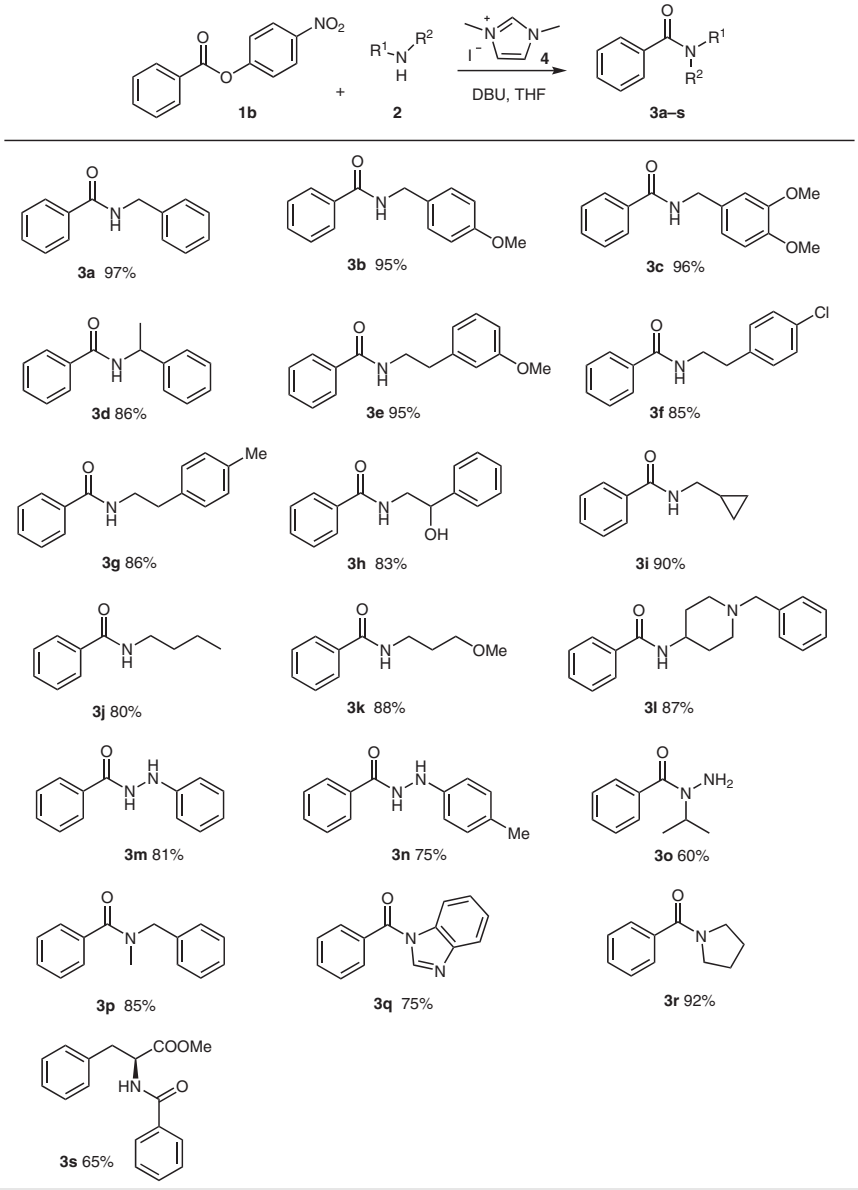


Entry	1	PreNHC	Base	Solvent	Time	Yield (%)[b]
1	**1a**	–	–	CH_2Cl_2	10 h	23
2	**1a**	**4**	DBU	CH_2Cl_2	1 h	68
3	**1b**	**4**	DBU	CH_2Cl_2	1 h	93
4	**1b**	**5**	DBU	CH_2Cl_2	1 h	41
5	**1b**	**6**	DBU	CH_2Cl_2	1 h	63
6	**1b**	**7**	DBU	CH_2Cl_2	1 h	32
7	**1b**	**8**	DBU	CH_2Cl_2	1 h	trace
8	**1b**	**9**	DBU	CH_2Cl_2	1 h	80
9	**1b**	**10**	DBU	CH_2Cl_2	1 h	66
10	**1b**	**4**	DMAP	CH_2Cl_2	1 h	88
11	**1b**	**4**	Cs_2CO_3	CH_2Cl_2	1 h	90
12	**1b**	**4**	K_2CO_3	CH_2Cl_2	1 h	92
13	**1b**	**4**	Et_3N	CH_2Cl_2	1 h	61
14	**1b**	**4**	*t*-BuOK	CH_2Cl_2	1 h	59
15	**1b**	**4**	DABCO	CH_2Cl_2	1 h	63
16	**1b**	**4**	DIPEA	CH_2Cl_2	1 h	62
17	**1b**	**4**	DBU	toluene	1 h	50
18	**1b**	**4**	DBU	THF	30 min	97
19	**1b**	**4**	DBU	MeOH	10 h	–
20	**1b**	**4**	DBU	MeCN	1 h	60
21[c]	**1b**	**4**	DBU	THF	3 h	88

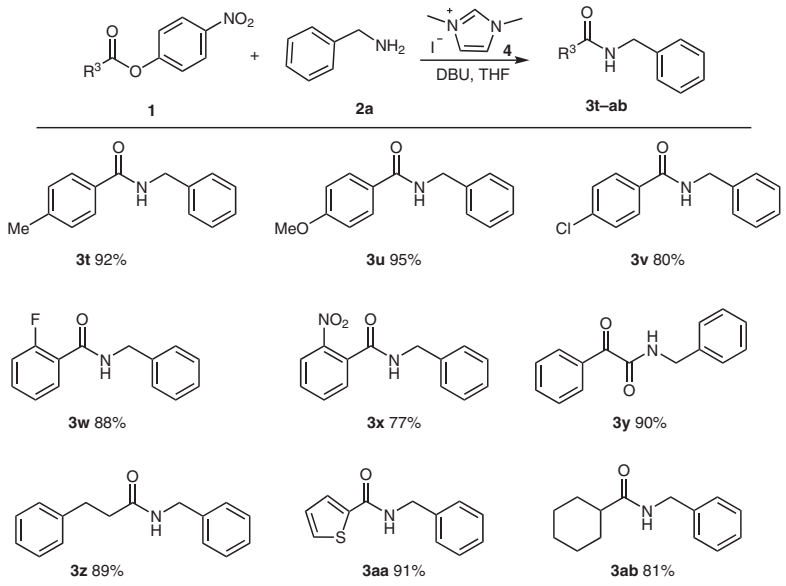
[a] Unless otherwise noted, all reactions were carried out using **1b** (0.5 mmol), **2a** (0.6 mmol), NHC precursor (0.1 mmol), and base (0.1 mmol) in solvent (2 mL) for 30 min to 10 h.
[b] Isolated yield.
[c] NHC precursor (0.05 mmol) and base (0.05 mmol) were used.

(entries 17, 19, and 20). Besides, if the catalyst loading was cut to half, the reaction needed longer time with slightly lower yield.

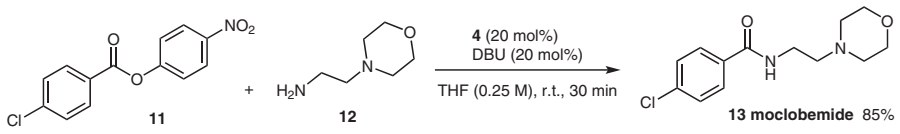
Under the optimized conditions, the scope of amidation promoted by NHC was further explored. A wide range of amines were tested. Scheme 2 shows that the reaction depended on both electronic and steric factors in some way, although almost all the reactions proceeded quite well and gave good to excellent yields. On the one hand, amines containing electron-withdrawing group like Cl, led to lower chemical yields than that with electron-donating group like Me and MeO. It is worth noting that secondary amines could also afford the desired amide in quite good yields (**3p**, **3q**, and **3r**: 85%, 75% and 92%, respectively). If the substrate containing a hydroxy group was used, no transesterification product was observed in the reaction. Additionally, hydrazines could also smoothly produce its corresponding acylhydrazides **3m–o** in good yields. For aliphatic hydrazine, it was worth noting that the reaction preferred to take place at the NH close to the alkyl group (**3o**). If there was a chiral center in the substrate, the enantiomeric excess could be evaluated by HPLC analysis (**3s**). However, aromatic amines like aniline or its derivatives could not undergo the amidation at room temperature.



Scheme 2 The scope of amidation with different amines (or hydrazines) promoted by NHC. *Reagents and conditions*: Unless otherwise noted, all reactions were carried out using **1b** (0.5 mmol), **2** (0.6 mmol), NHC precursor **4** (0.1 mmol), and DBU (0.1 mmol) in THF (2 mL) for 30 min.



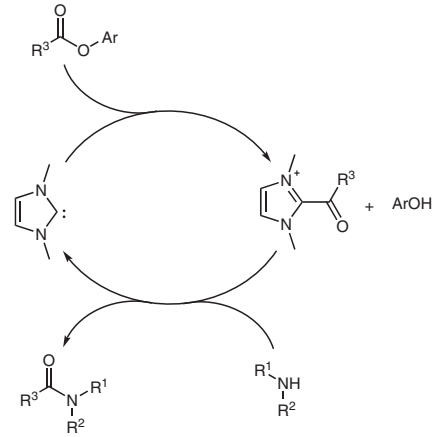
Scheme 3 The scope of amidation with different esters promoted by NHC. *Reagents and conditions*: Unless otherwise noted, all reactions were carried out using **1** (0.5 mmol), **2a** (0.6 mmol), NHC precursor **4** (0.1 mmol), and DBU (0.1 mmol) in THF (2 mL) for 30 min.



Scheme 4 Synthesis of antidepressant moclobemide

Further, we studied the substrate scope with respect to different esters for the synthesis of amides. The results are summarized in Scheme 3. Different esters, no matter from aromatic or aliphatic carboxylic acid, could smoothly afford the amidation to the corresponding amides in good yields. However, if there was an electron-donating group in the esters, the results were slightly better than that with electron-withdrawing group (Scheme 3, **3t–ab**). In order to expand on the potential of this approach to be used in practical applications, the synthesis of pharmaceutically relevant antidepressant moclobemide was performed smoothly to obtain the desired product in 85% yield (Scheme 4).

Based on the NHC-catalyzed saturated ester process, a plausible mechanism is proposed for this amidation using esters and amines (or hydrazines) in Scheme 5, which was similar to those described in other NHC-catalyzed reactions in the reported literature.[15] As esters and NHC were mixed before adding the amines, NHC catalyst only underwent a nucleophilic attack at the carbonyl group of the esters to form even more reactive intermediate, followed by the subsequent attack of amines to afford the desired amides or hydrazides, which avoided or reduced the interactions between the amine and NHC.



Scheme 5 Proposed mechanism for the amidation

In summary, we have demonstrated an efficient and convenient approach for amidation between aromatic esters and aliphatic amines catalyzed by NHC. This strategy tolerated a wide range of amines (including primary amines and secondary amines) or hydrazines with good to excellent yields in very short time, which is a valuable alternative approach for the synthesis of amides. Further explorations of NHCs are in progress.

^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ operating at 400 MHz and 100 MHz. ^{1}H NMR chemical shifts are reported relative to the residual proton signals of the deuterated solvent $CDCl_3$ (7.26 ppm). ^{13}C NMR chemical shifts were internally referenced to the deuterated solvent signals in $CDCl_3$ (77.16 ppm). Data are represented as follows: chemical shift, multiplicity (standard abbreviations), coupling constant in hertz (Hz), and integration. IR spectra were recorded on a PerkinElmer spectrometer. Mass spectra were recorded on a time-of-flight mass spectrometer with an ESI source. High-performance liquid chromatography (HPLC) was performed using a chromatograph equipped with a Chiralpak column (250 mm × 4.6 mm) with hexane/*i*-PrOH as the eluent. Products were identified by comparison to spectral data reported in the literature. Unless otherwise noted, all reagents were purchased from commercial supplies and used without further purification.

Amidation Promoted by PreNHC 4; General Procedure

An oven-dried 10 mL Schlenk tube was charged with ester **1** (0.50 mmol), NHC precursor **4** (22 mg, 0.1 mmol), and DBU (15 mg, 0.1 mmol) in THF (2.0 mL). The mixture was stirred for 20 min, and the amine **2** (0.6 mmol) was added. The reaction mixture was stirred at r.t. until the full consumption of the ester **1** (typically, about 30 min). The mixture was concentrated under reduced pressure and washed with aq 1% $NaHCO_3$ (3 ×) and purified by column chromatography on silica gel (PE/EtOAc as the eluent, typically 5:1 to 10:1) to furnish the corresponding amide.

***N*-Benzylbenzamide (3a)**[8g]

White solid; yield: 102.5 mg (97%); mp 60–61 °C.

IR (neat): 3285, 2366, 1653, 1558, 1489, 1316, 726, 693 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 4.0 Hz, 2 H), 7.50–7.46 (m, 1 H), 7.42–7.38 (m, 2 H), 7.34–7.25 (m, 5 H), 6.65 (s, 1 H), 4.61 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.3, 138.2, 134.3, 131.5, 128.7, 127.5, 127.8, 127.5, 126.9, 44.0.

MS (ESI): *m*/z = 212.1 [M + H]$^+$.

***N*-(4-Methoxybenzyl)benzamide (3b)**[16]

White solid; yield: 114.6 mg (95%); mp 95.8–96.2 °C.

IR (neat): 3326, 2361, 1653, 1558, 1238, 719 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 7.2 Hz, 2 H), 7.44 (t, *J* = 7.2 Hz, 1 H), 7.34 (t, *J* = 7.6 Hz, 2 H), 7.21 (d, *J* = 8.0 Hz, 2 H), 6.93 (s, 1 H), 6.81 (d, *J* = 8.0 Hz, 2 H), 4.49 (d, *J* = 4.0 Hz, 2 H), 3.74 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.5, 159.0, 134.5, 131.4, 130.5, 129.1, 128.4, 127.1, 114.0, 55.2, 43.4.

MS (ESI): *m*/*z* = 242.1 [M + H]$^+$.

***N*-(3,4-Dimethoxybenzyl)benzamide (3c)**[17]

White solid; yield: 130.2 mg (96%); mp 116–117 °C.

IR (neat): 3330, 2925, 2359, 1636, 1527, 1427, 1264, 1140, 800, 690 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 8.0 Hz, 2 H), 7.47–7.44 (m, 1 H), 7.36 (t, *J* = 8.0 Hz, 2 H), 7.03 (s, 1 H), 6.85 (t, *J* = 4.0 Hz, 2 H), 6.77 (d, *J* = 4.0 Hz, 1 H), 4.52 (d, *J* = 4.0 Hz, 2 H), 3.81 (s, 3 H), 3.78 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7, 136.6, 134.8, 131.5, 128.6, 127.5, 127.0 122.3, 119.6, 118.8, 113.0, 111.5, 40.4, 25.4.

MS (ESI): *m*/*z* = 272.1 [M + H]$^+$.

***N*-(1-Phenylethyl)benzamide (3d)**[17]

White solid; yield: 96.9 mg (86%); mp 120–121 °C.

IR (neat): 3338, 2925, 2360, 1635, 1539, 1457, 1311, 694 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 8.0 Hz, 2 H), 7.51–7.48 (m, 1 H), 7.41–7.29 (m, 7 H), 6.69 (d, *J* = 8.0 Hz, 1 H), 5.39–5.30 (m, 1 H), 1.61 (d, *J* = 8.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7, 143.4, 134.6, 131.4, 128.7, 128.5, 127.4, 127.1, 126.3, 49.3, 21.8.

MS (ESI): *m*/*z* = 248.1 [M + Na]$^+$.

***N*-(3-Methoxyphenethyl)benzamide (3e)**[18]

Colorless oil; yield: 121.2 mg (95%).

IR (neat): 3314, 2921, 2361, 1639, 1541, 1489, 1319, 784, 695 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.0 Hz, 2 H), 7.43 (t, *J* = 8.0 Hz, 1 H), 7.34 (t, *J* = 8.0 Hz, 2 H), 7.19 (t, *J* = 8.0 Hz, 1 H), 6.77 (t, *J* = 8.0 Hz, 2 H), 6.69 (s, 1 H), 3.74 (s, 3 H), 3.66 (dd, J_1 = 8.0 Hz, J_2 = 12.0 Hz, 2 H), 2.87 (t, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 160.0, 140.6, 134.7, 131.5, 129.8, 128.6, 127.0, 121.2, 114.5, 112.1, 55.3, 41.2, 35.8.

MS (ESI): *m*/*z* = 256.1 [M + H]$^+$.

***N*-(4-Chlorophenethyl)benzamide (3f)**[18]

White solid; yield: 110.4 mg (85%); mp 148–149 °C.

IR (neat): 3346, 2921, 2359, 1640, 1534, 1487, 1311, 1091, 714, 693 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.0 Hz, 2 H), 7.49 (t, *J* = 8.0 Hz, 1 H), 7.40 (t, *J* = 8.0 Hz, 2 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 6.32 (s, 1 H), 3.67 (dd, J_1 = 6.7 Hz, J_2 = 13.2 Hz, 2 H), 2.90 (t, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.0, 138.9, 138.2, 130.1, 128.9, 128.3, 128.0, 127.7, 44.1.

MS (ESI): *m*/*z* = 260.1 [M + H]$^+$.

***N*-(3-Methoxypropyl)benzamide (3g)**[19]

White solid; yield: 102.9 mg (86%); mp 96–97 °C.

IR (neat): 3326, 2374, 1639, 1541, 1458, 1307, 1311, 1192, 805, 692 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.0 Hz, 2 H), 7.44 (t, *J* = 8.0 Hz, 1 H), 7.36 (t, *J* = 8.0 Hz, 2 H), 7.10 (s, 4 H), 6.48 (s, 1 H), 3.65 (dd, J_1 = 8.0 Hz, J_2 = 12.0 Hz, 2 H), 2.86 (t, *J* = 8.0 Hz, 2 H), 2.31 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 136.1, 135.9, 134.8, 131.3, 129.4, 128.7, 128.5, 126.9, 41.3, 35.3, 21.0.

MS (ESI): *m*/*z* = 240.1 [M + H]$^+$.

***N*-(2-Hydroxy-2-phenylethyl)benzamide (3h)**[18]

White solid; yield: 100.1 mg (83%); mp 164–166 °C.

IR (neat): 3301, 2929, 2361, 1617, 1541, 1316, 1063, 705, 693 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.50 (s, 1 H), 7.83 (d, *J* = 8.0 Hz, 2 H), 7.51- 7.25 (m, 8 H), 5.52 (d, *J* = 4.0 Hz, 1 H), 4.81–4.77 (m, 1 H), 3.52–3.46 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.9, 144.3, 135.0, 131.6, 128.7, 128.5, 127.7, 127.5, 126.5, 71.7, 48.2.

MS (ESI): *m*/*z* = 242.1 [M + H]$^+$.

***N*-(Cyclopropylmethyl)benzamide (3i)**[18]

White solid; yield: 78.9 mg (90%); mp 78–80 °C.

IR (neat): 3309, 3097, 1632, 1543, 1493, 1296, 695 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 8.0 Hz, 2 H), 7.47 (t, *J* = 8.0 Hz, 1 H), 7.39 (t, *J* = 8.0 Hz, 2 H), 6.68 (s, 1 H), 3.29 (dd, J_1 = 4.0 Hz, J_2 = 8.0 Hz, 2 H), 1.08–1.02 (m, 1 H), 0.52 (dd, J_1 = 4.7 Hz, J_2 = 10.6 Hz, 2 H), 0.25 (dd, J_1 = 4.7 Hz, J_2 = 10.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 134.8, 131.3, 128.5, 127.0, 44.9, 10.8, 3.5.

MS (ESI): *m*/*z* = 198.1 $[M + Na]^+$.

***N*-Butylbenzamide (3j)**[8g]

Yellow oil; yield: 70.9 mg (80%).

IR (neat): 3317, 2962, 1637, 1541, 1490, 1308, 694 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.79–7.76 (m, 2 H), 7.47–7.36 (m, 3 H), 6.66 (s, 1 H), 3.41 (dd, J_1 = 4.0 Hz, J_2 = 12.0 Hz, 2 H), 1.61–1.54 (m, 2 H), 1.42–1.33 (m, 2 H), 0.92 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7, 135.0, 131.2, 128.5, 127.0, 39.9, 31.8, 20.2, 13.8.

MS (ESI): *m*/*z* = 200.1 $[M + Na]^+$.

***N*-(3-Methoxypropyl)benzamide (3k)**[18]

Colorless oil; yield: 85.0 mg (88%).

IR (neat): 3338, 2925, 1636, 1541, 1381, 1307, 1120, 915, 695 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.78–7.76 (m, 2 H), 7.48–7.37 (m, 3 H), 7.23 (s, 1 H), 3.56–3.50 (m, 4 H), 3.35 (s, 3 H), 1.90–1.84 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 134.8, 131.2, 128.4, 126.9, 72.0, 58.8, 38.6, 29.0.

MS (ESI): *m*/*z* = 194.1 $[M + H]^+$.

***N*-(1-Benzylpiperidin-4-yl)benzamide (3l)**[20]

White solid; yield: 128.7 mg (87%); mp 171.5–172.5 °C.

IR (neat): 3309, 2913, 2786, 2366, 1634, 1541, 1340, 739, 695 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 4.0 Hz, 2 H), 7.47–7.27 (m, 8 H), 6.23 (d, *J* = 8.0 Hz, 1 H), 4.01 (s, 1 H), 3.52 (s, 2 H), 2.86 (d, *J* = 12.0 Hz, 2 H), 2.17 (t, *J* = 12.0 Hz, 2 H), 2.01 (d, *J* = 12.0 Hz, 2 H), 1.60 (dd, J_1 = 8.0 Hz, J_2 = 20.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.9, 138.3, 134.8, 131.3, 129.1, 128.5, 128.2, 127.1, 127.0, 63.0, 52.3, 47.1, 32.2.

MS (ESI): *m*/*z* = 295.1 $[M + H]^+$.

***N*′-Phenylbenzohydrazide (3m)**[21]

Orange solid; yield: 86.0 mg (81%); mp 165–167 °C.

IR (neat): 3326, 2921, 2357, 1643, 1496, 1303, 691 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.07 (s, 1 H), 7.83 (d, *J* = 8.0 Hz, 2 H), 7.55 (t, *J* = 8.0 Hz, 1 H), 7.46 (t, *J* = 8.0 Hz, 2 H), 7.24 (t, *J* = 8.0 Hz, 2 H), 6.91 (d, *J* = 8.0 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.9, 150.1, 133.5, 132.1, 129.3, 129.0, 127.8, 119.2, 112.8.

MS (ESI): *m*/*z* = 213.1 $[M + H]^+$.

***N*′-(*p*-Tolyl)benzohydrazide (3n)**[21]

White solid; yield: 84.8 mg (75%); mp 134–135 °C.

IR (neat): 3242, 1647, 1511, 1483, 1327, 1245, 1070, 914, 820, 707, 693 cm^{-1}.

^1H-NMR (400 MHz, DMSO-d_6): δ = 10.34 (d, *J* = 2.8 Hz, 1 H), 7.92 (d, *J* = 3.2 Hz, 2 H), 7.73 (d, *J* = 3.2 Hz, 1 H), 7.59–7.55 (m, 1 H), 7.52–7.48 (m, 2 H), 6.97 (d, *J* = 8.4 Hz, 2 H), 6.72 (d, *J* = 8.4 Hz, 2 H), 2.16 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.2, 147.2, 133.1, 131.5, 129.1, 128.4, 127.2, 112.6.

MS (ESI): *m*/*z* = 227.1 $[M + H]^+$.

***N*-Isopropylbenzohydrazide (3o)**[22]

Yellow solid; yield: 53.5 mg (60%); mp 57–58 °C.

IR (neat): 3431, 3300, 2970, 2929, 1638, 1541, 1341, 1071, 900, 694 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.77–7.75 (m, 1 H), 7.51–7.39 (m, 4 H), 4.0 (d, *J* = 3.2 Hz, 2 H), 3.25–3.19 (m, 1 H), 1.18 (d, *J* = 8.0 Hz, 3 H), 1.10 (d, *J* = 8.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.5, 133.1, 131.8, 129.8, 128.7, 128.6, 127.0, 126.7, 51.5, 20.9.

MS (ESI): *m*/*z* = 179.1 $[M + H]^+$.

***N*-Benzyl-*N*-methylbenzamide (3p)**[17]

Colorless oil; yield: 95.7 mg (85%).

IR (neat): 3248, 1633, 1482, 1399, 1069, 719, 697 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.17 (m, 10 H), 4.76 (s, 1 H), 4.51 (s, 1 H), 2.95 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 170.8, 136.6, 136.3, 135.8, 129.0, 128.2, 127.8, 127.6, 126.9, 126.4, 54.5, 50.2, 36.3, 32.5.

MS (ESI): *m*/*z* = 248.1 $[M + Na]^+$.

(1*H*-Benzo[*d*]imidazol-1-yl)phenylmethanone (3q)[23]

White solid; yield: 83.3 mg (75%); mp 71–72 °C.

IR (neat): 3301, 2917, 2360, 1647, 1539, 1459, 1358, 749, 711 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.23–8.19 (m, 2 H), 7.86–7.80 (m, 3 H), 7.70 (t, *J* = 8.0 Hz, 1 H), 7.60 (t, *J* = 8.0 Hz, 2 H), 7.48–7.42 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.3, 144.2, 143.2, 133.4, 133.0, 132.3, 129.7, 129.2, 125.9, 125.5, 120.7, 115.6.

MS (ESI): *m*/*z* = 223.1 $[M + H]^+$.

Phenyl(pyrrolidin-1-yl)methanone (3r)[8g]

Colorless oil; yield: 80.6 mg (92%).

IR (neat): 2974, 1623, 1575, 1419, 792, 718, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.39 (m, 5 H), 3.64 (t, *J* = 8.0 Hz, 2 H), 3.42 (t, *J* = 8.0 Hz, 2 H), 1.99–1.92 (m, 2 H), 1.89–1.83 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7, 137.2, 129.7, 128.2, 127.0, 49.5, 46.1, 26.3, 24.4.

MS (ESI): *m*/*z* = 198.1 $[M + Na]^+$.

Methyl Benzoyl-L-phenylalaninate (3s)[18]

Colorless oil; yield: 92.1 mg (65%).

IR (neat): 3308, 2952, 1745, 1647, 1624, 1573, 1478, 1437, 1358, 1217, 1092, 1030, 914, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 8.0 Hz, 2 H), 7.49 (t, *J* = 8.0 Hz, 1 H), 7.40 (t, *J* = 8.0 Hz, 2 H), 7.30–7.24 (m, 3 H), 7.14 (d, *J* = 4.0 Hz, 2 H), 6.68 (s, 1 H), 5.11–5.06 (m, 1 H), 3.75 (s, 3 H), 3.29 (dd, J_1 = 4.0 Hz, J_2 = 12.0 Hz, 1 H), 3.22 (dd, J_1 = 4.0 Hz, J_2 = 16.0 Hz, 1 H),

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1, 167.0, 136.0, 134.0, 131.8, 129.4, 128.7, 127.2, 127.1, 53.7, 52.4, 38.0.

MS (ESI): *m*/*z* = 284.1 $[M + H]^+$.

***N*-Benzyl-4-methylbenzamide (3t)**[17]

White solid; yield: 103.6 mg (92%); mp 132–133 °C.

IR (neat): 3309, 2917, 2366, 1639, 1558, 1507, 1319, 721, 694 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (s, 2 H), 7.37–7.24 (m, 7 H), 6.53 (s, 1 H), 4.65 (s, 2 H), 2.42 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7, 143.3, 134.7, 131.4, 128.7, 128.5, 127.4, 127.1, 126.3, 49.3, 21.8.

MS (ESI): *m*/*z* = 226.1 $[M + H]^+$.

***N*-Benzyl-4-methoxybenzamide (3u)**[17]

White solid; yield: 114.6 mg (95%); mp 137–139 °C.

IR (neat): 3252, 2361, 1631, 1541, 1507, 1328, 1248, 1025, 842, 723 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.0 Hz, 2 H), 7.33 (d, *J* = 8.0 Hz, 4 H), 7.32–7.27 (m, 1 H), 6.89 (d, *J* = 8.0 Hz, 2 H), 6.51 (s, 1 H), 4.62 (d, *J* = 4.0 Hz, 2 H), 3.82 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.1, 162.4, 138.6, 128.9, 128.8, 128.0, 127.6, 126.8, 113.9, 55.5, 44.2.

MS (ESI): *m*/*z* = 242.1 $[M + H]^+$.

***N*-Benzyl-4-chlorobenzamide (3v)**[17]

White solid; yield: 98.3 mg (80%); mp 161.5–162.5 °C.

IR (neat): 3314, 2921, 2366, 1637, 1541, 1487, 1328, 1082, 845, 712 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 8.0 Hz, 2 H), 7.40 (d, *J* = 8.0 Hz, 2 H), 7.37–7.31 (m, 5 H), 6.56 (s, 1 H), 4.61 (d, *J* = 4.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5, 138.1, 137.9, 132.9, 129.0, 128.6, 128.0, 127.8, 44.4.

MS (ESI): *m*/*z* = 268.1 $[M + Na]^+$.

***N*-Benzyl-2-fluorobenzamide (3w)**[24]

White solid; yield: 100.9 mg (88%); mp 67–69 °C.

IR (neat): 3301, 2921, 1647, 1528, 1453, 1300, 1217, 755, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (t, *J* = 8.0 Hz, 1 H), 7.47–7.46 (m, 1 H), 7.35–7.25 (m, 6 H), 7.13 (dd, J_1 = 8.0 Hz, J_2 = 12.0 Hz, 2 H), 4.67 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.4, 160.7 (d, *J* = 246.0 Hz), 138.2, 133.4 (d, *J* = 9.0 Hz), 132.2, 128.8, 127.8, 127.6, 124.9 (d, *J* = 3.0 Hz), 121.2 (d, *J* = 11.0 Hz), 116.1 (d, *J* = 25.0 Hz), 44.2.

MS (ESI): *m*/*z* = 230.1 $[M + H]^+$.

***N*-Benzyl-2-nitrobenzamide (3x)**[25]

Brown solid; yield: 98.7 mg (77%); mp 121–122 °C.

IR (neat): 3280, 2925, 2366, 1653, 1540, 1489, 1345, 871, 726, 693 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.0 Hz, 1 H), 7.64 (d, *J* = 8.0 Hz, 1 H), 7.57–7.49 (m, 2 H), 7.37–7.33 (m, 5 H), 6.28 (s, 1 H), 4.61 (d, *J* = 4.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5, 146.4, 137.6, 133.7, 132.8, 130.5, 128.8, 128.0, 127.7, 124.5, 44.1.

MS (ESI): *m*/*z* = 257.1 $[M + H]^+$.

***N*-Benzyl-2-oxo-2-phenylacetamide (3y)**[26]

White solid; yield: 107.7 mg (90%); mp 96–97 °C.

IR (neat): 3256, 2925, 2353, 1646, 1558, 1454, 1226, 726, 688 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 8.0 Hz, 2 H), 7.53–7.50 (m, 1 H), 7.45–7.41 (m, 2 H), 7.37–7.31 (m, 5 H), 6.65 (s, 1 H), 4.65 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.7, 161.8, 137.3, 134.5, 133.5, 131.3, 128.9, 128.6, 128.0, 127.9, 43.6.

MS (ESI): *m*/*z* = 262.1 $[M + Na]^+$.

***N*-Benzyl-3-phenylpropanamide (3z)**[8a]

White solid; yield: 106.5 mg (89%); mp 87–89 °C.

IR (neat): 3293, 2921, 2366, 1638, 1542, 1458, 1311, 740, 694 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.25 (m, 5 H), 7.22–7.18 (m, 3 H), 7.13 (d, *J* = 8.0 Hz, 2 H), 5.73 (s, 1 H), 4.38 (d, *J* = 8.0 Hz, 2 H), 2.98 (t, *J* = 8.0 Hz, 2 H), 2.50 (t, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1, 140.8, 138.3, 128.6, 128.6, 128.4, 127.7, 127.4, 126.2, 43.5, 38.4, 31.7.

MS (ESI): *m*/*z* = 240.1 $[M + H]^+$.

***N*-Benzylthiophene-2-carboxamide (3aa)**[17]

White solid; yield: 98.9 mg (91%); mp 102.5–103.5 °C.

IR (neat): 3305, 2913, 2359, 1634, 1541, 1340, 1105, 743, 699 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (dd, J_1 = 4.0 Hz, J_2 = 20.0 Hz, 2 H), 7.34–7.26 (m, 5 H), 7.05 (t, *J* = 4.0 Hz, 1 H), 6.43 (s, 1 H), 4.60 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.6, 139.0, 135.0, 131.5, 131.2, 131.0, 128.6, 127.5, 41.0, 34.8.

MS (ESI): *m*/*z* = 218.1 $[M + H]^+$.

***N*-Benzylcyclohexanecarboxamide (3ab)**[27]

White solid; yield: 88.0 mg (81%); mp 113–114 °C.

IR (neat): 3424, 2924, 2859, 1635, 1459, 1041, 494 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.24 (m, 5 H), 5.90 (s, 1 H), 4.41 (d, *J* = 8.0 Hz, 2 H), 2.15–2.07 (m, 1 H), 1.89–1.86 (m, 2 H), 1.80–1.76 (m, 2 H), 1.66–1.63 (m, 1 H), 1.51–1.41 (m, 2 H), 1.31–1.16 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.1, 138.7, 128.8, 127.8, 127.5, 45.6, 43.4, 29.8, 25.8.

MS (ESI): *m*/*z* = 218.2 $[M + H]^+$.

4-Chloro-*N*-(2-morpholinoethyl)benzamide (13)[11]

White solid; yield: 114.2 mg (85%); mp 136–137 °C.

IR (neat): 3285, 2925, 2357, 1635, 1558, 1458, 1311, 1117, 1082, 1017, 866, 731, 682 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.0 Hz, 2 H), 7.37 (d, *J* = 8.0 Hz, 2 H), 6.89 (s, 1 H), 3.70 (t, *J* = 4.0 Hz, 4 H), 3.51 (dd, J_1 = 4.0 Hz, J_2 = 12.0 Hz, 2 H), 2.57 (t, *J* = 8.0 Hz, 2 H), 2.48 (s, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4, 137.7, 133.0, 128.9, 128.5, 77.5, 77.2, 76.8, 67.0, 57.0, 53.4, 36.2.

MS (ESI): *m*/*z* = 291.1 $[M + Na]^+$.

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Supporting Information

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