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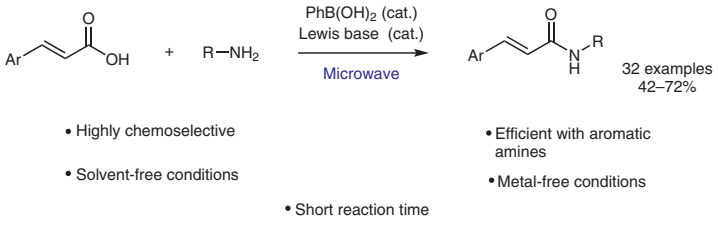
An Efficient Solvent-Free Microwave-Assisted Synthesis of Cinnamamides by Amidation Reaction Using Phenylboronic Acid/Lewis Base Co-catalytic System

Khadidja Khaldoun[a]
Abdelmounaim Safer[a]
Salima Saidi-Besbes[a]
Bertrand Carboni[b]
Rémy Le Guével[c]
François Carreaux*[b]

[a] Laboratoire de synthèse organique appliqué, Université Oran1, Bp 1524 El M'naouer 31000 Oran, Algeria
[b] Univ Rennes, CNRS, ISCR, UMR 6226, 263 avenue du Général Leclerc, Campus de Beaulieu, 35000 Rennes, France
francois.carreaux@univ-rennes1.fr
[c] Univ Rennes, ImPACell Platform, SFR Biosit, 2 avenue du Prof. Léon Bernard, 35043 Rennes, France



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Abstract A microwave-assisted dehydrative amide condensation reaction is reported as an efficient access to cinnamamide derivatives under solvent-free conditions. This protocol between conjugated carboxylic acids and amines is based on the use of a co-catalytic system, including the presence of the commercially available phenylboronic acid and 4-(*N*,*N*-dimethylamino)pyridine *N*-oxide (DMAPO), with a complete chemoselectivity in favor of the corresponding α,β-unsaturated amides. The implementation of the reaction needs no special precaution, and less reactive amines, such as substituted anilines, are also efficient under these conditions. A series of novel conjugated amides have been evaluated for their cytotoxic activities against several human cancer cell lines.

Key words cinnamamide derivatives, direct amide formation, boronic acid, microwave heating, catalytic system

Cinnamamide derivatives constitute a class of compounds with an important therapeutic potential. Some of them are natural products which can be found, more specifically, in plants of Rutaceae such as *Zanthoxylum rubescens*[1] as well as in several *Piper* species (*Piperaceae*)[2] (Figure 1). In the field of anticancer therapy, piplartine represents a very interesting compound as shown by in vitro and in vivo preclinical researches.[3] This class of compounds also exhibits other biological activities, such as antimicrobial,[4] antioxidant,[5] antiviral,[6] antidepressant,[7] and anti-inflammatory effects.[8] Moreover, the introduction of a cinnamamide scaffold in organic compounds can improve or modify their pharmacological activities, for instance, in the case of central and peripheral nervous system disorders.[9,10]

The α,β-unsaturated amide moiety can be prepared by condensation from cinnamic acids and amines using traditional, stoichiometric approaches via the formation of a transient-activated carboxylic acid.[11] Coupling reagents are generally employed in an efficient manner but the process generates one equivalent of waste that renders the purification of the expected amide in a pure form much more difficult. Considering the relevance of amide functionality in the drug development process,[12] the implementation of catalytic systems to perform the dehydrative condensation reaction starting from carboxylic acids and amines has become a very challenging goal.[13] Several metal-based catalysts have been developed to this end.[14] Among metal-free methods, the use of boronic acids as catalysts is particularly suitable for the preparation of compounds of biological interest due to their easy removal from the reaction mixture and their apparent non-toxicity.[15] Moreover, they are stable to air and moisture making them easier to handle. Different effective boron-based catalysts have been investigated successfully since the pioneering works of Yamamoto's group in this field.[16]

Generally, the use of commercially available arylboronic acids with electron-withdrawing substituents as catalysts requires elevated temperatures in an organic solvent and extremely long reaction times for a good conversion into

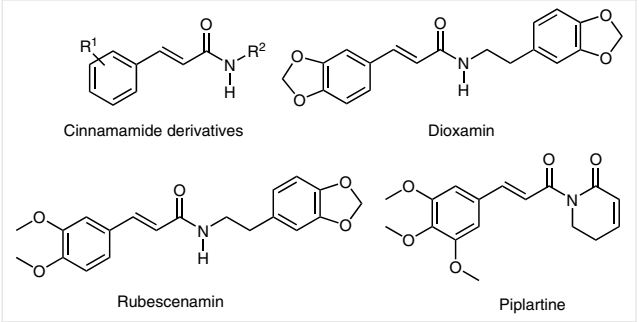

Figure 1 Some examples of natural cinnamamides

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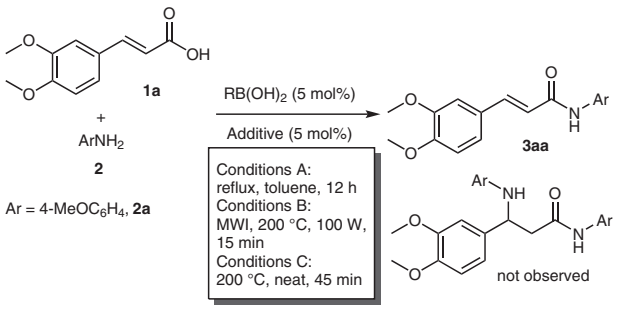
the desired amide. Nevertheless the direct amidation reaction can take place in more mild conditions using specially designed catalysts obtained by several more or less tedious synthetic transformations.[17] Immobilized boronic acids as reusable catalysts have also been prepared.[18] In view of the existing literature, it is interesting to note that aliphatic amines are generally employed in most catalytic processes developed with arylboronic acids. In contrast, arylamines are scarcely used as model substrates to assess the generality of methods probably due to their weaker nucleophilicity. On the other hand, to the best of our knowledge, only few examples of cinnamamide derivatives have been prepared using these boron-catalytic systems.[19] That may be explained by the low reactivity of conjugated acids, but also by the presence of two electrophilic sites, which can generate the formation of a side-product resulting from an aza-Michael addition. Indeed, this issue of chemoselectivity is a major drawback with this class of substrates that was previously recognized in the works of Ishihara et al.[19b] Using a cooperative catalytic process in the presence of arylboronic acids under azeotropic reflux conditions during several hours, the reaction between cinnamic acid derivatives and amines led to the formation of the corresponding conjugated amides in the presence of Michael adducts with a selectivity ranging from 82 to 99%.

Considering our interest to develop efficient environmentally friendly methodologies giving access to compound libraries of biological interest,[20] we envisaged to investigate the utility of the microwave technology as a non-conventional energy source, coupled with the use of inexpensive catalytic boronic acids, for a new practical and general preparation of cinnamamide derivatives by direct amidation.[21] Indeed, to the best of our knowledge, this is the first study for this kind of reaction combining these two parameters. In this paper, we report our outcomes on this microwave-assisted approach for this kind of reaction using boronic acids. The dehydrative condensation between cinnamic acid derivatives and amines using a catalytic amount of phenylboronic acid and 4-(dimethylamino)pyridine *N*-oxide (DMAPO) can be performed efficiently under microwave dielectric heating with an excellent selectivity in moderate-to-good yields. The reaction takes place in a short time (15 min) without solvent and the conditions are also effective with arylamines. The new conjugated amides obtained were evaluated for their in vitro possible antitumor activity against several human cancer cell lines.

As amine of choice to optimize the protocol, 4-methoxyaniline (**2a**) was selected to react with (*E*)-3-(3,4-dimethoxyphenyl)acrylic acid (**1a**) in an equimolar ratio (Table 1). First of all, the reaction was tried using boric acid as catalyst (5 mol%) under different solvent-free microwave conditions taking into account that no formation of the desired amide was observed in toluene at reflux for 12 hours (Table 1, entry 1). The best conversion of **3aa** was obtained at 200 °C with 100 W microwave power for 15 minutes (entry 2). A longer irradiation time had no significant impact on the conversion (entry 3). Note that in the absence of boric acid, a very low conversion rate was obtained (entry 4). Under the same conditions, with the replacement of boric acid by phenylboronic acid as stronger Lewis acid, the conversion rate reached 45% (entry 5). The additional use of a catalytic amount of nucleophilic additives such as *N*,*N*-diisopropylethylamine (*i*-Pr_2EtN) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) was not effective (entries 6 and 7). In contrast, the addition of DMAPO as co-catalyst was crucial for the formation of the conjugated amide in a good conversion (entry 8). Under these new conditions, the chemoselectivity observed was very high (>95%) since no product resulting from a Michael reaction was detected by ^{1}H NMR analysis of the crude mixture. The reaction was very clean allowing the purification of compound **3aa** in a simple manner, by solvent extraction processes in order to eliminate the unreacted starting materials, thus avoiding a column chromatography. The order of addition of catalysts had no effect on the yield (65%). The significance of two catalysts for an efficient amidation reaction was highlighted when only DMAPO was used (entry 9). It is important to mention that the implementation of this cooperative cata-

Table 1 Optimization of Protocol[a]

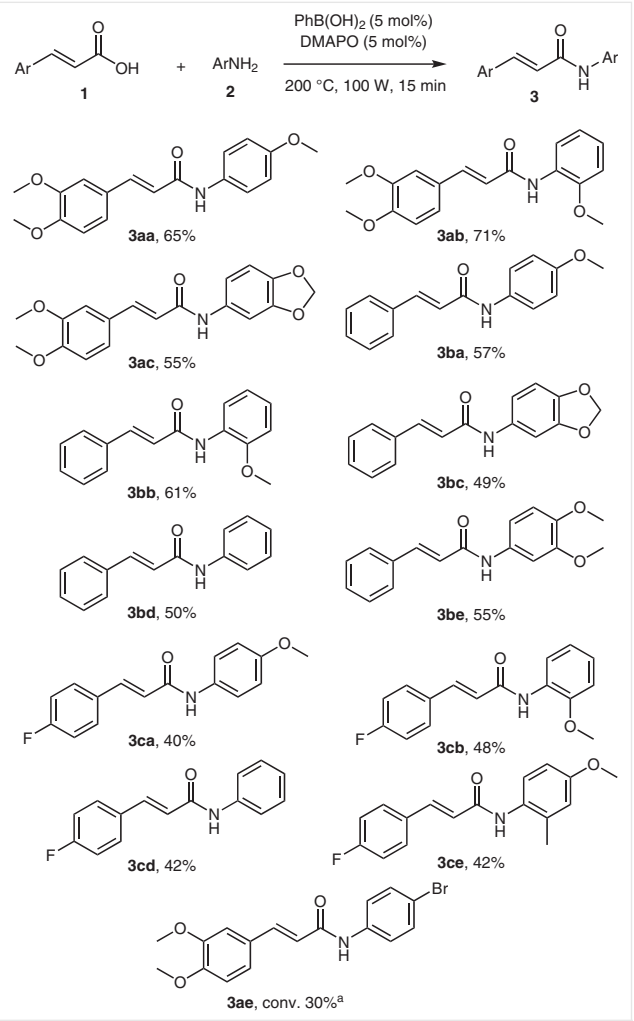


Entry	R	Additive	Conditions	Conv (%)[b]	Yield (%)[c]
1	OH	–	A[d]	–	–
2	OH	–	B	30	–
3	OH	–	B[e]	35	–
4	–	–	B	8	–
5	Ph	–	B	45	–
6	Ph	*i*-Pr_2NEt	B	45	–
7	Ph	DMAP	B	48	–
8	Ph	DMAPO	B	80	65
9	–	DMAPO	B	15	–
10	Ph	DMAPO	C	17	–

[a] Reaction scale: **1a** (0.5 mmol), **2a** (0.5 mmol).
[b] Conversion based on **1a**.
[c] Isolated yield of pure product.
[d] Toluene (0.1 M).
[e] Reaction time: 30 min instead of 15 min.

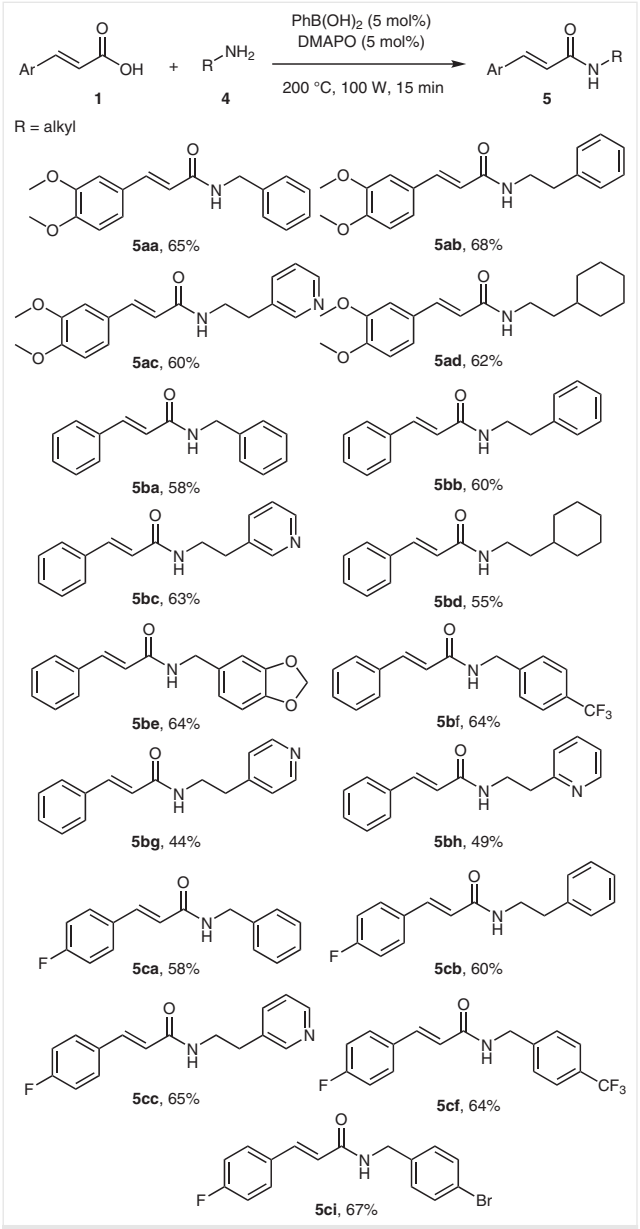
lytic system under conventional thermal conditions (200 °C, neat, 45 min) led to the formation of **3aa** in a low conversion rate showing the utility of microwave dielectric heating under solventless conditions (entry 10).

With these optimized conditions in hands, we explored the scope of this method employing a series of arylamines **2** and unsaturated carboxylic acids **1** (Scheme 1).



Scheme 1 Substrate scope of the reaction using aryl amines. *Reagents and conditions*: **1** (0.5 mmol), **2** (0.5 mmol), $PhB(OH)_2$ (5 mol%), DMAPO (5 mol%), 200 °C, 100 W, 15 min. Isolated yields are shown.
[a] 200 °C, 200 W, 30 min.

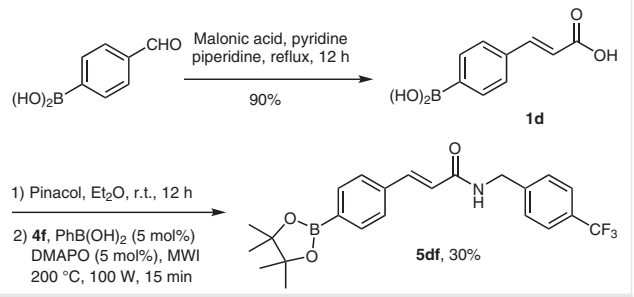
All compounds **3** were obtained in a highly chemoselective manner with moderate-to-good isolated yields. Some of them can be regarded as new analogues of very potent vanilloid receptor TRPV1 antagonists, such as AMG-9810[22] and SB-366791.[23] For the same arylamine, the better yields were obtained from the more electron-rich conjugated carboxylic acid **1a** when compared with **1b** and **1c** (see for example, **3aa**, **3ba**, and **3ca**). That could be explained by a potentially easier formation of the mixed anhydride intermediate generated from the carboxylic acid and phenylboronic acid before reaction with the nucleophile.[24] The steric hindrance had no major impact on the yield (**3aa** vs **3ab**). Electron-deficient arylamines have also been tested with less success. In effect, the conjugated amide **3ae** coming from the reaction between **1a** and 4-bromoaniline can be obtained with a low conversion rate by increasing the microwave power and irradiation time. Using alkylamines **4** as more reactive nucleophiles, no significant effect on the isolated yield was observed regardless of the electron density of conjugated carboxylic acid engaged (Scheme 2). The high



Scheme 2 Substrate scope of the reaction using alkyl amines. *Reagents and conditions*: **1** (0.5 mmol), **4** (0.5 mmol), $PhB(OH)_2$ (5 mol%), DMAPO (5 mol%), 200 °C, 100 W, 15 min. Isolated yields are shown.

chemoselectivity in favor of the conjugated amide formation was maintained. All compounds **5** were generally obtained in a pure form without having to perform a chromatographic purification, except for **5ad**, **5bc**, **5bg**, and **5bh**.[25] Our efforts to introduce secondary amines such as *N*-allylbenzylamine in a satisfactory way failed.

It should be emphasized that the natural product **5bb**[26] was obtained in 15% yield under conventional thermal conditions using the same catalyst.[19b] Subsequently in order to assess the functional group tolerance of this process, we decided to prepare a cinnamamide derivative possessing a boryl substituent, which could be a useful synthetic building block (Scheme 3). At first, we speculated that the *trans*-4-(2-carboxyethenyl)benzeneboronic acid (**1d**), prepared from (4-formylphenyl)boronic acid, could serve both as starting material and catalyst. Unfortunately, treatment of **1d** with the (4-trifluoromethyl)phenyl)methanamine (**4f**) in the presence of DMAPO under microwave irradiation (200 °C, 100 W, 15 min) afforded a complex mixture of compounds. The addition of catalytic amount of phenylboronic acid in the reaction medium had no effect. Finally, the desired new organoboron compound was obtained under the previously optimized conditions, after esterification of boronic acid group with pinacol. The yield of **5df** was moderate (30% over two steps), but can be considered as acceptable due to its difficult purification on silica gel.



Scheme 3 Synthesis of a borylated derivative **5df**

Given that some cinnamamide derivatives were new, we took the opportunity to evaluate them for their in vitro potential cytotoxicity against selected human cancer lines such as hepatocellular carcinoma (Huh7), colorectal adenocarcinoma (Caco 2), breast (MDA and MCF7), colorectal carcinoma (HCT 116), prostate (PC3), and lung (NCI) (Table 2).

The percentage of cell survival was measured at single dose of 25 µM. The IC_{50} values were determined only for the compounds exhibiting a survival percentage below 55% in triplicate, using roscovitine as reference (Table 2). Only compound **5ad** exhibited a moderate antitumor activity against MCF7 and HCT 116 cell lines (IC_{50} = 22 µM and 27 µM, respectively). However, a certain selectivity must be underlined with respect to other cell lines tested, which could justify further structure–activity relationship studies.

Table 2 Antiproliferative Activity of Cinnamamides **3** and **5** on Seven Representative Tumor Cell Lines[a]

Compound	Huh7	Caco2	MDA	MCF7	HCT116	PC3	NCI
Roscovitine	71 (14)[b]	80 (18)[b]	68 (15)[b]	30 (9)[b]	30 (9)[b]	73 (10)[b]	74 (28)[b]
3aa	97	99	104	107	107	101	109
3ab	99	100	110	87	103	100	92
3be	89	87	110	68	114	99	87
3ca	87	94	107	63	90	94	91
3cb	71	92	108	65	98	100	93
3ce	86	89	113	62	95	97	88
5ad	94 (>25)[b]	90 (>25)[b]	97 (>25)[b]	54 (22)[b]	62 (27)[b]	81 (73)[b]	100 (>25)[b]
5bc	96	102	99	106	109	107	101
5bg	104	107	112	94	112	106	118
5ca	95	9 4	104	97	101	112	103
5cb	96	104	92	88	110	92	93
5cc	103	104	98	123	114	102	100
5cf	94	100	105	115	109	100	100
5ci	89	96	98	92	106	105	95

[a] Percentage of survival measured at 25 µM.
[b] IC_{50} values in parentheses are expressed in µM and are the average of three assays, standard error ± 0.5 µM.

In conclusion, the synthesis of a library of cinnamamide derivatives was reported based on a new catalytic direct amidation reaction under microwave conditions. Using a convenient solventless procedure, the combination of phenylboronic acid with DMAPO proved to be an efficient co-catalytic system for the highly chemoselective preparation of conjugated amides. This methodology is complementary with those described employing boronic acid catalysts since a large variety of less reactive amines such as aniline derivatives also led to the formation of the desired amides. Unfortunately, electron-deficient arylamines continue to be not suitable substrates under these conditions. Besides that these new α,β-unsaturated amides could also be useful as building blocks in organic synthesis.[27] A moderate cytotoxic activity of some of them was unveiled.

All commercially available chemicals were used without further purification. NMR spectra were recorded at 300 or 400 MHz for ^{1}H and 75 or 101 MHz for ^{13}C. Chemical shifts for ^{1}H are expressed in parts per million downfield from TMS as an internal standard. Data are given in the following order: chemical shift, multiplicity (standard abbreviations), coupling constant *J* (Hz), and integration. Microwave reactions (S2 Wave platform SPS ScanMAT, Rennes) were carried out using an Anton Paar Monowave 300® microwave reactor (Anton Paar France) using 10 mL borosilicate glass vials equipped with snap-caps (at the end of the irradiation, cooling the reaction mixture was realized by compressed air). The microwave consists of a continuous focused microwave power output from 0 to 300 W. All the experiments were performed using stirring option. The target temperature is reached

with a ramp of 4 min and the chosen microwave power stay constant to hold the mixture at this temperature. The reaction temperature was monitored using calibrated infrared sensor and the reaction time includes the ramp period. All high-resolution mass spectra (HRMS) were recorded on a Bruker Micro-Tof-Q II or on a Waters Q-Tof 2 at the CRMPO (Centre Régional de Mesures de Physiques de l'Ouest, Rennes, France) using positive ion electronspray. Melting points were measured on a melting point apparatus Stuart SMP10. Purifications on a silica gel were carried out on an Acros silica gel 0.006–0.200 nm, 60 A. Analytical TLC was performed on Merck Silica gel 60 F_{254} plates. Cinnamic acid (**1b**) is commercially available [CAS Reg. No. 140-10-3].

Cinnamic Acid Derivatives 1; General Procedure

To a stirred solution of aldehyde (4.5 mmol) in pyridine (25 mL) was added malonic acid (10 mmol) and piperidine (4 mL). The resulting mixture was refluxed for 24 h. After cooling, the reaction mixture was neutralized with aq 1 M HCl. White crystals formed were filtered and washed with cold H_2O. If necessary, carboxylic acids **1** can be rather recrystallized from aq EtOH or purified by column chromatography on silica gel.

According to this procedure, the following known carboxylic acids were prepared: (*E*)-3-(3,4-Dimethoxyphenyl)acrylic acid (**1a**; 55%),[28], (*E*)-3-(4-fluorophenyl)acrylic acid (**1c**; 64%),[29] and (*E*)-3-(4-boronophenyl)acrylic acid (**1d**; 90%).[30] For the data of these compounds, see Supporting Information.

Cinnamamide Derivatives 3 and 5; General Procedure

A mixture of carboxylic acid **1** (0.5 mmol), amine **2** or **4** (0.5 mmol), phenylboronic acid (5 mol%), and DMAPO (5 mol%) was placed in a cylindrical quartz reactor (⌀ = 1.1 cm). The reactor was then introduced into an Anton Paar Monowave 300®. The stirred mixture was heated at 200 °C (P = 100 W) for 15 min. After microwave dielectric heating, the crude reaction mixture was allowed to cool down to r.t. and partitioned between CH_2Cl_2 (5 mL) and sat. aq $NaHCO_3$ (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with aq 1 N HCl (2 CH_2Cl_2 5 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum. The crude product was purified using cold diisopropyl ether as a trituration solvent or by silica gel chromatography.

(*E*)-3-(3,4-Dimethoxyphenyl)-*N*-(4-methoxyphenyl)acrylamide (3aa)

Prepared from (*E*)-3-(3,4-dimethoxyphenyl)acrylic acid (**1a**) and 4-methoxyaniline (**2a**). Purified by trituration using diisopropyl ether as solvent. After filtration, the product **3aa** was isolated as a white solid; yield: 101 mg (65%); mp 109–110 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 15.5 Hz, 1 H), 7.58–7.49 (m, 2 H), 7.35–7.25 (m, 1 H), 7.22–7.05 (m, 2 H), 6.96–6.82 (m, 3 H), 6.44 (d, *J* = 15.5 Hz, 1 H), 3.93 (s, 6 H), 3.82 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.3, 156.4, 150.7, 149.1, 141.6, 131.4, 127.7, 122.0, 121.7, 119.0, 114.2, 111.1, 109.9, 55.9, 55.8, 55.4.

HRMS (EI): *m*/*z* calcd for $C_{18}H_{19}NO_4Na$ [M + Na]$^+$: 336.1206; found: 336.1207.

(*E*)-3-(3,4-Dimethoxyphenyl)-*N*-(2-methoxyphenyl)acrylamide (3ab)

Prepared from **1a** and 2-methoxyaniline (**2b**). Purified by column chromatography using cyclohexane/EtOAc (9:1) as eluent. The product **3ab** was isolated as a grey solid; yield: 111 mg (71%); mp 104–105 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 7.5 Hz, 1 H), 7.97–7.92 (br s, 1 H), 7.68 (d, *J* = 15.5 Hz, 1 H), 7.15 (dd, *J* = 8.3, 1.8 Hz, 1 H), 7.12–6.96 (m, 3 H), 6.93–6.85 (m, 2 H), 6.46 (d, *J* = 15.5 Hz, 1 H), 3.94 (s, 3 H), 3.92 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.9, 150.7, 149.1, 147.8, 127.9, 127.7, 123.6, 122.3, 121.2, 119.9, 119.1, 111.0, 109.9, 109.7, 55.9, 55.7.

HRMS (EI): *m*/*z* calcd for $C_{18}H_{19}NO_4Na$ [M + Na]$^+$: 336.1206; found: 338.1208.

(*E*)-*N*-(Benzo[*d*][1,3]dioxol-5-yl)-3-(3,4-dimethoxyphenyl)acrylamide (3ac)

Prepared from **1a** and benzo[*d*][1,3]dioxol-5-amine (**2c**). Purified by column chromatography using cyclohexane/EtOAc (3:1) as eluent. The product **3ac** was isolated as a light brown solid; yield: 90 mg (55%); mp 190–191 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 15.5 Hz, 1 H), 7.42–7.38 (br s, 1 H), 7.14 (dd, *J* = 8.2, 2.0 Hz, 1 H), 7.07 (d, *J* = 2.0 Hz, 1 H), 6.92–6.86 (m, 2 H), 6.78 (d, *J* = 8.2 Hz, 1 H), 6.41 (d, *J* = 15.5 Hz, 1 H), 5.98 (s, 2 H), 3.93 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.1, 150.9, 149.2, 147.9, 142.1, 132.4, 127.6, 122.2, 118.5, 112.9, 111.2, 111.1, 109.8, 108.1, 102.7, 101.3. 56.0, 55.9.

HRMS (EI): *m*/*z* calcd for $C_{18}H_{17}NO_5Na$ [M + Na]$^+$: 350.0999; found: 350.1001.

(*E*)-*N*-(4-Methoxyphenyl)cinnanamide (3ba)[21c]

Prepared from cinnamic acid (**1b**) and 4-methoxyaniline (**2a**). Purified by trituration using diisopropyl ether as solvent. After filtration, the product **3ba** was isolated as a grey solid; yield: 72 mg (57%); mp 152–153 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 15.5 Hz, 1 H), 7.57–7.33 (m, 8 H), 6.88 (d, *J* = 8.9 Hz, 2 H), 6.55 (d, *J* = 15.5 Hz, 1 H), 3.80 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.7, 156.5, 142.1, 134.7, 131.1, 129.9, 128.9, 127.9, 121.6, 120.8, 114.3, 55.5.

HRMS (EI): *m*/*z* calcd for $C_{16}H_{15}NO_2Na$ [M + Na]$^+$: 276.0995; found: 276.0996.

(*E*)-*N*-(2-Methoxyphenyl)cinnamamide (3bb)[31]

Prepared from **1b** and 2-methoxyaniline (**2b**). Purified by trituration using diisopropyl ether as solvent. After filtration, the product **3bb** was isolated as a white solid; yield: 77 mg (61%); mp 143–144 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.55 (d, *J* = 7.8 Hz, 1 H), 8.01–7.93 (br s, 1 H), 7.77 (d, *J* = 15.5 Hz, 1 H), 7.63–7.54 (m, 2 H), 7.45–7.39 (m, 3 H), 7.15–6.97 (m, 2 H), 6.93 (dd, *J* = 7.8, 1.7 Hz, 1 H), 6.62 (d, *J* = 15.5 Hz, 1 H), 3.95 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.7, 147.9, 142.0, 134.8, 129.9, 128.8, 128.0, 127.8, 123.8, 121.3, 121.2, 120.0, 109.9, 55.7.

HRMS (EI): *m*/*z* calcd for $C_{16}H_{15}NO_2Na$ [M + Na]$^+$: 276.0995; found: 276.0995.

(*E*)-*N*-(Benzo[*d*][1,3]dioxol-5-yl)cinnamamide (3bc)

Prepared from **1b** and benzo[*d*][1,3]dioxol-5-amine (**2c**). Purified by trituration using diisopropyl ether as solvent. After filtration, the product **3bc** was isolated as a brown solid; yield: 65 mg (49%); mp 206–207 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 15.5 Hz, 1 H), 7.56–7.48 (m, 2 H), 7.42–7.33 (m, 5 H), 6.95–6.84 (m, 1 H), 6.76 (d, *J* = 8.2 Hz, 1 H), 6.55 (d, *J* = 15.5 Hz, 1 H), 5.96 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.7, 147.8, 144.3, 142.1, 134.6, 132.3, 129.9, 128.8, 127.9, 120.7, 113.1, 108.1, 102.7, 101.3.

HRMS (EI): *m*/*z* calcd for $C_{16}H_{13}NO_3Na$ [M + Na]$^+$: 290.0788; found: 290.0787.

(*E*)-*N*-Phenylcinnamamide (3bd)[31]

Prepared from **1b** and aniline (**2d**). Purified by trituration using diisopropyl ether as solvent. After filtration, the product **3bd** was isolated as a beige solid; yield: 56 mg (50%); mp 150–152 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 15.5 Hz, 1 H), 7.71–7.62 (m, 2 H), 7.58–7.52 (m, 2 H), 7.48–7.32 (m, 6 H), 7.21–7.12 (m, 1 H), 6.58 (d, *J* = 15.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.2, 142.4, 138.1, 134.6, 129.9, 129.1, 128.8, 127.9, 124.5, 120.9, 120.1.

HRMS (EI): *m*/*z* calcd for $C_{15}H_{13}NONa$ [M + Na]$^+$: 246.0889; found: 246.0889.

(*E*)-*N*-(3,4-Dimethoxyphenyl)cinnamamide (3be)

Prepared from **1b** and 3,4-dimethoxyaniline (**2e**). Purified by column chromatography using cyclohexane/EtOAc (7:3) as eluent. The product **3be** was isolated as a brown solid; yield: 78 mg (55%); mp 153–154 °C; R_f = 0.3 (EtOAc/cyclohexane 3:7).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 15.5 Hz, 1 H), 7.61–7.50 (m, 3 H), 7.44–7.35 (m, 4 H), 7.00–6.92 (m, 1 H), 6.84 (d, *J* = 8.5 Hz, 1 H), 6.56 (d, *J* = 15.5 Hz, 1 H), 3.93 (s, 3 H), 3.90 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.2, 149.1, 145.9, 141.9, 134.7, 131.9, 129.9, 128.8, 127.9, 121.0, 112.1, 111.4, 105.0, 56.1, 55.9.

HRMS (EI): *m*/*z* calcd for $C_{17}H_{17}NO_3Na$ [M + Na]$^+$: 306.1101; found: 306.1102.

(*E*)-3-(4-Fluorophenyl)-*N*-(4-methoxyphenyl)acrylamide (3ca)

Prepared from (*E*)-3-(4-fluorophenyl)acrylic acid (**1c**) and 4-methoxyaniline (**2a**). Purified by trituration using diisopropyl ether as solvent. After filtration, the product **3ca** was isolated as a grey solid; yield: 54 mg (40%); mp 194–195 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 15.5 Hz, 1 H), 7.62–7.49 (m, 4 H), 7.27–7.23 (br s, 1 H), 7.15–7.05 (m, 2 H), 6.92 (d, *J* = 8.7 Hz, 2 H), 6.47 (d, *J* = 15.5 Hz, 1 H), 3.90 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.6, 163.5 (d, $J_{C,F}$ = 240.0 Hz), 156.9, 140.7, 131.1, 130.9 (d, $J_{C,F}$ = 3.7 Hz), 129.7 (d, $J_{C,F}$ = 8.2 Hz), 121.8, 120.7, 116.0 (d, $J_{C,F}$ = 21.8 Hz), 114.3, 55.5.

^{19}F NMR (101 MHz, $CDCl_3$): δ = –110.2.

HRMS (EI): *m*/*z* calcd for $C_{16}H_{14}FNO_2Na$ [M + Na]$^+$: 294.0901; found: 294.0903.

(*E*)-3-(4-Fluorophenyl)-*N*-(2-methoxyphenyl)acrylamide (3cb)

Prepared from **1c** and 2-methoxyaniline (**2b**). Purified by trituration using diisopropyl ether as solvent. After filtration, the product **3cb** was isolated as a brown solid; yield: 65 mg (48%); mp 151–152 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.51 (d, *J* = 7.8 Hz, 1 H), 7.99–7.89 (br s, 1 H), 7.71 (d, *J* = 15.5 Hz, 1 H), 7.60–7.50 (m, 2 H), 7.13–6.95 (m, 4 H), 6.90 (dd, *J* = 7.8, 1.6 Hz, 1 H), 6.52 (d, *J* = 15.5 Hz, 1 H), 3.92 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.5 (d, $J_{C,F}$ = 276.0 Hz), 163.4, 147.9, 140.8, 131.0 (d, $J_{C,F}$ = 2.3 Hz), 129.7 (d, $J_{C,F}$ = 6.0 Hz), 127.8, 123.8, 121.2, 121.1, 120.0, 115.9 (d, $J_{C,F}$ = 15.8 Hz), 109.9, 55.7.

^{19}F NMR (101 MHz, $CDCl_3$): δ = –110.4.

HRMS (EI): *m*/*z* calcd for $C_{16}H_{14}FNO_2Na$ [M + Na]$^+$: 294.0901; found: 294.0902.

(*E*)-3-(4-Fluorophenyl)-*N*-phenylacrylamide (3cd)[32]

Prepared from **1c** and aniline (**2d**). Purified by trituration using diisopropyl ether as solvent. After filtration, the product **3cd** was isolated as a white solid; yield: 51 mg (42%); mp 158–159 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 15.5 Hz, 1 H), 7.65–7.59 (m, 2 H), 7.58–7.52 (m, 2 H), 7.42–7.35 (m, 3 H), 7.25–7.05 (m, 3 H), 6.49 (d, *J* = 15.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.8, 163.7 (d, $J_{C,F}$ = 247.0 Hz), 141.2, 127.9, 130.8 (d, $J_{C,F}$ = 3.8 Hz), 129.8 (d, $J_{C,F}$ = 9.0 Hz), 129.1, 124.5, 120.5, 120.0, 116.0 (d, $J_{C,F}$ = 21.8 Hz).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{12}FNONa$ [M + Na]$^+$: 264.0796; found: 264.0796.

(*E*)-3-(4-Fluorophenyl)-*N*-(4-methoxy-2-methylphenyl)acrylamide (3ce)

Prepared from **1c** and 4-methoxy-2-methylaniline (**2e**). Purified by trituration using diisopropyl ether as solvent. After filtration, the product **3ce** was isolated as a purple solid; yield: 60 mg (42%); mp 210–211 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80–7.7.65 (m, 2 H), 7.60–7.45 (m, 1 H), 7.40–7.30 (m, 1 H), 7.20–6.95 (m, 3 H), 6.30–6.20 (m, 2 H), 6.51 (d, *J* = 15.5 Hz, 1 H), 3.79 (s, 3 H), 2.27 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.0, 163.6 (d, $J_{C,F}$ = 187.0 Hz), 157.1, 140.7, 132.1, 131.0, 129.7 (d, $J_{C,F}$ = 4.5 Hz), 128.6, 125.5, 120.5, 116.0 (d, $J_{C,F}$ = 16.5), 115.9, 111.6, 55.4, 18.2.

^{19}F NMR (101 MHz, $CDCl_3$): δ = –110.4.

HRMS (EI): *m*/*z* calcd for $C_{17}H_{16}FNO_2Na$ [M + Na]$^+$: 308.1057; found: 308.1056.

(*E*)-*N*-Benzyl-3-(3,4-dimethoxyphenyl)acrylamide (5aa)[33]

Prepared from (*E*)-3-(3,4-dimethoxyphenyl)acrylic acid (**1a**) and phenylmethanamine (**4a**). Purified by trituration using diisopropyl ether as solvent. After filtration, the product **5aa** was isolated as a white solid; yield: 96 mg (65%); mp 118–120 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.53 (t, *J* = 6.0 Hz, 1 H), 7.42 (d, *J* = 15.7 Hz, 1 H), 7.38–7.25 (m, 5 H), 7.18–7.10 (m, 2 H), 6.98 (d, *J* = 8.3 Hz, 1 H), 6.59 (d, *J* = 15.7 Hz, 1 H), 4.40 (d, *J* = 6.0 Hz, 2 H), 3.79 (s, 3 H), 3.78 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.7, 150.5, 149.3, 140.0, 139.5, 128.8, 128.1, 127.8, 127.3, 121.8, 120.2, 112.1, 110.4, 56.0, 55.8, 42.7.

HRMS (EI): *m*/*z* calcd for $C_{18}H_{19}NO_3Na$ [M + Na]$^+$: 320.1257; found: 320.1258.

(*E*)-3-(3,4-Dimethoxyphenyl)-*N*-phenylethylacrylamide (5ab)[34]

Prepared from **1a** and 2-phenylethan-1-amine (**4b**). Purified by trituration using diisopropyl ether as solvent. After filtration, the product **5ab** was isolated as a white solid; yield: 106 mg (68%); mp 120–121 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 15.6 Hz, 1 H), 7.37–7.20 (m, 5 H), 7.10–7.05 (m, 1 H), 7.03–6.97 (m, 1 H), 6.85 (d, *J* = 8.3 Hz, 1 H), 6.18 (d, *J* = 15.6 Hz, 1 H), 5.63–5.50 (br s, 1 H), 3.90 (s, 6 H), 3.67 (dt, *J* = 6.7, 6.7 Hz, 2 H), 2.89 (t, *J* = 6.7 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2, 150.5, 149.1, 140.8, 138.9, 128.8, 128.7, 128.6, 128.5, 127.8, 126.5, 121.9, 118.6, 111.1, 109.8, 55.9, 55.8, 40.8, 35.7.

HRMS (EI): *m*/*z* calcd for $C_{19}H_{21}NO_3Na$ [M + Na]$^+$: 334.1413; found: 334.1413.

(*E*)-3-(3,4-Dimethoxyphenyl)-*N*-[2-(pyridin-3-yl)ethyl]acrylamide (5ac)

Prepared from **1a** and 2-(pyridin-3-yl)ethan-1-amine (**4c**). Purified by trituration using diisopropyl ether as solvent. The product **5ac** was isolated as a beige solid; yield: 93 mg (60%); mp 115–116 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.52–8.47 (m, 2 H), 7.60–7.52 (m, 2 H), 7.10 (d, *J* = 8.3 Hz, 1 H), 7.00 (s, 1 H), 6.84 (d, *J* = 8.3 Hz, 1 H), 6.21 (d, *J* = 15.5 Hz, 1 H), 5.82–5.65 (br s, 1 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.65 (td, *J* = 6.8, 6.8 Hz, 2 H), 2.90 (t, *J* = 6.8 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.3, 150.6, 150.0, 149.1, 147.9, 141.1, 136.4, 134.6, 127.7, 123.6, 122.0, 118.3, 111.1, 109.7, 55.9, 55.8, 40.5, 32.9.

HRMS (EI): *m*/*z* calcd for $C_{18}H_{20}N_2O_3Na$ [M + Na]$^+$: 335.1366; found: 335.1369.

(*E*)-*N*-(2-Cyclohexylethyl)-3-(3,4-dimethoxyphenyl)acrylamide (5ad)

Prepared from **1a** and 2-cyclohexylethan-1-amine (**4d**). Purified by column chromatography using cyclohexane/EtOAc (1:1) as eluent. The product **5ad** was isolated as a hygroscopic solid; yield: 98 mg (62%); R_f = 0.30 (EtOAc/cyclohexane 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 15.5 Hz, 1 H), 7.05 (d, *J* = 8.3 Hz, 1 H), 7.00–6.98 (m, 1 H), 6.81 (d, *J* = 8.3 Hz, 1 H), 6.28 (d, *J* = 15.5 Hz, 1 H), 5.85–5.77 (br s, 1 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 3.58 (td, *J* = 6.5, 6.5 Hz, 2 H), 1.75–1.63 (m, 6 H), 1.48–1.38 (m, 3 H), 1.32–1.12 (m, 2 H), 0.98–0.85 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1, 150.4, 149.0, 140.5, 127.9, 121.8, 118.8, 111.0, 109.6, 55.9, 55.8, 37.5, 37.1, 35.4, 33.2, 26.5, 26.2.

HRMS (EI): *m*/*z* calcd for $C_{19}H_{27}NO_3Na$ [M + Na]$^+$: 340.1883; found: 340.1885.

(*E*)-*N*-Benzyl-3-phenylacrylamide (5ba)[21c]

Prepared from cinnamic acid (**1b**) and phenylmethanamine (**4a**). Purified by trituration using diisopropyl ether as solvent. After filtration, the product **5ba** was isolated as a white solid; yield: 69 mg (58%); mp 100–102 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 15.6 Hz, 1 H), 7.56–7.47 (m, 2 H), 7.42–7.33 (m, 8 H), 6.44 (d, *J* = 15.6 Hz, 1 H), 6.20–5.80 (br s, 1 H), 4.58 (dd, *J* = 5.9, 2.4 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.7, 141.4, 138.2, 134.8, 129.7, 128.8, 128.7, 127.9, 127.8, 127.6, 120.4, 43.9.

HRMS (EI): *m*/*z* calcd for $C_{16}H_{15}NONa$ [M + Na]$^+$: 260.1045; found: 260.1046.

(*E*)-*N*-Phenethylcinnamamide (5bb)[35]

Prepared from **1b** and 2-phenylethan-1-amine (**4b**). Purified by trituration using diisopropyl ether as solvent. After filtration, the product **5bb** was isolated as a white solid; yield: 75 mg (60%); mp 126–127 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62 (d, *J* =15.6 Hz, 1 H), 7.54–7.44 (m, 2 H), 7.40–7.29 (m, 6 H), 7.29–7.20 (m, 2 H), 6.32 (d, *J* = 15.6 Hz, 1 H), 5.71–5.55 (br s, 1 H), 3.67 (dt, *J* = 6.7, 6.7 Hz, 2 H), 2.90 (t, *J* = 6.7 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 141.0, 138.9, 134.8, 129.6, 128.8, 128.7, 127.8, 126.6, 120.6, 40.8, 35.7.

HRMS (EI): *m*/*z* calcd for $C_{17}H_{17}NONa$ [M + Na]$^+$: 274.1202; found 274.1203.

(*E*)-*N*-(2-(Pyridin-3-yl)ethylcinnamamide (5bc)

Prepared from **1b** and 2-(pyridin-3-yl)ethan-1-amine (**4c**). Purified by column chromatography using cyclohexane/EtOAc (1:1) as eluent. The product **5bc** was isolated as a white solid; yield: 79 mg (63%); mp 160–161 °C; R_f = 0.23 (EtOAc/cyclohexane 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.52–8.47 (m, 2 H), 7.63 (d, *J* = 15.6 Hz, 1 H), 7.60–7.55 (m, 1 H), 7.52–7.48 (m, 2 H), 7.39–7.33 (m, 3 H), 6.33 (d, *J* = 15.6 Hz, 1 H), 5.68–5.55 (br s, 1 H), 3.67 (td, *J* = 6.8, 6.8 Hz, 2 H), 2.92 (t, *J* = 6.8 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.2, 150.0, 147.8, 141.1, 136.4, 134.7, 134.6, 129.7, 128.8, 127.7, 124.0, 120.5, 40.6, 32.9.

HRMS (EI): *m*/*z* calcd for $C_{16}H_{16}N_2ONa$ [M + Na]$^+$: 275.1155; found: 275.1155.

(*E*)-*N*-(2-Cyclohexylethyl)cinnamamide (5bd)

Prepared from **1b** and 2-cyclohexylethan-1-amine (**4d**). Purified by trituration using diisopropyl ether as solvent. After filtration, the product **5bd** was isolated as a beige solid; yield: 71 mg (55%); mp 108–110 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 15.6 Hz, 1 H), 7.56–7.44 (m, 2 H), 7.42–7.32 (m, 3 H), 6.37 (d, *J* = 15.6 Hz, 1 H), 5.61–5.45 (br s, 1 H), 3.42 (dt, *J* = 8.7, 8.7 Hz, 2 H), 1.82–1.64 (m, 6 H), 1.52–1.45 (m, 1 H), 1.41–1.15 (m, 4 H), 1.12–0.87 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.9, 140.7, 134.9, 129.5, 128.8, 127.7, 121.0, 37.6, 37.1, 35.4, 33.2, 26.5, 26.2.

HRMS (EI): *m*/*z* calcd for $C_{17}H_{23}NONa$ [M + Na]$^+$: 280.1672; found: 280.1670.

(*E*)-*N*-(Benzol[*d*][1,3]dioxol-5-ylmethyl)cinnamamide (5be)

Prepared from **1b** and benzo[*d*][1,3]dioxol-5-ylmethanamine (**4e**). Purified by trituration using diisopropyl ether as solvent. After filtration, the product **5be** was isolated as a beige solid; yield: 89 mg (64%); mp 160–161 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 15.6 Hz, 1 H), 7.58–7.47 (m, 2 H), 7.42–7.36 (m, 3 H), 6.90–6.76 (m, 3 H), 6.41 (d, *J* = 15.6 Hz, 1 H), 5.97 (s, 2 H), 5.89–5.78 (br s, 1 H), 4.50 (d, *J* = 5.8 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8. 147.9, 147.0, 141.3, 134.8, 132.1, 129.7, 128.8, 127.8, 121.2, 120.5, 108.5, 108.3, 101.0, 43.6.

HRMS (EI): *m*/*z* calcd for $C_{17}H_{15}NO_3Na$ [M + Na]$^+$: 304.0944; found: 304.0946.

(*E*)-*N*-[4-(Trifluoromethyl)benzyl]cinnamamide (5bf)[6]

Prepared from **1b** and (4-(trifluoromethyl)phenyl)methanamine (**4f**). Purified by trituration using diisopropyl ether as solvent. After filtration, the product **5bf** was isolated as a white solid; yield: 98 mg (64%); mp 129–130 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 15.6 Hz, 1 H), 7.65–7.55 (m, 2 H), 7.53–7.42 (m, 4 H), 7.40 (m, 3 H), 6.43 (d, *J* = 15.6 Hz, 1 H), 6.08–5.95 (br s, 1 H), 4.54 (d, *J* = 6.0 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.1, 142.4, 141.9, 134.6, 129.9, 129.7 (q, $J_{C,F}$ = 32.3 Hz), 128.8, 127.9, 127.8, 125.6 (q, $J_{C,F}$ = 3.8 Hz), 124.1 (q, $J_{C,F}$ = 285 Hz), 120.0, 43.2.

HRMS (EI): *m*/*z* calcd for $C_{17}H_{14}F_3NONa$ [M + Na]$^+$: 328. 0919; found: 328.0920.

(*E*)-*N*-[2-(Pyridin-4-yl)ethyl]cinnamamide (5bg)

Prepared from **1b** and 2-(pyridin-4-yl)ethan-1-amine (**4g**). Purified by column chromatography using cyclohexane/EtOAc (1:1) as eluent. The product **5bg** was isolated as a beige solid; yield: 56 mg (44%); mp 136–137 °C; R_f = 0.25 (EtOAc/cyclohexane 1:1)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.51 (d, *J* = 5.0 Hz, 2 H), 7.63 (d, *J* = 15.6 Hz, 2 H), 7.51–7.43 (m, 2 H), 7.38–7.32 (m, 3 H), 7.17 (d, *J* = 5.0 Hz, 1 H), 6.35 (d, *J* = 15.6 Hz, 1 H), 5.92 (t, *J* = 6.0 Hz, 1 H), 3.67 (dt, *J* = 6.0, 6.0 Hz, 2 H), 2.91 (t, *J* = 6.0 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1, 149.8, 148.2, 141.3, 134.7, 129.8, 128.8, 127.8, 124.2, 120.3, 39.9, 35.1.

HRMS (EI): *m*/*z* calcd for $C_{16}H_{16}N_2ONa$ [M + Na]$^+$: 275.1155; found: 275.1156.

(*E*)-*N*-[2-(Pyridin-2-yl)ethyl]cinnamamide (5bh)[36]

Prepared from **1b** and 2-(pyridin-2-yl)ethan-1-amine (**4h**). Purified by column chromatography using cyclohexane/EtOAc (1:1) as eluent. The product **5bh** was isolated as a beige solid; yield: 62 mg (49%); mp 92–93 °C; R_f = 0.25 (EtOAc/cyclohexane 1:1)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.58 (d, *J* = 4.9 Hz, 1 H), 7.69–7.58 (m, 2 H), 7.56–7.45 (m, 2 H), 7.42–7.33 (m, 3 H), 7.25–7.17 (m, 2 H), 6.82–6.70 (br s, 1 H), 6.40 (d, *J* = 15.6 Hz, 1 H), 3.83 (dt, *J* = 6.2, 6.2 Hz, 2 H), 3.09 (t, *J* = 6.2 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 159.7, 149.1, 140.6, 136.7, 135.0, 129.5, 128.7, 127.7, 123.5, 121.6, 121.1, 38.8, 36.8.

HRMS (EI): *m*/*z* calcd for $C_{16}H_{16}N_2ONa$ [M + Na]$^+$: 275.1155; found: 275.1155.

(*E*)-*N*-Benzyl-3-(4-fluorophenyl)acrylamide (5ca)

Prepared from (*E*)-3-(4-fluorophenyl)acrylic acid (**1c**) and phenylmethanamine (**4a**). Purified by trituration using diisopropyl ether as solvent. After filtration, the product **5ca** was isolated as a white solid; yield: 75 mg (58%); mp 121–122 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 15.6 Hz, 1 H), 7.51–7.42 (m, 2 H), 7.40–7.27 (m, 5 H), 7.15–6.96 (m, 2 H), 6.33 (d, *J* = 15.6 Hz, 1 H), 6.02–5.87 (br s, 1 H), 4.57 (d, *J* = 5.8 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.6, 163.6 (d, $J_{C,F}$ = 250,4 Hz), 140.2, 138.1, 131.0 (d, $J_{C,F}$ = 3.5 Hz), 129.6 (d, $J_{C,F}$ = 8.4 Hz), 128.8, 127.9, 127.6, 120.1 (d, $J_{C,F}$ = 2.4 Hz), 115.9 (d, $J_{C,F}$ = 13.5 Hz), 43.9.

^{19}F NMR (101 MHz, $CDCl_3$): δ = –110.4.

HRMS (EI): *m*/*z* calcd for $C_{16}H_{14}FNONa$ [M + Na]$^+$: 278.0952; found: 278.0952.

(*E*)-3-(4-Fluorophenyl)-*N*-phenylethylacrylamide (5cb)

Prepared from **1c** and 2-phenylethan-1-amine (**4b**). Purified by trituration using diisopropyl ether as solvent. After filtration, the product **5cb** was isolated as a beige solid; yield: 81 mg (60%); mp 154–155 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 15.5 Hz, 1 H), 7.49–7.43 (m, 2 H), 7.37–7.28 (m, 2 H), 7.26–7.21 (m, 2 H), 7.05 (t, *J* = 8.6, 8.6 Hz, 2 H), 6.23 (d, *J* = 15.5 Hz, 1 H), 5.63–5.52 (br s, 1 H), 3.67 (dt, *J* = 6.7, 6.7 Hz, 2 H), 2.89 (t, *J* = 6.8 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 163.5 (d, $J_{C,F}$ = 186.8 Hz), 139.7, 138.8, 131.0 (d, $J_{C,F}$ = 3.4 Hz), 129.5 (d, $J_{C,F}$ = 8.4 Hz), 128.8, 128.7, 126.6, 120.4, 115.8 (d, $J_{C,F}$ = 21.9 Hz), 40.9, 35.7.

^{19}F NMR (101 MHz, $CDCl_3$): δ = –110.7.

HRMS (EI): *m*/*z* calcd for $C_{17}H_{16}FNONa$ [M + Na]$^+$: 292.1108; found: 292.1109.

(*E*)-3-(4-Fluorophenyl)-*N*-[2-(pyridine-3-yl)ethyl]acrylamide (5cc)

Prepared from **1c** and 2-(pyridin-3-yl)ethan-1-amine (**4c**). Purified by trituration using diisopropyl ether as solvent. After filtration, the product **5cc** was isolated as a white solid; yield: 88 mg (65%); mp 135–136 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.51–8.46 (m, 2 H), 7.60 (d, *J* = 15.6 Hz, 1 H), 7.58–7.53 (m, 1 H), 7.50–7.43 (m, 2 H), 7.30–7.23 (m, 1 H), 7.10–7.00 (m, 2 H), 6.25 (d, *J* = 15.60 Hz, 1 H), 5.80–5.70 (br s, 1 H), 3.65 (td, *J* = 6.9, 6.9 Hz, 2 H), 2.91 (t, *J* = 6.9 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 163.6 (d, $J_{C,F}$ = 249.0 Hz), 150.1, 148.1, 140.2, 136.3, 134.4, 130.9 (d, $J_{C,F}$ = 3.0 Hz), 129.6 (d, $J_{C,F}$ = 9.0 Hz), 123.6, 120.0, 119.9, 115.9 (d, $J_{C,F}$ = 22.0 Hz), 40.6, 32.9.

HRMS (EI): *m*/*z* calcd for $C_{16}H_{15}FN_2ONa$ [M + Na]$^+$: 293.1061; found: 293.1061.

(*E*)-3-(4-Fluorophenyl)-*N*-[4-(trifluoromethyl)benzyl]acrylamide (5cf)

Prepared from **1c** and [4-(trifluoromethyl)phenyl]methanamine (**4f**). Purified by trituration using diisopropyl ether as solvent. After filtration, the product **5cf** was isolated as a white solid; yield: 103 mg (64%); mp 140–141 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 15.6 Hz, 1 H), 7.58 (d, *J* = 8.0 Hz, 2 H), 7.50–7.40 (m, 4 H), 7.08–7.00 (m, 2 H), 6.36 (d, *J* = 15.6 Hz, 1 H), 6.25–6.12 (br s, 1 H), 4.61 (d, *J* = 6.0 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 163.6 (d, $J_{C,F}$ = 249.0 Hz), 142.3, 140.7, 130.8 (d, $J_{C,F}$ = 3.4 Hz), 129.5 (d, $J_{C,F}$ = 7.5 Hz), 127.9, 125.6 (q, $J_{C,F}$ = 3.8 Hz), 124.0 (q, $J_{C,F}$ = 270.0 Hz), 122.2, 119.7, 116.0 (d, $J_{C,F}$ = 21.7 Hz), 43.3.

^{19}F NMR (101 MHz, $CDCl_3$): δ = –62.3, –110.2.

HRMS (EI): *m*/*z* calcd for $C_{17}H_{13}F_4NONa$ [M + Na]$^+$: 346.0825; found: 346.0824.

(*E*)-*N*-(4-Bromobenzyl)-3-(4-fluorophenyl)acrylamide (5ci)

Prepared from **1c** and (4-bromophenyl)methanamine (**4i**). Purified by trituration using diisopropyl ether as solvent. After filtration, the product **5ci** was isolated as a white solid; yield: 111 mg (67%); mp 182–183 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 15.6 Hz, 1 H), 7.54–7.40 (m, 4 H), 7.20 (d, *J* = 8.4 Hz, 2 H), 7.06 (dd, *J* = 8.6, 8.6 Hz, 2 H), 6.32 (d, *J* = 15.6 Hz, 1 H), 5.93–5.86 (br s, 1 H), 4.53 (d, *J* = 5.9 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.7, 163.6 (d, $J_{C,F}$ = 249.8 Hz), 140.5, 137.2, 131.8, 130.8 (d, $J_{C,F}$ = 2.3 Hz), 129.6 (d, $J_{C,F}$ = 9.8 Hz), 129.5, 121.5, 119.8, 116.0 (d, $J_{C,F}$ = 21.8 Hz), 43.2.

^{19}F NMR (101 MHz, $CDCl_3$): δ = –110.4.

HRMS (EI): *m*/*z* calcd for $C_{16}H_{13}BrFNONa$ [M + Na]$^+$: 356.0057; found: 356.0055.

(*E*)-3-[4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-*N*-[4-(trifluoromethyl)benzyl]acrylamide (5df)

Prepared from (*E*)-3-(4-boronophenyl)acrylic acid (**1d**) after esterification and [4-(trifluoromethyl)phenyl]methanamide (**4f**). Purified by column chromatography using cyclohexane/diisopropyl ether (1:1) as eluent (pretreatment of silica gel with Et_3N is advised). The product **5df** was isolated as a hygroscopic solid; yield: 64 mg (30%) over two steps.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 7.8 Hz, 2 H), 7.71 (d, *J* = 15.6 Hz, 1 H), 7.62 (d, *J* = 8.0 Hz, 2 H), 7.52 (d, *J* = 7.8 Hz, 2 H), 7.46 (d, *J* = 8.0 Hz, 2 H), 6.50 (d, *J* = 15.6 Hz, 1 H), 6.02 (br s, 1 H), 4.66 (d, *J* = 6.0 Hz, 2 H), 1.36 (s, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.7, 142.3, 141.8, 137.1, 135.3, 128.0, 127.0, 125.7, 125.6, 125.4, 120.8, 84.0, 43.3, 24.9. Carbon atom α to boron is often not visible.

^{19}F NMR (101 MHz, $CDCl_3$): δ = –62.6.

HRMS (EI): *m*/*z* calcd for $C_{23}H_{25}BF_3NO_3Na$ $[M + Na]^+$: 454.1771; found: 454.1772.

Cell Culture

HuH7, Caco-2, MDA-MB-231, HCT116, PC3, MCF7, and NCI-H727 cancer cell lines were obtained from the ECACC collection (Porton Down, UK). Cells are grown at 37 °C, 5% CO_2 in ECACC recommended media: DMEM for HuH7; MDA-MB-231 and fibroblast, and EMEM for MCF7 and CaCo-2; McCoy's for HCT116; and RPMI for PC3 and NCI-H727. All culture media are supplemented by 10% of FBS, 1% of penicillin-streptomycin, and 2 mM glutamine.

Cytotoxic Assays

Some compounds **3** and **5** were solubilized in DMSO at a concentration of 10 mM (stock solution) and diluted in culture medium to the desired final concentrations. The dose effect cytotoxic assay of compounds was performed at 25 µM. Cells were plated in 96-well plates (4000 cells/well). Twenty-four hours after seeding, cells were exposed to chemicals. After 48 h of treatment, cells were washed in PBS and fixed in cold 90% EtOH/5% AcOH for 20 min and the nuclei were stained with Hoechst 33342 (B2261 Sigma). Image acquisition and analysis were performed using a Cellomics ArrayScan VTI/HCS Reader (ThermoScientific). The survival percentages were calculated as the percentage of cell number after compound treatment over cell number after DMSO treatment. For the IC_{50} determination (**5ad**), the dose effect cytotoxic assay was performed by increasing concentration, ranging from 0.1 to 25 µM. The IC_{50} were graphically determined using the curve fitting XLfit 5.5.0.5 (idbs). The 4 Parameter Logistic Model or Sigmoidal Dose-Response Model was used: fit = A + (B–A)/[1 + (C/x)^D].

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Supporting Information

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