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Solvent-Free Synthesis of Carboxylic Acids and Amide Analogs of CAPE (Caffeic Acid Phenethyl Ester) under Infrared Irradiation Conditions

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Abstract

A convenient and easy method is described for the formation of carboxamides from carboxylic acids and primary amines in solventless conditions using infrared (IR) light. Thus, under IR light, cinnamic acid derivatives and amines can produce yields ranging from 50% to 85% of the resulting amide.

Keywords

Amides, Carboxylic Acids, Amines, Infrared Light, Solventless, CAPE, CAPA, Cinnamic Acid Analogs

1. Introduction

Caffeic acid phenethyl ester (CAPE) is a natural phenolic chemical compound found in a variety of plants. It is also a component of propolis from honeybee hives, used as a sealant and to keep the hive clean from fungus and other contaminants [1].

Several *in vitro* pharmacokinetic effects have been reported for CAPE, including a positive effect on reducing

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carcinogenic incidence by boosting cytoprotection against oxidative stress. Antimitogenic, anticarcinogenic, anti-inflammatory and immunomodulatory properties have also been reported [2]. CAPE has been shown to suppress acute immune and inflammatory responses and to hold promise for therapeutic anti-inflammatory applications activating certain enzymatic systems that have antioxidant properties [3]. An anti-cancer effect was observed when mice skin, exposed to TPA to induce skin papillomas, was then treated with bee propolis; CAPE significantly reduced the number of papillomas [4] [5].

The purpose of this study was to synthesize a series of CAPE amide derivatives and previously reported CAPE analogs via a solvent-free procedure. Previous studies of caffeic acid phenethyl amides (CAPA) note that it can act as an antioxidant against lipid peroxidation [6] as well as a potential anti-inflammatory agent through inhibition of 5-lipoxygenase [7]. Using a 2,2-diphenyl-1-picrylhydrazyl assay, CAPA has also been shown to exhibit significant radical scavenging activity [8]. Although various CAPA analogs have been investigated both for radical scavenging activity and for α-glucosidaseinhibition [9], new entities with other functionalities have not yet been studied. Tests have shown CAPA to have stronger *in vitro* cytoprotective effects than CAPE [10].

Amides are of considerable interest in a number of areas, from drug discovery to polymer industry, and therefore their synthesis has been, and remains, a topic of significant interest for organic chemists. The synthesis of these compounds involves a transformation of general synthetic interest that often requires harsh conditions (high temperatures and long reaction times) or the use of often highly toxic catalysts or reagents.

While there are few reports of amide synthesis from cinnamic derivatives, there are some reports that amides derived from cinnamic acids have antioxidant, anti-atherogenic, antiviral, cytotoxic and antifungal properties, with sundry action mechanisms from enzyme inhibition to free radical scavenging. The synthesis of these compounds from different functional groups has also recently been described by different authors, who have synthesized them from ketones (hidrazoic acid [11] [12], via Beckmann rearrangement [13], and via azido-Schmidt reaction with $FeCl_3$ [14]); from aldehydes (aldehydes with alkyl azides [15], oxidative amination with amines [16], oxidative amination catalyzed by zinc [17], and oxidative amination catalyzed by palladium with hydrogen peroxide [18]); from acid halides via Schotten-Baumann reaction [19]; from carboxylic acid (with amines and carbodiimides [20]); using amines and a molecular sieve [21]; from amines with nanosulfated titanium dioxide [22]; using epimerization-prone carboxylic acids and amines with T3P and Pyridine [23]; using triacyloxyboranes [24]; using trimethylaluminium [25]; with tosyl chloride in solventless conditions [26]; with urea using microwaves [27]; using solid phase synthesis with polymer bound reagents [28]; using isonitriles [29]; from esters and lactones [30]; from imines [31]; and from esters (assisted by potassium tert-butoxide [32], with magnesium nitride [33], and from methyl ketones or carbinols [34]).

On this occasion and as a part of the research agenda of the bioactive molecules program, we report the synthesis of amides from cinnamic acid analogs and from phenylacetic acid with aliphatic amines in the absence of solvent. We also report the synthesis of cinnamic acid derivatives. Some of these amides—compounds 10 and 11 (see **Table 2**)—have presented biological activity against liver cancer [10]. The use of infrared light as an alternate source of energy allows reactions to be faster as it shortens the reaction time, thus the heating is faster. Although this does not compare to the use of microwaves, that allows much shorter reaction times, the cost of one IR lightbulb is much lesser, so minimizing costs is a priority now. We use as energy source a 300 W infrared lightbulb connected to a rheostat to control the amount of energy supplied to the reaction.

2. Results and Discussion

The CAPE analogs were synthesized using the methodology described in “experimental” section. Our method using IR energy allows us to prepare both amides and cinnamic acids analogs. Cinnamic acid analogs were prepared in good yields with short reaction times (see **Table 1**); this allows to an efficient preparation and purification. Our results are consistent with those reported on literature achieving in some cases better yields.

In **Table 2**, we show the molecules synthesized using our methodology, some of them have high yields, and others have very low yields. This increase of yield is due to the presence of halogens and phenoxy moieties in the acids and in the amines used to prepare these molecules. On the other hand nitro and methoxy moieties decreased yield. The presence of trifluoromethyl moiety diminished the yield in the presence of phenoxyacetic acid while with cinnamic acid result in good yields.

Table 1. Prepared cinnamic acid analogs and yields.

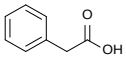
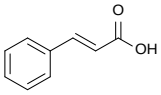
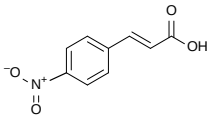
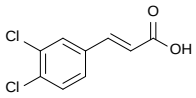
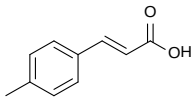
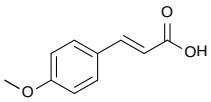
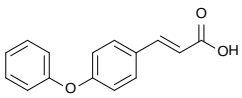
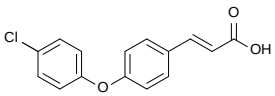
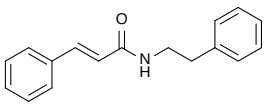
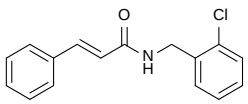
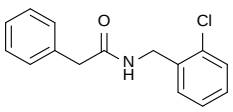
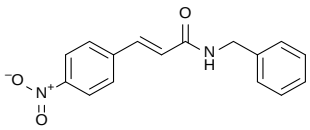
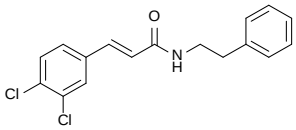
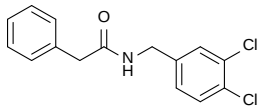
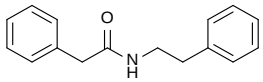
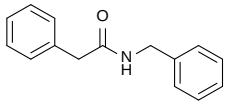
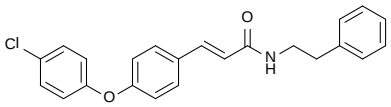
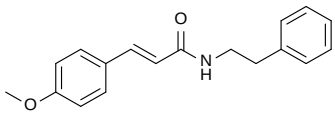
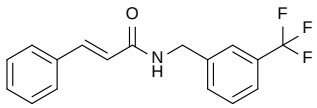
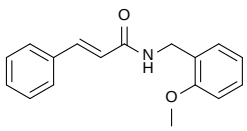
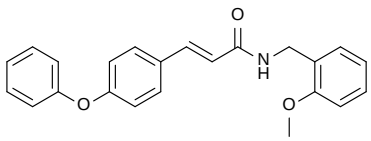
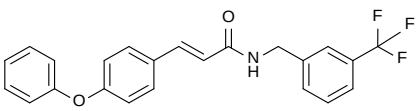
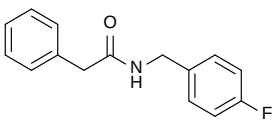
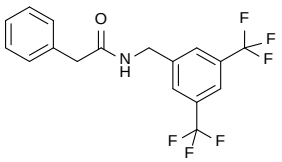
Entry	Structure	Yield (%)	Reaction Time (h)	Melting Point (˚C)	Reference
1		Acquired from Sigma Aldrich®			
2		80	1	133 - 137	[36] [37] mp: 132˚C - 133˚C 82% Yield
3		80	1	239 - 241	[38] [39] mp: 292˚C - 293˚C 82% Yield
4		80	1	218 - 200	[40] mp: 214˚C - 216˚C 88% Yield
5		81	1	199 - 200	[41] [42] mp: 196˚C - 198˚C 93% Yield
6		74	1	174 - 176	[41] mp: 170˚C - 173˚C 97% Yield
7		85	1.5	156 - 157	[43] mp: 155˚C - 157˚C 83% Yield
8		75	1	190 - 193	[44] [45] mp: 218˚C - 220˚C 70% Yield

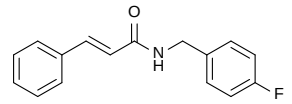
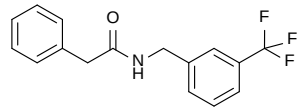
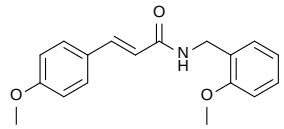
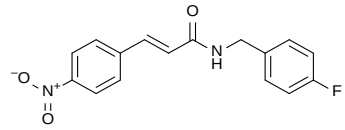
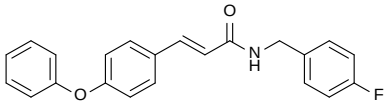
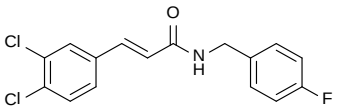
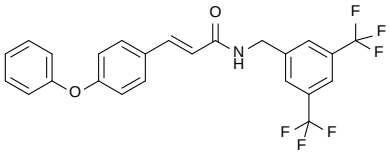
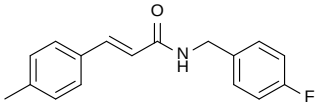
Table 2. Prepared amides and yields.

Entry	Structure	Yield (%)	Reaction Time (h)	Melting Point (˚C)	Reference
9		65	1	112-14	[46]-[48] mp: 113˚C - 115˚C 70% Yield
10		80	1	128-130	[49] mp: 129˚C - 130˚C 70% Yield
11		80	1	128-130	New*
12		15	1.5	189-190	[50] [51] mp: 185 - 186 60% Yield
13		51	1	132-133	New

Continued

14		70	1	104-105	New
15		49	0.75	93-94	[52] [53] mp: 94 - 96 52%Yield
16		73	1	121-122	[52] [54] [55] mp: 118 92%Yield
17		28	1	123-124	New
18		53	1	125-126	[56] [57] mp: 128 - 131 60%Yield
19		50	2	112-113	New
20		61	1	144-146	New
21		71	1	123-124	New
22		73	1	102-104	New
23		54	0.5	134-136	[52] 77%Yield
24		28	0.5	91-95	New

Continued

25		62	1	114-116	[55] mp: 121 84% Yield
26		27	1	68-70	[56] mp: 72 - 75 46%Yield
27		13	0.5	94-96	New
28		14	1	180-182	New
29		72	1	140-142	New
30		58	1	136-138	New
31		68	0.5	140-142	New
32		49	1	144-146	New

*This compound's first synthesis is reported in this paper, the reference [10] is for biological activity.

Our working group proposed the synthesis of amides from carboxylic acids and amines without the presence of solvent and using infrared energy. This method has facilitated the production of the amides listed above using a relatively clean procedure that generates few reaction by-products.

This procedure also eases the purification process, as what remains are only any unreacted raw materials and trace amounts of the by-products. This produces good yields and amides with a high degree of purity after separation treatment. This is also a low-cost procedure, because, as mentioned above, it does not require the use of expensive catalysts or solvents that must be recovered, nor any treatment is required as a result of their use.

3. Conclusion

This paper presents a novel methodology for the synthesis of cinnamic acid analogs via a Knövenagel-Döbner modification and CAPA amide analogs in the absence of solvent and with good yields, using infrared radiation as energy source.

4. Experimental

4.1. Synthesis of Cinnamic Analogs

Our team prepared the cinnamic acid analogs that were not commercially available—4-(4-chlorophenoxy) cin-

namic acid and 4-phenoxy cinnamic acid—via a Knövenagel-Döbner condensation using piperidine and glacial acetic acid as catalyst and solvent, respectively [35] [51]. The other cinnamic acid analogs (cinnamic acid, 4-nitro cinnamic acid, 3,4-dichloro cinnamic acid, 4-methoxy cinnamic acid, and 4-methyl cinnamic acid) were also synthesized, onlyphenylacetic acid was purchased from Sigma Aldrich Co.® (**Scheme 1**).

The corresponding substituted benzaldehyde and malonic acid weighed on a 1:1 ratio were placed in a flask with piperidine (1 mL for each part of substituted benzaldehyde (ratio 1.25:1)) and glacial acetic acid (2.5 mL for each part of substituted benzaldehyde (ratio 1.77:1)). This flask was connected to the reflux apparatus at 140˚C - 160˚C, which is the temperature necessary to carry out the reaction, followed by TLC (hexane: EtOAc, 80:20). Upon completion of the reaction, ice or cold water was added to the flask until the acid precipitated; it was then filtered and washed repeatedly with water (3 × 100 mL). Recrystallization from EtOAc produces the corresponding acid.

If the acid did not precipitate but formed an emulsion, liquid-liquid extraction with EtOAc (5 × 50 mL)was performed. Following this step, some acetic acid was dissolved in the EtOAc. Brine (3 × 30 mL) was then used to remove this acetic acid, and anhydrous sodium sulfate was then used to remove water from the organic phase (EtOAc) to allow recrystallization.

4.1.1. General Procedure, for 3-(4-Phenoxyphenyl)-2-Propenoic Acid and 3-[4-(4-Chlorophenoxy) Phenyl]-2-Propenoic Acid

4-(4-chlorophenoxy) benzaldehyde (1 g, 3.640 mmol) and malonic acid (1 g, 9.6097 mmol) were weighed in a round bottom flask; piperidine (1 mL, 11.76 mmol) and glacial acetic acid (2.5 mL, 41.66 mmol) were added. This was taken to the IR light at 130˚C - 140˚C. After 1 hour the reaction mixture was cooled and cold water with ice was added until precipitation. The flask was brought to room temperature and then filtered and rinsed with water at room temperature until no signs of the aldehyde were present. Sufficient AcOEt was added to dissolve the crystals, and anhydrous sodium sulfate was added to remove water captured by crystals. Recrystallization then occurred, with the appearance of white needles.

1) 3-(4-phenoxyphenyl)-2-propenoic acid (7)

Yield (85%) mp 156˚C - 157˚C. IR (Diamond, cm^{-1}): ν_{max}1588, 3031, 3200 - 2200. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.30 (1H, d), 6.90 (5H, m), 7.24 (4H, m), 7.64 (1H, d, J = 15.6 Hz), 8.95 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 116.02 (-CH=), 117.02, 117.32, 121.61, 125.69, 128.21, 128.91 (Ph), 144.64 (-CH=), 155.32, 156.13 (Ph) 169.64 (COOH).

2) 3-[4-(4-chlorophenoxy) phenyl]-2-propenoic acid (8)

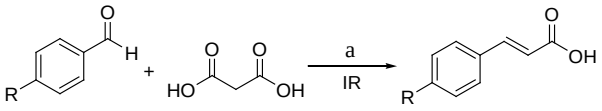
Yield (75%) mp 190˚C - 193˚C. IR (Diamond, cm^{-1}): ν_{max} 1570, 3025, 3200-2200. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.41 (1H, d), 6.87 (4H, m), 7.25 (4H, m), 7.61 (1H, d, J = 15.6 Hz), 8.45 (1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 116.97 (-CH=), 117.22, 118.73, 125.69, 126.94, 128.21, 128.91 (Ph), 145.70 (-CH=), 154.23, 155.13 (Ph) 171.78 (COOH).

4.2. Amide Synthesis

The acid and amine, weighed on a 1:1 ratio, were placed in a flask and connected to the reflux apparatus at 140˚C - 160˚C with the 300W IR light bulb, followed by TLC(hexane: EtOAc, 50:50). Upon completion of the reaction, sufficient AcOEt was added to dissolve the reaction product.

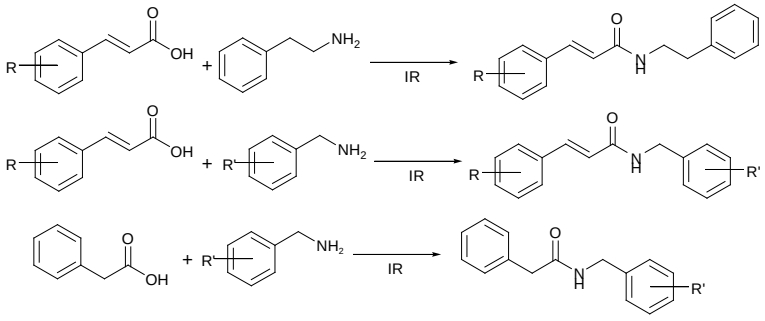
A small amount of activated charcoal was added to the reaction mixture and filtered over diatomaceous earth (Hyflo Super Cel.® Diatomaceous earth) purchased from Sigma Aldrich® to remove the activated charcoal. Recrystallization from EtOAc produced the corresponding amide.

Further recrystallizations were made with an AcOEt: hexane 90:10 mixture only when necessary (**Scheme 2**).



R: phenoxy, 4-chlorophenoxy
a: piperidine, glacial acetic acid

Scheme 1. Knövenagel-Döbner condensation used to prepare cinnamic acid analogs.



Scheme 2. Reactions involved on the preparation of amides.

4.2.1. General Procedure for the Preparation of Amides (9-32). Exemplified by 3-Phenyl-N-(2-Phenylethyl)-2-Propenamide

Cinnamic acid (0.5 g, 3.374 mmol) was weighed in a round bottom flask, and phenylethylamine (0.5 g, 4.1261 mmol) was added dropwise at 140˚C - 160˚C without solvent. After 1 hour the reaction mixture was cooled to room temperature. AcOEt and active charcoal were added and filtered over diatomaceous earth (celite). Solvent was removed under reduced pressure until crystallization and recrystallized from a mixture of AcOEt and hexane.

*Only data for new amides are shown

1) N-(2-chlorobenzyl)-2-phenylacetamide (11)

Yield (3.9 g, 79.83%); mp 118˚C - 120˚C. IR (Diamond, cm^{-1}): ν_{max}1546, 2923, 3274.^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ3.63 (2H, s), 4.46 (2H, d, J = 4.0), 5.90 (1H, br, s, NH), 7.29 (9H, m); ^{13}C NMR (75 MHz; $CDCl_3$; Me_4Si) δ42.05 (CH_2), 44.18 (CH_2), 127.44, 127.85, 129.28, 129.48, 129.88, 129.89, 130.32, 133.91, 135.05, 135.86 (Ph), 171.29 (-CO-).Analysis Calc. for $C_{15}H_{14}ClNO$: C,69.3; H, 5.4; N, 5.3.Found C, 69.35; H, 5.05; N, 5.71.

2) 3-(3,4-dichlorophenyl)-N-(2-phenylethyl)-2-propenamide(13)

Yield (2.55 g, 51%), mp 132˚C - 133˚C IR (Diamond, cm^{-1}): ν_{max}1550, 2315, 2920, 3281.^{1}H NMR (200 MHz; DMSO-d_6; Me_4Si) δ2.79 (2H, t, J = 7.4), 3.44 (2H, m), 6.72 (1H, d, J = 15.8). 7.43 (8H, m, Ph), 7.85 (1H, d, J = 1.8), 8.29 (1H, t, NH, J = 11.2); ^{13}C NMR (50 MHz; DMSO-d_6; Me_4Si) δ35.09 (-CH_2-Ph), 124.49(-CH=), 126.12, 127.27, 128.36, 128.66, 129.41, 131.01, 131.56, 131.68, 135.88, 136.00 (Ph), 139.41 (-CH=), 164.47 (-CO-). Calc. for $C_{17}H_{15}Cl_2NO$: C, 63.7; H, 4.7; N, 4.3. Found C, 60.25; H, 4.71; N, 4.4.

3) N-(3,4-dichlorobenzyl)-2-phenylacetamide (14)

Yield (1.51 g, 70%), mp 132˚C - 133˚C. IR (Diamond, cm^{-1}): ν_{max}1534, 2908, 3265. ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ3.62 (2H, s), 4.32 (2H, d, J = 6.1), 6.13 (1H, s, NH), 7.23 (8H, m); ^{13}C NMR (75 MHz; $CDCl_3$; Me_4Si) δ42.63 (-CH_2-CO-), 43.98 (CH_2-Ph), 127.59, 128.36, 129.98, 130.12, 130.22, 131.39, 132.17, 133.44, 135.51, 139.54 (Ph), 172.32 (-CO-). Calc. for $C_{15}H_{13}Cl_2NO$: C, 61.2; H, 4.4; N, 4.7. Found C, 61.08; H, 3.81; N, 4.8.

4) N-(2-phenylethyl)-3-[4-(4-chlorophenoxy)phenyl]-2-propenamide (17)

Yield (0.37 g, 28%), mp 123˚C - 124˚C. IR (Diamond, cm^{-1}): ν_{max}1541, 2922, 3279. ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ2.88 (2H, td, J = 6.9, 6.8, 2.5), 3.64 (2H, qd, J =6.9, 2.5), 5.78 (1H, t, J = 5.4), 6.26 (1H, dd, J = 15.6, 8.9), 7.16 (13H, m), 7.57 (1H, dd, J = 15.6, 8.6);^{13}C NMR (75 MHz; $CDCl_3$; Me_4Si) δ35.67 (CH_2-Ph), 40.87 (CH_2), 120.28 (-CH=), 117.32, 126.62, 128.73, 128.81, 128.84, 129.49, 129.88, 129.93, 130.29, 138.83 (Ph), 140.17 (-CH=), 157.39, 155.90 (Ph), 165.58 (-CO-). Calc. for $C_{23}H_{20}ClNO_2$: C, 73.1; H, 5.3; N, 3.7. Found C, 73.05; H, 4.62; N, 4.03.

5) N-[3-(trifluoromethyl)benzyl]-3-phenyl-2-propenamide (19)

Yield (1.03 g, 50%), mp 112˚C - 113˚C. IR (Diamond, cm^{-1}): ν_{max}1588, 2924, 3261. ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ4.50 (2H, d, J = 6.0), 6.40 (2H, m, NH), 7.33 (9H, m), 7.58 (1H, d, J = 15.6); ^{13}C NMR (75 MHz; $CDCl_3$; Me_4Si) δ42.42 (-CH_2-Ph), 124.13 (-CH=), 126.30, 126.97, 127.45, 128.39, 128.63, 136.72, 141.49, 145.50, (Ph), 139.11 (-CH=), 164.26 (-CO-).Calc. for $C_{17}H_{14}F_3NO$: C, 66.8; H, 4.6; N, 4.5. Found C, 66.64; H, 4.03, N, 5.0.

6) N-(2-methoxybenzyl)-3-phenyl -2-propenamide (20)

Yield (1.10 g, 61%), mp 144˚C - 146˚C. IR (Diamond, cm^{-1}): ν_{max}1538, 2926, 3275. ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ3.76 (3H, s), 4.48 (2H, d, *J* = 5.9), 6.27 (1H, brs, NH), 6.34 (1H, d, *J* = 15.6), 6.82 (2H, m), 7.27 (7H, m), 7.54 (1H, d, *J* = 15.6);^{13}C NMR (75 MHz; $CDCl_3$; Me_4Si) δ39.81 (CH_2-Ph), 55.74 (CH_3), 121.54 (-CH=), 111.03, 121.74, 127.02, 128.62, 129.62, 129.76, 130.40, 130.73, 135.83, 158.56(Ph), 141.79 (-CH=), 166.74 (-CO-).Calc. for $C_{17}H_{17}NO_2$: C, 76.3; H, 6.4; N 5.2. Found C, 76.38; H, 6.36; N, 5.26.

7) N-(2-methoxybenzyl)-3-(4-phenoxyphenyl)-2-propenamide (21)

Yield (1.06 g, 71%), mp 123˚C - 124˚C. IR (Diamond, cm^{-1}): ν_{max}1541, 2946, 3289. ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ4.47 (2H, d, *J* = 5.9), 6.24 (2H, m), 6.87 (6H, m), 7.06 (1H, d, *J* = 7.4), 7.23 (6H, ddd, *J* = 19.2, 16.3, 7.7), 7.50 (1H, d, *J* = 15.6); ^{13}C NMR (75 MHz; $CDCl_3$; Me_4Si) δ 39.55 (CH_2-Ph), 55.39 (CH_3), 110.32, 118.50 (Ph), 119.54 (-CH=), 120.77, 123.96, 126.27, 128.93, 129.40, 129.83, 129.89, 129.94 (Ph), 140.16 (-CH=), 156.37, 157.55, 158.78 (Ph), 165.81 (-CO-). Calc. for $C_{23}H_{21}NO_3$: C, 76.8; H, 5.8; N, 3.9% Found C, 76.22; H, 5.61; N, 4.1.

8) N-[3-(trifluoromethyl)benzyl]-3-(4-phenoxyphenyl)-2-propenamide (22)

Yield (1.20 g, 73%), mp 102˚C - 104˚C. IR (Diamond, cm^{-1}): ν_{max}1562, 3076, 3266, 1158. ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ4.62 (2H, d, *J* = 6.0), 6.45 (1H, d, *J* = 15.6), 6.61 (1H, s), 6.97 (3H,d, *J* = 8.7), 7.08 (2H, d, *J* = 7.6), 7.2 (1H, t, *J* = 7.4), 7.48 (7H, m), 7.68 (1H, d, *J* = 15.6); ^{13}C NMR (75 MHz; $CDCl_3$; Me_4Si) δ43.24 (CH_2-Ph), 118.45 (Ph), 118.86 (-CH=), 119.64, (CF_3, *J* = 58.9), 124.09, 124.32, 124.33, 124.36, 124.38, 129.21, 129.41, 129.51, 129.97, 131.19, 139.43 (Ph), 141.07 (-CH=), 156.21, 159.11 (Ph), 166.31 (-CO-).Calc. for $C_{23}H_{18}F_3NO_2$: C, 69.5; H, 4.5; N, 3.5.Found C, 69.78; H,3.80; N, 3.9.

9) N-[3,5-bis(trifluoromethyl)benzyl]-2-phenylacetamide (24)

Yield (0.37 g, 28%), mp 91˚C - 95˚C. IR (Diamond, cm^{-1}): ν_{max}1548, 3068, 3254, 1117. ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ3.55 (2H, s), 4.49 (2H, d, *J* = 6.0), 7.33 (5H, d, *J* = 4.0), 7.91 (2H, s), 7.98 (1H,s), 8.80 (1H, t, NH, *J* = 5.8); ^{13}C NMR (75 MHz; $CDCl_3$; Me_4Si) δ42.07 (CH_2-Ph), 43.17 (CH_2-Ph), 121.71 (CF_3), 122.78, 126.42, 127.75, 129.05, 129.55, 130.14, 137.53, 144.72 (Ph), 172.26 (-CO-).Calc. for $C_{17}H_{13}F_6NO$: C, 56.5; H, 3.6; N, 3.8. Found C, 57.00; H, 3.12; N, 4.15.

10) N-(2-methoxybenzyl)-3-(4-methoxyphenyl)-2-propenamide (27)

Yield (0.11 g, 13%), mp 94˚C - 96˚C. IR (Diamond, cm^{-1}): ν_{max}1552, 3075, 3261. ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ3.62 (3H, s), 3.71 (3H, s), 4.44 (2H, d, *J* = 5.9), 6.11 (1H, brs, NH), 6.91 (2H, ddd, *J* = 21.2, 13.8, 4.6), 7.33 (8H, m);^{13}C NMR (75 MHz; $CDCl_3$; Me_4Si) δ38.14 (CH_2-Ph), 56.15 (CH_3O), 111.67 (Ph), 115.69 (-CH=), 128.02, 128.80, 129.25, 129.43, 130.38, 139.86 (Ph), 140.24, (-CH=), 158.18, 161.80 (Ph), 166.86 (-CO-). Calc. for $C_{18}H_{19}NO_3$: C, 72.7; H, 6.4; N, 4.7. Found C, 72.82; H, 6.21; N, 5.7.

11) N-(4-fluorobenzyl)-3-(4-nitrophenyl)-2-propenamide (28)

Yield (0.22 g, 14%), mp 180˚C - 182˚C. IR (Diamond, cm^{-1}): ν_{max}1509, 3040, 3272, 1334, 1605, 1209. ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ4.44 (2H, d, *J* = 5.9), 6.91 (1H, d, *J* = 15.8), 7.19 (2H, t, *J* = 8.9), 7.38 (2H, dd, *J* = 8.8, 5.6), 7.62 (1H,d, *J* = 15.9), 7.87 (2H,d, *J* = 8.7), 8.30 (2H, m), 8.82 (1H, t, NH, *J* = 5.9); ^{13}C NMR (75 MHz; $CDCl_3$; Me_4Si) δ42.48 (CH_2-Ph), 116.14 (Ph), 125.35 (-CH=), 127.52, 129.89, 130.66, 130.77, 136.73, 138.09 (Ph), 124.86 (-CH=), 148.92 (Ph), 165.82 (-CO-).Calc. for $C_{16}H_{13}FN_2O_3$: C, 64.0; H, 4.3; N, 9.3. Found C, 64.36; H, 3.80; N, 9.65.

12) N-(4-fluorobenzyl)-3-(4-phenoxyphenyl)-2-propenamide (29)

Yield (1.04 g, 72%), mp 140˚C - 142˚C. IR (Diamond, cm^{-1}): ν_{max}1458, 3044, 3274, 1151. ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ4.52 (2H, d, *J* = 5.8), 5.97 (1H, t, NH, *J* = 5.0), 6.31 (1H, d, *J* = 15.6), 6.99 (6H, m), 7.14 (1H,t, *J* = 7.4), 7.27 (2H, m), 7.35 (2H, t, *J* = 7.9), 7.43 (2H, d, *J* = 8.7), 7.63 (1H, d, *J* = 15.6);^{13}C NMR(75 MHz; $CDCl_3$; Me_4Si) δ43.08 (CH_2-Ph), 115.43, 115.64, 118.42, 118.89 (Ph), 119.56 (-CH=), 123.98, 129.39, 129.88, 134.03 (Ph), 140.86 (-CH=), 156.19, 159.01, 160.96 (Ph), 163.40 (C-F), 165.86 (-CO-). Calc. for $C_{22}H_{18}FNO_2$: C, 76.0; H, 5.2; N, 4.0. Found C, 76.32; H, 4.40, N, 4.34.

13) 3-(3,4-dichlorophenyl)-N-(4-fluorobenzyl)-2-propenamide (30)

Yield (0.85 g, 55%), mp 136˚C - 138˚C. IR (Diamond, cm^{-1}): ν_{max}1553, 3075, 3247, 1131. ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ6.00 (1H, brs, NH), 6.37 (1H, d, *J* = 14.8), 7.01 (2H, t, *J* = 8.6), 7.27 (3H, m), 7.41 (1H, d, *J* = 8.3), 7.54 (2H, t, *J* = 7.7); ^{13}C NMR(75 MHz; $CDCl_3$; Me_4Si) δ43.17 (CH_2-Ph), 115.50 (Ph), 121.97 (-CH=), 126.93, 129.17, 129.51, 130.80, 133.11 (Ph), 133.64, 134.71, (C-Cl), 139.06 (-CH=), 161.00 (Ph), 163.45 (C-F), 164.99 (-CO-); Calc. for $C_{16}H_{12}Cl_2FNO$: C, 59.2; H, 3.7; 4.3. Found C, 59.62; H, 3.33; N, 4.34.

14) N-[3,5-bis(trifluoromethyl)benzyl]-3-(4-phenoxyphenyl)-2-propenamide (31)

Yield (0.66 g, 68%), mp 140˚C - 142˚C. IR (Diamond, cm^{-1}): ν_{max}1509, 3050, 3272, 1124. ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ4.68 (2H, d, J = 6.1), 6.12 (1H, t, NH, J = 5.8), 6.35 (1H, d, J = 15.6), 6.96 (2H, d, J = 8.6), 7.03 (2H, d, J = 8.6), 7.15 (1H, t, J = 7.9), 7.25 (1H, s), 7.36 (2H, t, J = 7.7), 7.46 (2H, d, J = 8.7), 7.66 (1H, d, J = 15.5), 7.77 (2H, d, J = 5.4); ^{13}C NMR(75 MHz; $CDCl_3$; Me_4Si) δ42.83 (CH_2-Ph), 118.05, 118.41 (Ph), 119.61 (-CH=), 121.46 (C-F), 124.06, 127.77, 129.16, 129.56, 129.53, 129.90, 131.78, 132.12 (Ph), 141.08 (-CH=), 141.74, 156.11, 159.26 (Ph), 166.16 (-CO-).Calc. for $C_{24}H_{17}F_6NO_2$: C, 61.9; H, 3.6; N, 3.0 Found C, 62.12; H, 2.64; N, 3.43.

15) N-(4-fluorobenzyl)-3-(4-methylphenyl)-2-propenamide (32)

Yield (0.49 g, 49%), mp 144˚C - 146˚C. IR (Diamond, cm^{-1}): ν_{max}1509, 3036, 3261, 1209. ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) δ2.34 (3H, s), 4.51 (2H, d, J = 5.8), 6.03 (1H, brs, NH), 6.36 (1H, d, J = 15.6), 6.99 (2H, t, J = 8.7), 7.14 (2H, d, J = 7.9), 7.27 (2H, m), 7.37 (2H, d, J = 8.1), 7.62 (1H, d, J = 15.6); ^{13}C NMR(75 MHz;$CDCl_3$; Me_4Si) δ21.38 (CH_3), 43.04 (CH_2-Arom), 115.40 (Ph), 119.15 (-CH=), 127.75, 129.52, 131.90, 134.08, 140.07 (Ph), 141.51 (-CH=), 160.93 (C-F), 163.38 (Ph), 165.97 (-CO-).Calc. for $C_{17}H_{16}FNO$: C, 75.8; H, 5.9; N, 5.2. Found C, 76.29; H, 5.23; N, 5.39.

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