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An Efficient approach for the Synthesis of N-aryl/ heterocycle/ alkyl Benzamides derivatives and evolution of anticancer activities

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Abstract: An efficient approach for the preparation of *N*-aryl/heterocyclic/alkyl benzamides derivatives **3a–3ac** by using 4-methyl benzoic acid **1a**, amine **2a–2ac** with HOBt under very mild reaction condition. The synthesized compounds were further characterized by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, IR and mass spectroscopy. The majority of synthesized compounds were obtained in good to excellent yield and screened for their anticancer activity against MCF–7 cell line and showed interesting results.

Keywords: 4-Methylbenzoicacid, HOBt, Peptide coupling, anticancer activity.

Introduction

The amide functionality is one of the most fundamental chemical building blocks found in nature and having wide range of applications in medicines and agro chemicals.[1-3] It constitutes the backbone of the biologically crucial proteins, and it is present in a vast number of synthetic structures. Literature reveals that, amide functionality is found in up to 25% of all pharmaceuticals present in the market.[4-5] It is estimated that 16% of reactions involved in the synthesis of modern pharmaceuticals are the acylation of an amine, and the fact makes it the most valuably performed reaction in the field of organic synthesis.[6-7] In addition, the amide bond is widely applicable of most prolific moieties in agrochemicals molecules.[8-9] Benzamides and its derivatives have attracted much attention due to their presence in biologically active agrochemicals, pharmaceuticals and play significant role in the bioactive molecules in process development.

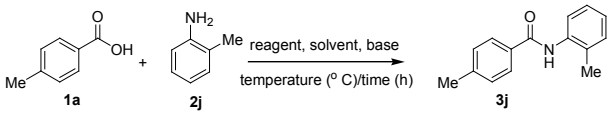
In 2011, C. Zimmer et al. synthesized a panel of *N*-(pyridin-3-yl)benzamides for the evaluation of human aldosterone synthase inhibitor (CYP11B2), The highest selectivity was observed from fluoro and difluoro substitution at para-position of the benzamide moiety.[10]

In 2012, Baek et. al. has reported a series of polyhydroxylated *N*-benzylbenzamide derivatives containing an adamantyl moiety for the depigmenting and tyrosinase inhibitory activities.[11] The expressive biological importance of *N*–aryl/alkyl/heterocycle benzamides and limitations of well reported processes such as use of expensive reagents and requirement of multistep procedures attracted our attention towards the development of improved prominent method development for the synthesis of *N*–aryl/heterocycle/alkyl benzamide derivatives which can serve the mankind. Thus, as a part of our ongoing research, on the synthesis of heterocycles,[12] here in we reported a convenient and efficient method for synthesis of *N*–aryl/alkyl/heterocycle benzamide derivatives with good to excellent yield.

Results and Discussion

To search for most optimal system for the *carboxamide synthesis*, we initiated our investigation with 1.0 mmol of 4-methyl benzoicacid **1a** and 1.0 equiv of *o*-Toluidine **2j** in the presence of peptide reagent as coupling reagents and base at rt under N_2 atmophere in solvent and time. This set of condition afforded desired product **3j** in good yield (**Table** 1, **entry** 12).

Table 1. Optimization of the reaction conditions.[a]



Entry	Reagent	Base	Solvent	T(h) / T(°C)	Yield (%)[b]
1	HOBT/EDC.HCl	Et_3N	DMF	6 / 25	53
2	HOBT/EDC.HCl	Et_3N	THF	6 / 60	80
3	HOBT	Et_3N	THF	12 / 25	-
4	EDC.HCl	Et_3N	THF	12 / 25	-
5	HOBT/EDC.HCl	Et_3N	DMF	12 / 70	53
6	HATU	Et_3N	DMF	12 / 25	50
7	PyBOP	Et_3N	DMF	12 / 25	48
8	HBTU	Et_3N	DMF	12 / 25	50
9	TBTU	Et_3N	DMF	12 / 25	40
10	HOBT/EDC.HCl	DIPA	DMF	12 / 25	40
11	HOBT/EDC.HCl	K_2CO_3	DMF	12 / 25	15
12	**HOBT/EDC.HCl**	**Et_3N**	**THF**	**12 / 25**	**90**
13	HOBT/EDC.HCl	DIPEA	DMF	12 / 25	48
14	HOBT/EDC.HCl	Et_3N	THF	24 / 25	92
15	HOBT/EDC.HCl	Et_3N	THF	8 / 25	90
16	HOBT/EDC.HCl	Et_3N	DMSO	12 / 25	27
17	HOBT/EDC.HCl	Et_3N	MeCN	12 / 25	41
18	HOBT/EDC.HCl	Et_3N	Dioxan	12 / 25	67
19	HOBT/EDC.HCl	Et_3N	THF	6 / 25	80
20	HOBT/EDC.HCl	Et_3N	THF	8/ 25	80[c]
21	HOBT/EDC.HCl	Et_3N	THF	8/ 25	82[d]

[a] Reaction were performed using 1.0 mmol of acid **1a**, 1.0 equiv. of *o*-Toluidine **2a**, base (3.0 equiv.) in 10 mL of solvent under N_2 atmosphere. [b]Isolated yields. [c] 2.0 equiv. of amine was used. [d] 1.5 equiv. of amine was used.

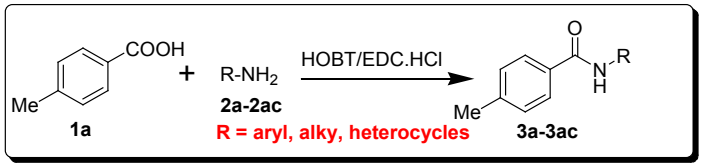
Reaction performed with various bases like DIPEA, DIPA and K_2CO_3 were used to afford the desired product **3j** in poor to good yields (**Table 1**, entry 7-9). Whereas changes of solvents from DMF, MeCN, DMSO, dioxane to THF was found effective (**Table 1**, entry 12) where as only EDC.HCl used a peptide reagent with DMF to get poor yield with racemized products observed. when changed the peptide reagent like HATU, PyBOP, HBTU and TBTU to get a moderate yields (**Table** 1, entries 6–9). Where as using increase the mole equivalent of *o*-Toluidine from 1 to 1.5 and 2.0 mol equivalent to get desired product with good yield (**Table 1**, entries 20–21).

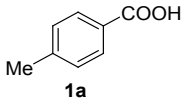
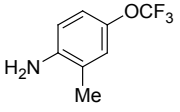
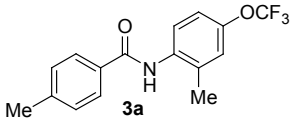
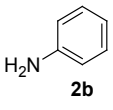
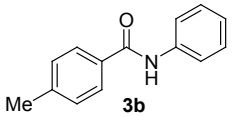
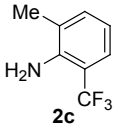
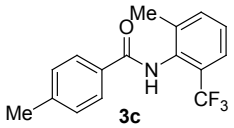
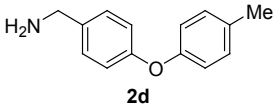
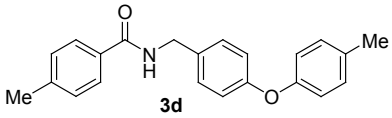
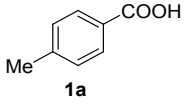
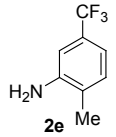
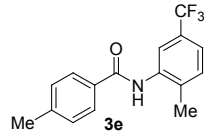
Scope and Limitation of the Reaction

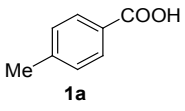
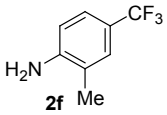
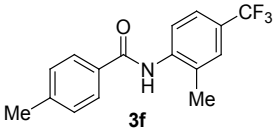
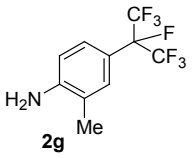
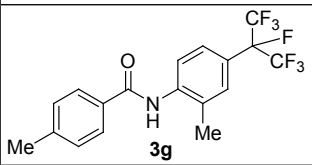
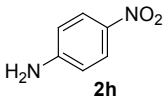
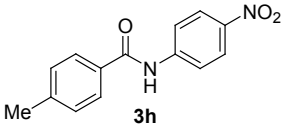
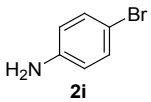
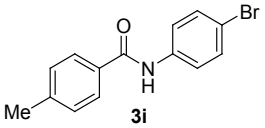
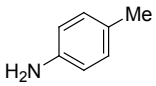
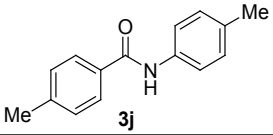
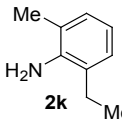
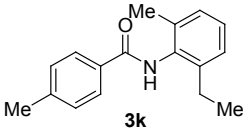
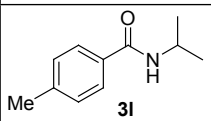
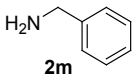
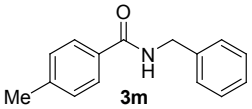
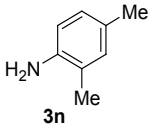
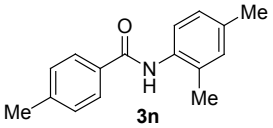
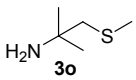
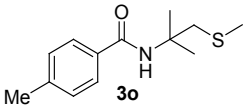
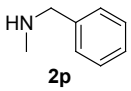
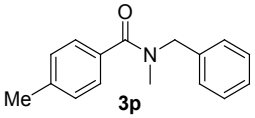
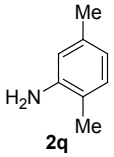
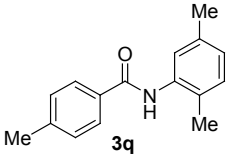
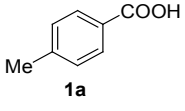
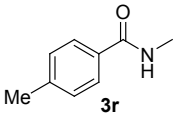
With this standard protocol in hand (**Table** 1, **entry** 1–29), we examined the scope and generality of the reaction with a number of substituted alkyl, aryl and heterocyclic amines

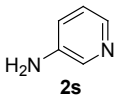
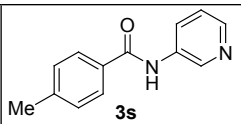
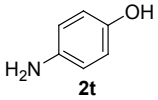
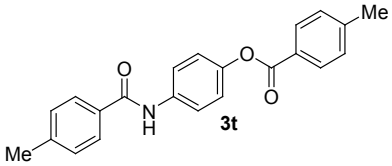
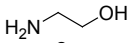
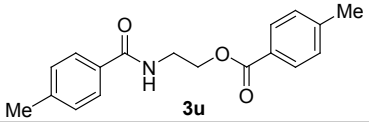
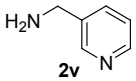
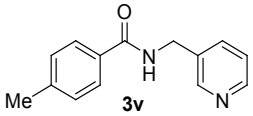
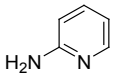
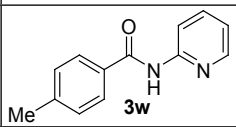
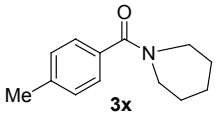
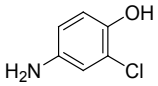
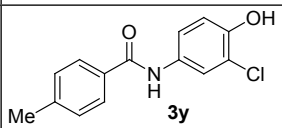
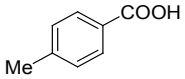
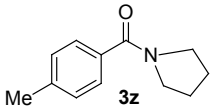
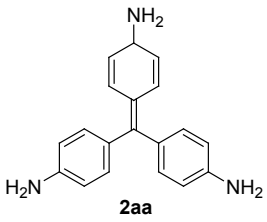
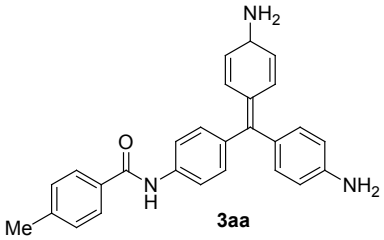
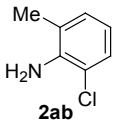
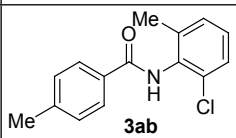
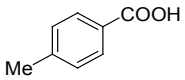
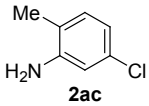
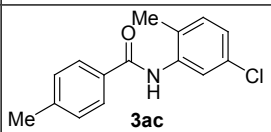
with **4-methylbenzoic acid (Table** 2, **entries** 1-29). The amines (**2a-2z, 2aa, 2ab** and **2ac**) bearing electron–donating substituents such as –Me, –OMe, –Et, butyl, *i*-Pr, N–Me, –H with **4-methylbenzoic acid 1a** and afforded the desired products **3b, 3d, 3j, 3k, 3l, 2m, 3n, 3p, 3q** and **3r** in yields 85–90.7% (**Table** 2). Where as aromatic bearing ~~with~~ electron withdrawing groups like, $–NO_2$ substituted amine provided the desired products **3h** comparatively in lower yield 62 % (**Table** 2, **entry** 8), this may be due to the reduced necluophility at the proximal end of the amine moiety thereby reducing the efficiency of the desired coupling. Amine having both electron donating as well as strong electron withdrawing groups these coupling products **3c, 3e, 3f** and **3g** gave yield 62–74.5 % (**Table** 2). Amines having both –OH and $–NH_2$ group compounds **2t** and **2u** chemoselective coupling between hydroxy and amine with acid to gave compound **3t** and **3u** with yield 45.5% and 42.5 % respectively (**Table** 2). Aromatic Amine having both electron donating as well as electron withdrawing group (**–Cl**) these coupling products **3a, 3y, 3ab** and **3ac** gave yield 45–68 % (**Table** 2). Whereas amine (**2o**) with 4-methyl benzoicacid coupling product **3o** gave yield 86.1% (**Table** 2). Aromatic amine bearing moderate electron with group (**–Br**) coupling with acid **1a** gave yield 65% (**Table** 2). Whereas dye compound no coupling with acid **1a** (**Table**2, **Entry** 27). Aromatic heterocyclic amines **2s, 2w** coupling with acid **1a** gave products **3s, 3w** respectively with yield 53.9 % and 63.8 % (**Table**2). Whereas heterocyclic amines **2x** and **2z** coupling with 4-methyl benzoicacid **1a** gave products **3x** and **3z** with yield 73.8% and 80.6% respectively (**Table** 2).

Table 2. Synthesis of *N*-aryl, alkyl and *N*-heterocycle benzamide derivatives.[a]



Entry	substrate	amine	product	Yield [b]	m.p.[c]
1				68%	161–162 °C
2	1a			90.3%	146–147 °C
3	1a			71.92%	85–86 °C
4	1a			85.52%	122–123 °C
5				74.5%	145–146 °C

6	 **1a**	 **2f**	 **3f**	73.1%	168–169 °C
7	**1a**	 **2g**	 **3g**	62%	151–152 °C
8	**1a**	 **2h**	 **3h**	62%	200–202 °C
9	**1a**	 **2i**	 **3i**	65%	-
10	**1a**	 **2j**	 **3j**	88.1%	158–159 °C
11	**1a**	 **2k**	 **3k**	89%	165–166 °C
12	**1a**	 **2l**	 **3l**	90.7%	133–135 °C
13	**1a**	 **2m**	 **3m**	88.4%	143–144 °C
14	**1a**	 **3n**	 **3n**	89%	-
15	**1a**	 **3o**	 **3o**	86.1%	69–70 °C
16	**1a**	 **2p**	 **3p**	86%	149–150 °C
17	**1a**	 **2q**	 **3q**	89.8%	137–138 °C
18	 **1a**	 **2r**	 **3r**	90.7%	143–144 °C

19	**1a**	 **2s**	 **3s**	53.9%	125–126 °C
20	**1a**	 **2t**	 **3t**	45.5%	195–196 °C
21	**1a**	 **2u**	 **3u**	42.5%	-
22	**1a**	 **2v**	 **3v**	65%	-
23	**1a**	 **2w**	 **3w**	63.8%	-
24	**1a**	 **2x**	 **3x**	73.8%	35–37 °C
25	**1a**	 **2y**	 **3y**	59.0%	-
26	 **1a**	 **2z**	 **3z**	80.6%	90–91 °C
27	**1a**	 **2aa**	 **3aa**	-	-
28	**1a**	 **2ab**	 **3ab**	45.0%	-
29	 **1a**	 **2ac**	 **3ac**	60%	-

[a] Reaction were performed using 1.0 equiv. of acid **1a**, 0.95 equiv. of amine **(2a–2ac)**, TEA (3.0 equiv.) in THF as solvent under N_2 atmosphere; [b] Isolated yields; [c] melting points. '-' means no product formed.

Biological activities

Anticancer activity: The *in vitro* anticancer activities of compounds **3a, 3c, 3d, 3e, 3f** and **3g Figure 1** were determined against the human breast cancer MCF-7 cell lines at four dosage levels of 10, 20, 40 and 80 µg/mL in DMSO. A test consisted of a 48 h continuous drug exposure protocol using SRB assay to estimate cell growth. Suitable positive controls were run in every experiment. Each experiment was repeated in triplicate, and growth relative to the control was plotted as a function of drug concentration (**Figure 2**) to calculate numerous parameters.

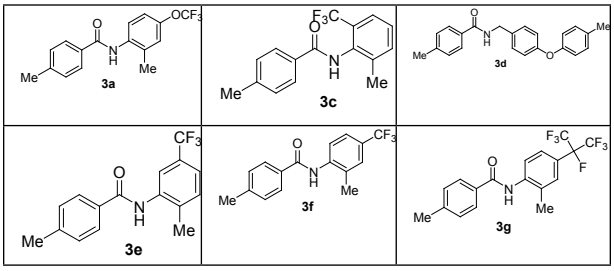


Figure 1. Screening molecules for anticancer activity

Results are given in terms of GI_{50} (concentration of drug that produces 50% inhibition of the cell), TGI (concentration of the drug that produces total inhibition of the cells) and LC50 (concentration of the drug that kills 50% of the cells) values calculated from the mean graphs (**Fig.** 2) and are given in **Table** 3. Adriamycin (ADR), which is chemotherapy drug often used to kill cancerous cells, was used as the standard anticancer drug. Reported parameters are given in **Table** 3. The compounds which have GI_{50} values of <10 µg/mL were considered to demonstrate anticancer activity against MCF-7 cell line. The GI_{50} of each pyrazole carboxamide against the MCF-7 cell line exceeded 80 µg/mL, hence these *N*-aryl/alkyl benzamide derivatives were found to inactive; in contrast, ADR showed a better result (GI_{50} ~**21.6** µg/mL).

In general the LC_{50}, which is a parameter of cytotoxicity and reflects the molar concentration needed to kill 50% of the cells, was found to exceed 80 µg/mL for the benzamide derivatives as well as ADR for the MCF-7 cell line. Thus, it can be concluded that benzamide derivative **3d** compound showing good activity due to benzyl part showed good activity because rest of the 4-Me-phenyl group is there in all selected molecules.

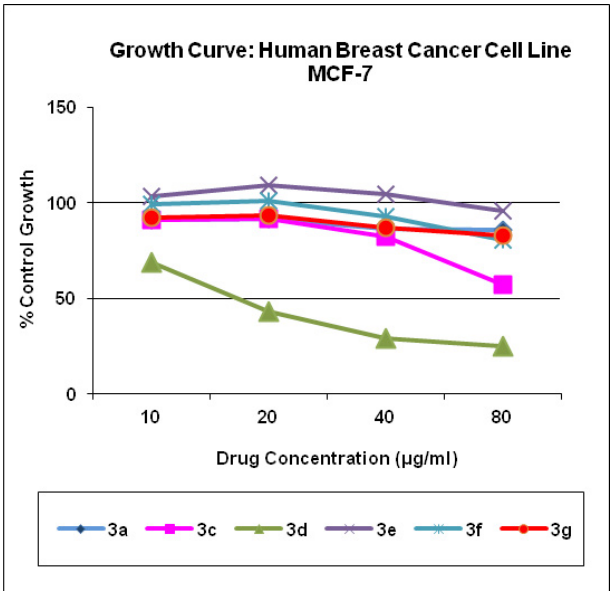


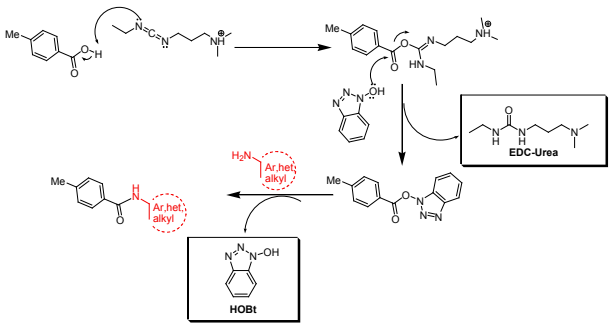
Fig. 2 MCF-7 cell line growth as a percentage as a percentage of the control *versus* drug (benzamide derivative and ADR) concentration.

Table 3. *In vitro* testing expressed as growth inhibition of human breast cancer cell line MCF-7 by *N*–aryl/alkyl benzamide derivatives [a]

MCF-7			
N-aryl/alky benzamide derivatives	LC_{50}*	TGI*	GI_{50}*
3a	>80	>80	>80
3c	>80	>80	>80
3d	>80	>80	**21.6**
3e	>80	>80	>80
3f	>80	>80	>80
3g	>80	>80	>80
ADR	62.5	<10	<10

[a] Data represents mean of three replicates for each concentration DMSO was used as solvent. *LC_{50} = Concentration of drug causing 50% cell kill. *GI_{50} = Concentration of drug causing 50% inhibition of cell growth. TGI = Concentration of drug causing total inhibition of cell growth. *ADR = Adriamycin, Positive control compound. GI_{50} value of ≤ 10 µg/mL is considered to demonstrate anticancer against MCF-7 cell line.

Plausible mechanistic pathways



Conclusion

In conclusion, we have developed excellent reaction methodology for the synthesis of substituted *N*-aryl/heterocyclic/alkyl benzamide derivatives with high molecular complexity in good to excellent yields and their characterization was done by using ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, IR and mass spectroscopy and these synthesized compounds were screened for anticancer activity. Among these *N*-(4-(p-tolyloxy)benzyl)-4-methylbenzamide **3d** compound showing good anticancer activity against MCF-7 cell line compare to standard ADR. This protocol is efficiently developed 1-hydroxy benzotriazole mediated peptide coupling of *N*-aryl/heterocyclic/alkyl benzamides derivatives. Owing to the great skeletal diversity of substitution pattern, this developed chemistry is potentially attractive for the synthesis of libraries of bioactive *carboxamide* derivatives compounds by using peptide chemistry.

Experimental section

General

^{1}H NMR (400 MHz), ^{19}F NMR (376 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$/DMSO-d_6. Chemical shifts for carbons are reported in ppm from TMS and are referenced to the carbon resonance of the solvent. Data are reported as follows: chemical shift, multiplicity (s = singlet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet), coupling constants in Hertz, and integration. Mass spectra were recorded with electrospray mass spectrometer. FTIR spectra were recorded with a Perkin Elmer spectrum 65 FTIR spectrometer using KBr pellets, and characteristic wave numbers are given in cm^{-1}. TLC analysis was performed on commercially prepared 60 F_{254} silica gel plates and visualized by either UV irradiation or by staining with I_2 and ninhydrin stain. All purchased chemicals were used as received. All melting points are done by using M-565, Buchi melting point apparatuses and are uncorrected.

Anticancer activity

In *vitro* anticancer activities of synthesized compounds were investigated at Anticancer Drug Screening Facility, Tata Memorial Advanced Centre for Treatment, Research and Education in Cancer (ACTREC) Kharghar, Navi Mumbai, India.

The *in vitro* anticancer activity of compounds **3a, 3c, 3d, 3e, 3f** and **3g** were performed on the breast cancer cell line MCF-7 at four dose levels 10,20, 40 and 80 µg/L in DMSO, the test consisted of 48 h continuous drug exposure protocol using sulforhodamine B (SRB) assay to estimate cell growth.[10] This assay relies on the uptake of the negatively charged pink aminoxanthine dye, sulforhodamine B (SRB) by basic amino acids in the cells. The greater the number of cells, the greater amount of dye

is taken up and, after fixing, when the cells are analyzed, the released dye gives a greater absorbance. The SRB assay was found to be more reliable, sensitive, simple, reproducible and more rapid than the formazan-based assay and gives better results.[13]

General procedure for the synthesis of Carboxamides

The starting materials were prepared by reported procedure. The structure and purity of known materials were confirmed by comparison of their physical and spectral data (^{1}H NMR and ^{13}C NMR) with those reported in literature.

A solution of (0.3 g, 2.203 mmol) 4-methylbenzoic acid in 10 mL of THF was treated sequentially with (0.354 g, 2.313 mmol) of HOBT, (0.359 g, 2.313 mmol) of EDC. HCl and (0.441 g, 2.313 mmol) of aniline. The suspension was stirred for 15 min at 5 °C, (0.93 mL, 6.609 mmol) of TEA was added, and the mixture stirred for 8-10 h at r.t.; The reaction was quenched by pouring into 50 mL of ethyl acetate and extracting with 30 mL of 1N aq. HCl, 20 mL of water, 10 mL of brine, 20 mL of saturated aqueous $NaHCO_3$ and finally washed with 10 mL of brine. The solution was then dried over Na_2SO_4, filters and concentrated under reduced pressure. The crude material was purified by column chromatography on silicagel (15 g, 20:80 ethyl acetate/hexanes) to provide 0.98 g of product as off-white solid.

Characterization of representative 4-methyl-*N*-(2-methyl-4-(trifluoromethoxy)phenyl) benzamide (3t):

4-methyl-*N*-(2-methyl-4-(trifluoromethoxy) phenyl)benzamide **(3t)** was synthesized by **4-methylbenzoic acid** with 2-methyl-4-(trifluoromethoxy)benzenamine in presence of base and peptide coupling reagents. The product was obtained as a colorless needles in 68% yield with m.p. 161–162 °C. The structure of compound **3t** was established on the basis of spectral data analysis. In the ^{1}H NMR spectrum in DMSO-d_6 at 400 MHz, the characteristic peak of amide linkage proton appeared at δ 9.88 ppm, a singlet appeared at δ 2.38 ppm and δ 2.26 ppm corresponds to –Me of phenyl ring respectively and also the proton of amide linkage further confirmed by DMSO-d_6 with D_2O exchange it is disappered. Similarly in the ^{13}C NMR spectrum (CDCl3, 100 MHz), the characteristic peak corresponds to carbonyl (C_a) attched to –NH group of phenyl appeared at δ 168.90, another carbon corresponds to corbonyl attched phenyl ring appears at δ 134.60 ppm and carbon corresponds to –NH group attched to phenyl appears at δ 131.89 ppm respectively confirmed the coupling of 4-methylbenzoic acid with amine of 2-methyl-4-(trifluoromethoxy) benzenamine. The ^{19}F NMR spectrum ($CDCl_3$, 376 MHz), the characteristic peak corresponds to $–CF_3$ of phenyl ring appears at δ –57.90 ppm. The peaks of all other protons, carbon and flourine of the molecules were presented in ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra of the molecule. Its resolution mass specturm showed $[M+H]^+$ peak at 309.0976, which confirmed its molecular formula to be $C_{16}H_{14}F_3NO_2$.

4-Methyl-*N*-phenyl benzamide(3b): The product was obtained as white needles (420 mg, 90.3% yield); m.p. 146-147 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.78 (d, J = 8.30 Hz, 2H,), 7.35–7.52 (m, 5H), 7.22 (d, J = 8.17 Hz, 2H), 2.43 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.2, 120.4, 127.6, 128.9, 129.5, 131.5, 134.5, 135.9, 134, 165.9 ppm. HRMS (ESI): calcd. for $C_{14}H_{13}NO$ $[M+H]^+$ 211.0997; found 212.1002.

***N*-(2-(trifluoromethyl)-6-methylphenyl)-4-methylbenzamide(3c)**: The product was obtained as white needles (797 mg, 71.9% yield); m.p. 86–87 °C. ^{1}H NMR (400 MHz, DMSO–d_6): δ 9.88 (s, 1H), 7.89 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.8 Hz, 1H), 7.30-7.35 (m, 3H),

7.22 (d, *J* = 8 Hz, 1H), 2.38 (s, 3H), 2.26 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.81, 21.49, 120.38, 121.83, 127.19, 128.17, 131.01, 131.37, 134.05, 138.47, 142.80, 166.10 ppm. HRMS (ESI): calcd. for $C_{16}H_{14}F_3NO$ $[M+H]^+$ 293.1027; found 294.1029. IR (KBr, cm^{-1}): ν_{max}= 36177, 2925, 1654, 1520, 1396, 1032.

***N*-(4-(p-tolyloxy)benzyl)-4-methylbenzamide(3d)**: The product was obtained as white needles (1.04 g, 85.52% yield); m.p. 122–123 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 8.0, 2.0 Hz, 2H), 7.14 (d, *J* = 8.4, 2.0 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.33 (br s, 1H), 4.60 (d, *J* = 5.6 Hz, 2H), 2.39 (s, 3H), 2.33 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO–d_6): δ 20.24, 20.94, 39.73, 118.16, 118.56, 127.26, 128.83, 128.91, 130.35, 132.40, 134.58, 141.08, 154.46, 155.88, 166.0 ppm.HRMS (ESI): calcd. for $C_{22}H_{21}NO_2$ $[M+H]^+$ 331.1572; found 332.1573. IR (KBr, cm^{-1}): ν_{max}= 3618, 2923, 1632, 1524, 1394, 1059.

***N*-(5-trifluoromethyl)-2-methylphenyl)-4-methylbenzamide(3e)**: The product was obtained as white needles (803 mg, 74.5 % yield); m.p. 145–146 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 7.79 (d, *J* = 8 Hz), 7.71 (s, 1H), 7.37 (d, *J* = 9.6 Hz, 2H), 7.32 (d, *J* = 7.6 Hz, 2H), 2.44 (s, 3H), 2.39 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.83, 21.48, 120.39, 121.81, 127.18, 128.15, 130.91, 131.36, 134.01, 138.37, 142.78, 166.06 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ –62.25 ppm HRMS (ESI): calcd. for $C_{16}H_{14}F_3NO$ $[M+H]^+$ 293.1027; found 294.1029. IR (KBr, cm^{-1}): ν_{max}= 36178, 2926, 1656, 1521, 1395, 1033.

***N*-(4-(trifluoromethyl)-2-methylphenyl)-4-methylbenzamide(3f)**: The product was obtained as white needles (810 mg, 73.1% yield); m.p. 168–169 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, *J* = 8.8 Hz, 2H), 7.79 (d, *J* = 8 Hz, 3H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.47 (s, 1H), 7.32 (d, *J* = 8 Hz, 2H), 2.44 (s, 3H), 2.39 (s, 3H) ppm^{13}C NMR (100 MHz, $CDCl_3$): δ 17.85, 21.56, 120.36, 121.79, 127.19, 128.27, 131.24, 131.47, 134.10, 138.26, 142.80, 166.09 ppm. HRMS (ESI): calcd. for $C_{16}H_{14}F_3NO$ $[M+H]^+$ 293.1027; found 294.1029. IR (KBr, cm^{-1}): ν_{max}= 36174, 2923, 1651, 1522, 1394, 1034.

4-methyl-*N*-(2-methyl-4-(perfluoropropan-2-yl)phenyl)benzamide(3g): The product was obtained as white needles (893.5 mg, 62% yield); m.p. 150–151 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, *J* = 8.8 Hz, 1H), 7.79 (d, *J* = 8 Hz, 2H), 7.74 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.45 (s, 1H), 7.33 (d, *J* = 8 Hz, 2H), 2.44 (s, 3H), 2.40 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO–d_6): δ 18.02, 21.032, 126.80, 127.18, 127.80, 129.01, 131.31, 134.53, 139.86, 141.91, 165.34 ppm. HRMS (ESI): calcd. for $C_{18}H_{14}F_7NO$ $[M+H]^+$ 393.0964; found 394.0997. IR (KBr, cm^{-1}): ν_{max}= 3617, 2925, 1657, 1520, 1394, 1034.

4-Methyl-*N*-*p*-tolylbenzamide(3j): The product was obtained as a white needles (752 mg, 88.1% yield); m.p. 158–160 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.73 (d, *J* = 8.7 Hz, 2H,), 7.51 (d, J = 8.7 Hz, 2H), 7.21 (d, *J* = 8.2 Hz, 2H), 7.12 (d, J = 8.2 Hz, 2H), 2.38 (s, 3H), 2.31 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8, 21.4, 120.3, 127.0, 129.2,129.4,132.1, 133.9, 135.4, 142.0, 165.7 ppm. HRMS (ESI): calcd. for $C_{15}H_{15}NO$ $[M+H]^+$ 225.1154; found 226.1159.

***N*-(2-ethyl-6-methylphenyl)-4-methylbenzamide(3k)**: The product was obtained as white needles (828 mg, 89% yield); m.p. 165–166 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.0 Hz, 2H), 7.36 (br s, 1H), 7.31 (d, *J* = 8.0 Hz, 2H,), 7.13–7.22 (m, 3H), 2.66 (q, *J* = 7.6 Hz, 2H), 2.44 (s, 3H), 2.28 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO–d_6): δ 14.51, 18.07, 21.024.49, 126.05, 126.93, 127.51,

127.67, 128.95, 131.60, 136.02, 165.26 ppm. HRMS (ESI): calcd. for $C_{17}H_{19}NO$ $[M+H]^+$ 253.1467; found 254.1468. IR (KBr, cm^{-1}): ν_{max} = 3619, 2925, 1636, 1525, 1396, 1058.

***N*-isopropyl-4-methylbenzamide(3l)**: The product was obtained as white needles (519 mg, 90.7% yield); m.p. 134–135 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 5.87 (br s, 1H), 4.30 (septet, *J* = 7.0 Hz, 1H), 2.38 (s, 3H), 1.26 (d, *J* = 6.4 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 141.8, 132.3, 129.3, 127.0, 42.0, 23.1, 21.6 ppm. HRMS (ESI): calcd. for $C_{11}H_{15}NO$ $[M+H]^+$ 177.1154; found 178.2428.

***N*-benzyl-4-methylbenzamide(3m)**: The product was obtained as white needles (754 mg, 89% yield); m.p. 133–135 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.1 Hz, 2H), 7.70-7.18 (m, 7H), 6.61 (br s, 1H), 4.58 (d, *J* = 5.7 Hz, 2H), 2.37 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 141.8, 138.3, 131.5, 129.1, 128.7, 127.8, 127.4, 126.9, 44.0, 21.4 ppm. HRMS (ESI): calcd. for $C_{15}H_{15}NO$ $[M+H]^+$ 225.1154; found 226.2834.

4-methyl-*N*-(2-methyl-1-(methylthio) propan-2-yl)benzamide(3o): The product was obtained as cream white needles (750 mg, 86.1% yield); m.p. 69–70 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 6.16 (br s, 1H), 3.05 (s, 1H), 2.38 (s, 3H), 2.14 (s, 3H), 1.51 (s, 6H) ppm. ^{13}C NMR (100 MHz, DMSO–d_6): δ 16.84, 20.94, 26.56, 43.53, 54.28, 127.41, 128.57, 132.80, 140.68, 166.45 ppm. HRMS (ESI): calcd. for $C_{13}H_{19}NOS$ $[M+H]^+$ 237.1187; found 238.1189. IR (KBr, cm^{-1}): ν_{max} = 3619, 2925, 2369, 1657, 1520, 1317, 1034.

***N*-benzyl-*N*,4-dimethylbenzamide(3p)**: The product was obtained as a white needles (755 mg, 86 %yield); m.p. 149–150 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20-7.42 (m, 9H), 4.78 (s, 1H), 4.55 (s, 1H), 3.05 (s, 1.5H), 2.37 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 172.1, 140.0, 139.7, 137.3, 136.9, 133.4, 129.3, 120.0, 128.9, 128.4, 127.7, 127.3, 127.1, 126.9, 122.4, 119.1, 55.4, 51.1, 37.3, 33.5, 21.6 ppm. HRMS (ESI): calcd. for $C_{16}H_{17}NO$ $[2M+Na]^+$ 501.2601; found 502.4732

***N*,4-dimethylbenzamide(3r)**: The product was obtained as white needles (519 mg, 90.7% yield); m.p. 143–145 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 6.13 (br s, 1H), 3.0 (d, *J* = 4.8 Hz, 3H), 2.36 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.14, 141.68, 131.77, 129.17, 126.78, 26.75, 21.39 ppm. HRMS (ESI): calcd. for $C_9H_{11}NO$ $[M+H]^+$ 149.0841; found 150.1871.

4-methyl-*N*-(pyridin-3-yl)benzamide(3s): The product was obtained as white needles (420 mg,53.9% yield); m.p. 126–127 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (s, 1H), 7.82 (d, *J* = 8 Hz, 2H), 7.72 (d, *J* = 8 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.36 (m, 1H), 7.25 (d, *J* = 8 Hz, 2H), 2.36 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.96, 145.40, 142.96, 141.39, 131.30, 129.58, 127.51, 127.08, 123.78, 21.53 ppm. HRMS (ESI): calcd. for $C_{13}H_{12}N2O$ $[M+H]^+$ 212.095; found 213.1859.

4-methyl-*N*-(pyridin-2-yl)benzamide(3w): The product was obtained as light brown needles (490 mg,63.8% yield); m.p. 105–106 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (br s, 1H), 8.37 (dd, *J* = 8.4, 0.6 Hz, 1H), 8.20 (m, 1H), 7.80 (m, 1H), 7.71 (m, 1H), 7.25 (d, *J* = 7.8 Hz, 2H), 7.01 (m, 1H), 2.39 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 151.7, 147.8, 142.7, 138.4, 131.4, 129.4, 127.2, 119.7, 114.2, 21.4 ppm. HRMS (ESI): calcd. for $C_{13}H_{12}N2O$ $[M+H]^+$ 212.095; found 213.1859.

(piperidin-1-yl)(*p*-tolyl)methanone(3x): The product was obtained as light yellow oil (566.8 mg, 73.8% yield); ^{1}H NMR (400 MHz, $CDCl_3$):

δ 7.29 (d, *J* = 8 Hz, 2H), 7.19 (d, *J* = 8 Hz, 2H), 3.68 (d, 2H), 3.34 (d, 2H), 1.79–1.511 (br m, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 139.5, 133.7, 129.1, 127.0, 48.9, 43.3, 26.7, 25.9, 24.8, 21.5 ppm. HRMS (ESI): calcd. for $C_{13}H_{17}NO$ $[M+H]^+$ 203.131; found 204.2831.

***N*-(3-chloro-4-hydroxyphenyl)-4-methylbenzamide(3y)**: The product was obtained as White needles (390 mg, 59.0% yield)); m.p. 217–218 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.07 (br s, 1H), 9.97 (s, 1H), 7.84 (d, *J* = 8 Hz, 1H), 7.52 (dd, *J* = 9.0 Hz, 1H), 7.31-7.87 (dd, *J* = 8.1 Hz, 4H), 6.95 (d, *J* = 8.7 Hz, 1H), 2.38 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 165, 149.3, 141.5, 132.0, 128.9, 127.6, 122.0, 120.5, 119.0, 116.4, 21.0 ppm. HRMS (ESI): calcd. for $C_{14}H_{12}ClNO_2$ $[M+H]^+$ 261.0557; found 262.7153.

(pyrrolidine-1-yl)(*p*-tolyl)methanone(3z): The product was obtained as light yellow needles (560.5 mg, 80.6% yield)); m.p. 90–91 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8 Hz, 2H), 7.18 (d, *J* = 7.6 Hz, 2H), 3.64 (t, *J* = 6.8 Hz, 2H), 3.44 (t, *J* = 6.8 Hz, 2H), 1.97 (m, 2H), 1.86 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 139.8, 134.3, 128.8, 127.2, 49.6, 46.2, 26.4, 24.4, 21.4 ppm. HRMS (ESI): calcd. for $C_{12}H_{15}NO$ $[M+H]^+$ 189.1154; found 190.2378.

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References

1. J. R. Dunetz, J. Magano, G. A. Weisenburger, *Org. Process Res. Dev.* **2016**, 20, 140-177; (b) Y. Zhu, P. Mampuys, S. Sergeyev, S. Ballet, B. U. W. Maes, *Advan synth catal* **2017**, 359, 17, 2481-2498.
2. Elguero, J.; Goya, P.; Jagerovic, N.; Silva, A. M. S. Targets *Heterocycl. Syst*. **2002**, 6, 52.
3. Lamberth, C. *Heterocycles* **2007**, 71, 1467.
4. A.K. Ghose, V. N. Viswanadhan and J. J. Wendoloski, *J. Comb. Chem.,* **1999**, 1, 55–68.
5. J. S. Carey, D. Laffan, C. Thomson and M. T. Williams, *Org. Biomol. Chem.,* **2006**, 4, 2337–2347.
6. S. D. Roughley and A. M. Jordan, *J. Med. Chem.,* **2011**, 54, 3451–3479.
7. T. J. Deming, *Prog. Polym. Sci.,* **2007**, 32, 858–875.
8. A. P. Wight and M. E. Davis, *Chem. Rev.*, **2002**, 102, 3589-3614.
9. V. R. Pattabiraman and J. W. Bode, *Nature*, **2011**, 480, 471-479.
10. C. Zimmer , *Bioorg. Med. Chem. Lett.* **2011**, 21, 186–190
11. H. S. Baek, *Bioorg. Med. Chem. Lett*. **2012**, 22, 2110–2113
12. P. Houghton, R. Fang, I. Techatanawat, G. Steventon, P. J. Hylands, C. C. Lee, *Methods*, **2007**, 42, 377-387.
13. V. R. Solomon, C. Hu and H. Lee, *Bioorg.Med. Chem*. **2009**, 17, 7585-7592.