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Process optimization for acid-amine coupling: a catalytic approach

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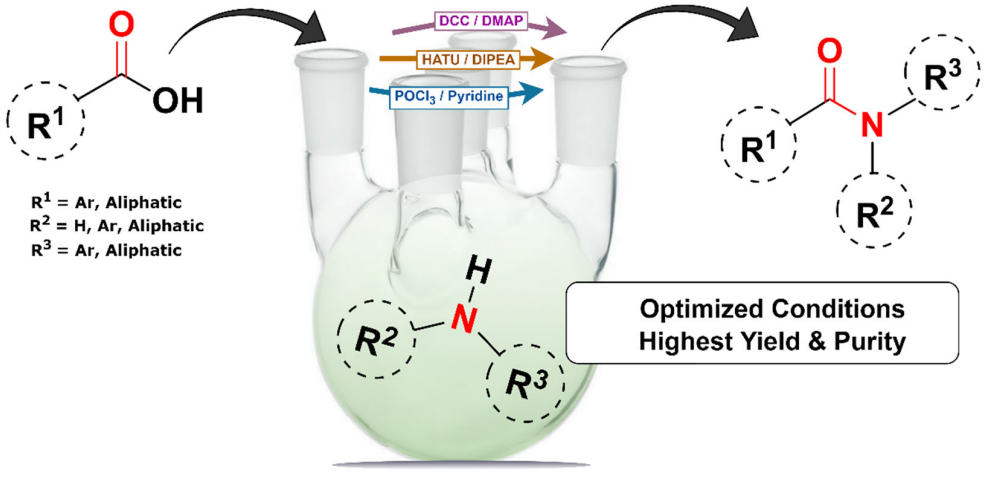
Proficient routes were devised for coupling different aromatic/aliphatic acids with amines to form amide linkage using various catalysts. Under the optimized reaction conditions, highest conversion was possible without formation of any by-products. All synthesized compounds were purified using column chromatography and characterized by mass spectrometry, nuclear magnetic resonance spectrometry and liquid chromatography-mass spectrometric analysis.



Graphical Abstract

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List of all the Abbreviations

DCC = *N*,*N*′-Dicyclohexylcarbodiimide
DIC = *N*,*N*′-Diisopropylcarbodiimide
EDC = *N*-Ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide
HATU = Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium
DIPEA = *N*,*N*-Diisopropylethylamine
NMR = Nuclear Magnetic Resonance
DMAP = 4-Dimethylaminopyridine
DMF = *N*,*N*-Dimethylformamide
RT = Room Temperature
THF = Tetrahydrofuran
DCM = Dichloromethane
LCMS = Liquid Chromatography-Mass Spectrometry
TMS = Tetramethylsilane
DMSO = Dimethylsulfoxide
ESI = Electrospray Ionization
EI = Electron Ionization
TLC = Thin Layer Chromatography

1. Introduction

The amide coupling is one of the most widely used reactions in the field of medicinal chemistry. The most common procedure to form the amide bond is the condensation of a carboxylic acid with an amine. Synthesis of amide occurs by coupling an amine with a carboxylic acid either in presence of an acid activating reagent or through a suitable catalyst.[1] Due to higher stability, the amide bonds are found in various pharmaceutical products[2], natural products[3], peptides[4], polymers[5], and food additives[6]. Several top-selling drugs such as lenalidomide, apixaban, rivaroxaban, penicillin, paracetamol, atorvastatin, etc. possess amide linkage (**Fig. 1**).[7] Due to plethora of readily available carboxylic acids and amine derivatives there is an unlimited scope to prepare novel compounds with unique medical properties.

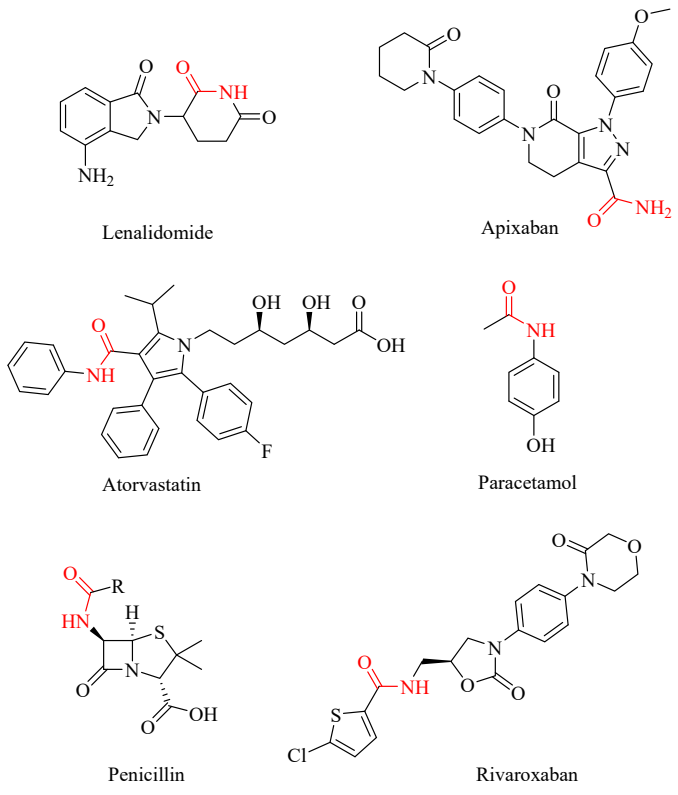


Fig. 1. Several top-selling drugs containing amide bond

Nearly infinite assemblies of reagents and protocols have been established to facilitate easy transformations of amide bonds from amines and acids followed by many coupling-reactions[8-13] for synthesis of potent bio-active molecules. Amides are eternally synthesized through formation of active fragment/moiety of carboxylic acid such as generation of acyl halide,

acyl imidazole, acyl azide, anhydride and active ester followed by aminolysis process.[14-17] The significant concern is that many of the reported coupling reagents have not been related to others, and hence it is challenging for factual evaluation. However, it is important to select the coupling reagent and bases for individual types of acids and amines.

In this context, we report substantial progress in this field and address the significance of catalysts for the synthesis of amides. Recently, favourable acid-amine coupling reagents such as carbodiimides (DCC, DIC, EDC), phosphonium and aminium salts, acyl halide have been used with suitable bases (**Fig. 2**).[18-20] HATU (Hexafluorophosphate azabenzotriazole tetramethyl uronium) is a well-known reagent that reacts to produce an active ester intermediate from carboxylic acid. Further, addition of an amine in the presence of suitable base such DIPEA (*N,N*-Diisopropylethylamine) or triethylamine can lead to the formation of amide bonds.[21-23]

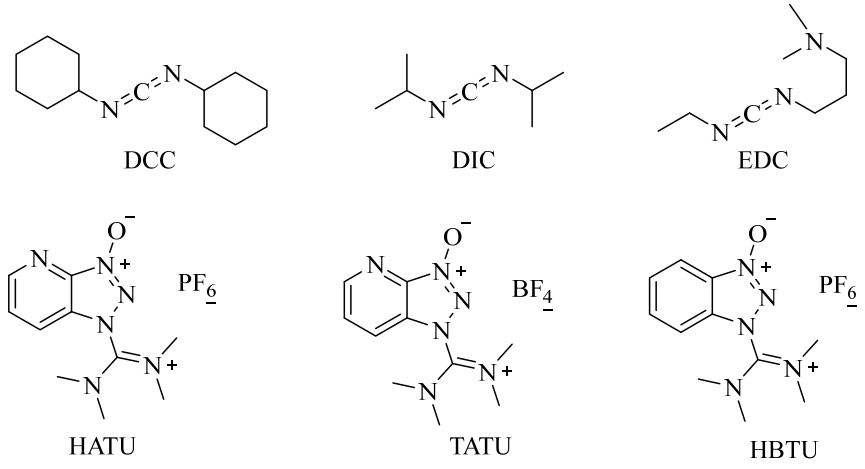
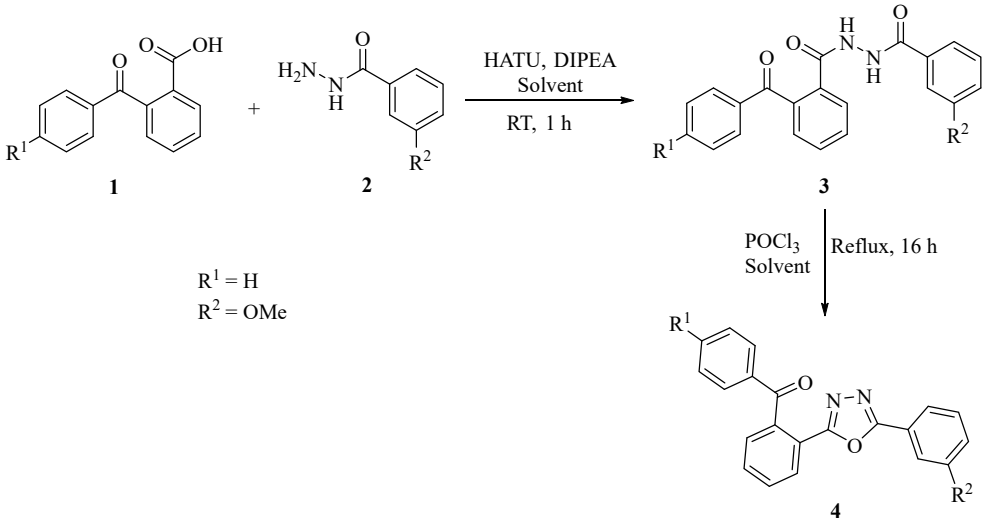


Fig. 2 - Carbodiimides, Uronium-based coupling reagents

Moreover, amide can be derived by generating acyl chlorides from an acid using phosphorus oxychloride ($POCl_3$) or thionyl chloride ($SOCl_2$) at low temperature, followed by addition of desired amine in the presence of pyridine as a suitable base.[24,25] Our study depicts a protocol for amidation by using simple and easily available catalysts and bases which is efficient for diverse substrates. Major product conversion could enhance the synthetic approach from milligram to pilot scale of title synthesis.

2. Results and Discussion

2-Benzoylbenzoic acid **1** reacted with 3-methoxybenzohydrazide **2** in presence of HATU catalyst and poor nucleophile DIPEA to give 2-benzoyl-*N*'-(3-methoxybenzoyl)benzohydrazide **3**. After stirring at ambient temperature for 1 h, white precipitation was observed. The structure of the desired product is confirmed by NMR analysis. Singlet peak of three protons at δ 3.786 ppm clearly indicates the presence of a methoxy group in **3**. Other coupling reagents with suitable bases such $POCl_3$/pyridine, DCC/DMAP were tried, but the reactants were not totally consumed even up to 48 h. The results of all the trials conducted for method optimization in addition to HATU are summarized in **Table 1**.



Scheme 1 - Synthesis of compound **3** & **4**

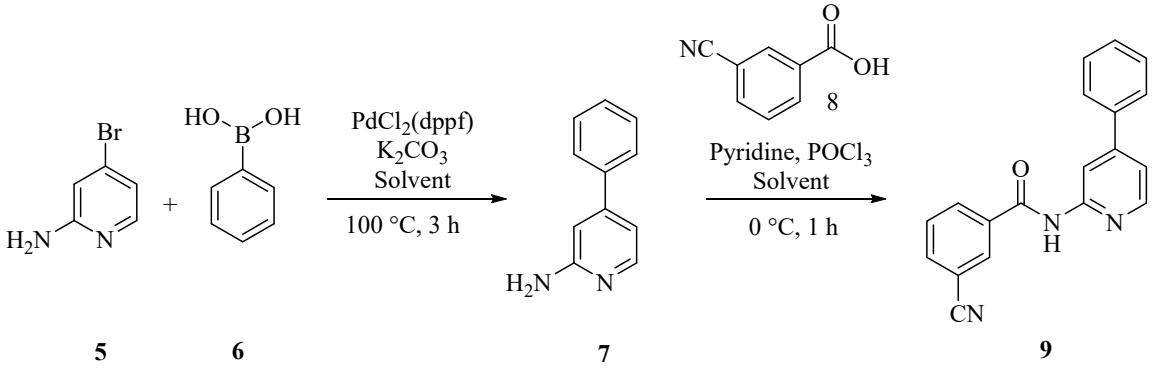
Further, 2-benzoyl-*N'*-(3-methoxybenzoyl)benzohydrazide **3** was heated with $POCl_3$ in DMF solvent for 16 h to produce novel oxadiazol derivative **4**. After the completion of reaction, the colour of the reaction mixture converted from pale-yellow to dark blue. The product obtained was purified by column chromatography. Singlet peak corresponding to three hydrogens at δ 3.8 ppm in NMR data clearly indicates the presence of methoxy group in (2-(5-(3-methoxyphenyl)-1,3,4-oxadiazol-2-yl)phenyl)(phenyl)methanone **4**. These protons were relatively deshielded due to the presence of oxadiazole nucleus (**Scheme 1**).

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

Entry	Catalyst	Base	Solvent	Temperature (°C)	Time (h)	Yield[z]
1	DCC	DMAP	DMF	90	24	45
2	DCC	DMAP	DCM	60	24	20
3	HATU	DMAP	THF	90	16	38
4	HATU	DIPEA	THF	RT	1	77
5	**HATU**	**DIPEA**	**THF**	**RT**	**1.5**	**92**
6	HATU	DIPEA	DMF	RT	12	20
7	$POCl_3$	Pyridine	DMF	RT	24	52
8	$POCl_3$	Pyridine	THF	0	24	61
9	$POCl_3$	DMAP	DMF	RT	24	30

[†]Reaction conditions: All the reactions were performed under nitrogen atmosphere with catalyst (1.5 eq.) and solvent (10 volume). [z]Yield of the isolated product. RT= Room temperature

2-Amino-4-bromopyridine **5** was reacted with phenylboronic acid **6** in presence of (1,1'-bis(diphenylphosphino)ferrocene)palladium(II) dichloride [$PdCl_2$(dppf)] catalyst and K_2CO_3 to produce 4-phenylpyridin-2-amine **7**. Initially, the colour of the solution turned light brown, which subsequently converted to dark brown colour upon heating. The purity was checked by LC-MS analysis. The purified intermediate **7** was brown in colour. Singlet peak corresponding to two hydrogens at δ 5.99 ppm in NMR spectra clearly indicates the presence of an amino group. Further, 4-phenylpyridin-2-amine **7** reacted with 3-cyanobenzoic acid **8** in presence of pyridine and $POCl_3$ to produce 3-cyano-*N*-(4-phenylpyridin-2-yl)benzamide **9** (**Table 2**). This could be due to the amino group at the second position of pyridine being unable to react easily with esters of 3-cyanobenzoic acid with HATU.



Scheme 2 - Synthesis of compound **7** & **9**

Initially, the colour of the solution turned light-yellow. However, after completion of the reaction in 1 h, a white coloured product **9** was obtained. The product was purified by column chromatography. A singlet at δ 11.195 ppm for one proton in NMR spectra clearly indicates the presence of a secondary amine group (**Scheme 2**).

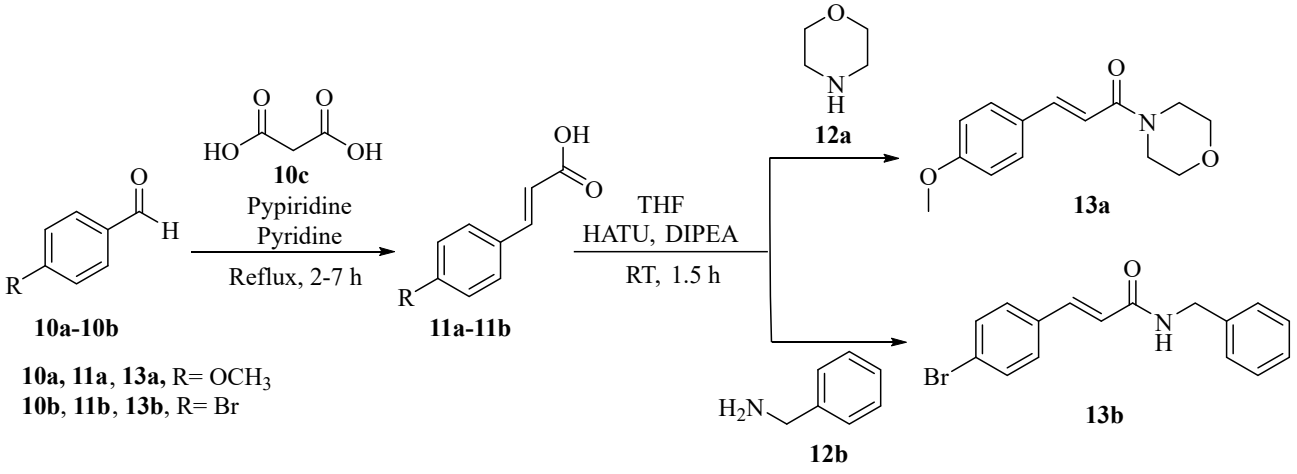
Table 2. Optimization of the reaction conditions[†]

Entry	Catalyst	Base	Solvent	Temperature (°C)	Time (h)	Yield[ǂ]
1	DCC	DMAP	DMF	90	24	21
2	DCC	DMAP	DCM	60	24	0
3	HATU	DMAP	THF	90	16	17
4	HATU	DIPEA	DMF	RT	12	60
5	HATU	DIPEA	THF	RT	24	57
6	HATU	DIPEA	THF	90	18	37
7	$POCl_3$	Pyridine	DMF	RT	20	34
8	**$POCl_3$**	**Pyridine**	**THF**	**0**	**5**	**87**
9	$POCl_3$	DMAP	DMF	RT	20	22

[†]Reaction conditions: All the reactions were performed under nitrogen atmosphere with catalyst (1.5 eq.) and solvent (10 volume). [ǂ]Yield of the isolated product. RT= Room temperature

The synthetic approach to prepare different α, β-unsaturated compounds using Doebner Modification[26] is profiled in **Scheme 3**. *p*-Methoxy and *p*-bromo cinnamic acid derivatives were prepared by condensing malonic acid **10c** with *p*-

methoxybenzaldehyde **10a** and *p*-bromobenzaldehyde **10b**, respectively. The progress of the reaction was monitored by analytical TLC. The *p*-bromo derivative required only 2 h for completion of the reaction as compared to 7 h for the *p*-methoxy derivative. This could be due to the electron withdrawing nature of bromine. Piperidine, which was used as an organocatalyst[27], facilitated pyridine-induced decarboxylation and elimination as observed in Knoevenagel condensation.



Scheme 3 - Synthesis of compound **13a** & **13b**

White precipitation was observed during the preparation of 4-methoxycinnamic acid **11a**. LC-MS data of **11a** endorsed maximum purity. Reaction of compound **11a** and **11b** with morpholine **12a** and phenylmethanamine **12b**, respectively in presence of HATU with DIPEA readily gave the final products **13a** and **13b,** respectively in quantitative yields. The colour of solution turned yellow after the addition of morpholine during the synthesis of 3-(4-methoxyphenyl)-1-morpholinoprop-2-en-1-one **13a**, and gave a yellow coloured product. The colour of solution become light brown during the synthesis of *N*-benzyl-3-(4-bromophenyl)acrylamide **13b**. However, the final colour of the product **13b** was white. Base peak and purity was checked by LC-MS analysis. The weak base (DIPEA) deprotonated the carboxylic acid to give carboxylate ion, which upon reaction with HATU gave an active ester, Further reaction with amines (compound **12a** & **12b**) gave respective amide products (compound **13a** & **13b**) (**Scheme 3**). In the case of morpholine **12a** and phenylmethanamine **12b** moiety the reaction was carried out using different reagents with suitable bases such as $POCl_3$/pyridine, DCC/DMAP, $SOCl_2$/pyridine, and HATU/DIPEA. However, the best results were obtained using HATU/DIPEA with no side products (**Table 3**).

Table. 3. Optimization of the reaction conditions[†]

Entry	Catalyst	Base	Solvent	Temperature (°C)	Time (h)	Yield[z]
1	DCC	DMAP	DMF	90	24	45
2	DCC	DMAP	DCM	60	24	20
3	HATU	DMAP	THF	90	16	38
4	HATU	DIPEA	THF	RT	1	77
5	**HATU**	**DIPEA**	**THF**	**RT**	**1.5**	**92**
6	HATU	DIPEA	DMF	RT	12	20
7	$POCl_3$	Pyridine	DMF	RT	24	52
8	$POCl_3$	Pyridine	THF	0	24	61
9	$POCl_3$	DMAP	DMF	RT	24	30

[†]Reaction conditions: All the reactions were performed under nitrogen atmosphere with catalyst (1.5 eq.) and solvent (10 volume). [z]Yield of the isolated product. RT= Room temperature

3. Conclusions

In summary, we have developed some facile and efficient protocols for the synthesis of some novel compounds (**4** & **9**) as well as newly reported molecules (**13a** & **13b**). We conclude that HATU catalyst is efficient for a diverse variety of carboxylic acid and aliphatic amines/hydrazide, frequently providing the desired product in good to excellent yield. Except in the case of compound 9, where the other methods failed to give satisfactory results, this catalyst was more suited for different types of reactions.

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4. Experimental

4.1. Materials and Methods

All solvents and compounds used in the study were purchased from Sigma-Aldrich, TCI, Spectrochem and used without further purification. Melting points of the synthesized compounds were determined in open capillary tubes and are uncorrected. The reactions were carried out at an appropriate temperature and the progress of reactions were checked by analytical TLC silica gel 60 F_{254} using different solvent systems for different reactions and the spot were visualized under ultraviolet light. The products were purified by column chromatography using 100-200 mesh size silica gel using ethyl acetate in *n*-hexane as the mobile phase. Synthesized compounds were characterized by ^{1}H NMR spectroscopy (400 MHz, Bruker) in DMSO-d_6 using tetramethylsilane (TMS) as an internal standard. Mass spectrometry was measured by analytical grade solvents (ESI method, Waters). Comparative purity of compounds was confirmed by LC-MS instrument (C-18 column, Agilent). Solvents were removed using Heidolph rotary evaporator.

4.2. Experimental procedure

4.2.1 Procedure for the synthesis of 2-benzoyl-N'-(3-methoxybenzoyl)benzohydrazide (**3**).

To a stirred solution of 2-benzoylbenzoic acid **1** (1 g, 4.42 mmol) in THF (15 mL), HATU (2.35 g, 6.18 mmol) was added at 0 °C in an ice bath and stirred for 10 min. Thereafter, the ice bath was removed and 3-methoxybenzohydrazide **2** (0.88 g, 5.30 mmol) and DIPEA (2.3 mL, 13.26 mmol) were added. The resulting mixture was then stirred for 1 h and progress of reaction was monitored by TLC. Upon completion of reaction, the reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (50 mL × 3). The organic phases were combined, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the desired product 2-benzoyl-*N'*-(3-methoxybenzoyl)benzohydrazide **3**. Yield 1.55 g (94%), white powder, mp: 174–176 ℃, Rf: 0.5 (EtOAc– *n*-hexane, 4:6). ^{1}H NMR spectrum, δ ppm (*J*, Hz): 10.43 (1H, s), 8.28–7.18 (14H, m), 3.78 (3H, s, OCH_3). Mass spectrum (EI), *m/z* (*I* rel, %): 375 $[M+H]^+$ (97), 343 $[M-OCH_3-H]^+$ (100).

4.2.2 Procedure for the synthesis of (2-(5-(3-methoxyphenyl)-1,3,4-oxadiazol-2-yl)phenyl)(phenyl)methanone (**4**).

Added $POCl_3$ drop by drop to the solution of 2-benzoyl- *N'*-(3-methoxybenzoyl)benzohydrazide **3** (1 g, 6.02 mmol) in DMF at 0-5 ℃. Removed the ice bath and stirred the resulting mixture for 16 h at 90 °C and progress of reaction was monitored by TLC. After the completion of reaction, the reaction mixture was bashed by the slow addition of sodium bicarbonate solution. The product was extracted with ethyl acetate (50 mL × 3). The combined organic extracts were washed with brine solution (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give desire product (2-(5-(3-methoxyphenyl)-1,3,4-oxadiazol-2-yl)phenyl)(phenyl) methanone **4**. Yield 0.44 g (46%), redish powder, mp: 150-151 °C, Rf: 0.4 (EtOAc– *n*-hexane, 1:1). ^{1}H NMR spectrum, δ ppm (*J*, Hz): 8.28–7.18 (13H, m, H Ar), 3.80 (3H, s, OCH_3). Mass spectrum (EI), *m/z* (*I* rel, %): 357 $[M+H]^+$ (100), 343 $[M-OCH_3-H]^+$ (100). LC-Mass spectrum (EI), *m/z* (*I* rel, %): 357.26 $[M+H]^+$ (95.75).

4.2.3 Procedure for the synthesis of 4-Phenylpyridin-2-amine (**7**).

In 100 mL RBF, stirred solution of 4-bromopyridin-2-amine **5** (1.0 g, 5.78 mmol), phenylboronic acid **6** (0.70 g, 5.78 mmol), K_2CO_3 (2.39 g, 17.3 mmol) and DMF (10 mL): water (2 mL). The reaction mixture was degassed by nitrogen gas for 5 min. $PdCl_2$(dppf) (0.423 g, 0.578 mmol) was added to this reaction mixture at room temperature. The resulting mixture was heated for 3 h at 100 °C temperature and progress of reaction was monitored by TLC. Upon completion of reaction, the reaction mixture was diluted with water (50 mL), extracted with ethyl acetate (50 mL × 3). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure to get crude product. It was purified by column chromatography with 40% ethyl acetate in *n*-hexane as mobile phase to give the desired product 4-phenylpyridin-2-amine **7**. Yield 0.61 g (62%), brown powder, mp: 166–168 °C, Rf: 0.3 (EtOAc– *n*-hexane, 1:1). ^{1}H NMR spectrum, δ ppm (*J*, Hz): 7.98 (1H, d), 7.65 (2H, d), 7.45 (2H, t), 7.42 (1H, d), 6.79 (1H, d), 6.70 (1H, s), 5.99 (2H, s, NH_2). LC-MS (ESI), *m/z* (*I* rel, %): 171.16 $[M+H]^+$ (100).

4.2.4 Procedure for the synthesis of 3-Cyano-N-(4-phenylpyridin-2-yl)benzamide (**9**).

To a stirred solution of 4-phenylpyridin-2-amine **7** (115.63 mg, 0.68 mmol) and 3-cyanobenzoic acid **8** (100.04 mg, 0. 68 mmol) in THF (2 mL) was added pyridine (2 mL) in RBF at 0 °C temperature. Stirred the reaction mixture for 15 min, then $POCl_3$ (2 mL) added drop wise and stirred for 60 min at 0 °C temperature and progress of reaction was monitored by TLC. Upon completion of the reaction polar spot formed on TLC, the reaction mixture was diluted with water (25 mL) and extracted with ethyl acetate (25 mL × 2). The combined organic extracts were washed with brine solution (25 mL), dried over Na_2SO_4, and concentrated under reduced pressure to get crude product. It was purified by column chromatography using 100-200 mesh size silica gel, using 40% ethyl acetate in *n*-hexane as mobile phase to give desired product **9**. Yield

0.13 g (87%), brown powder, mp: 194–196 °C, Rf: 0.5 (EtOAc– *n*-hexane, 3:2). ^{1}H NMR spectrum, δ ppm (*J*, Hz): 11.195 (1H, s, NH), 8.491-8.528 (3H, q), 8.328 (1H, d), 8.088-8.108 (1H, d), 7.749-7.807 (3H, q), 7.508-7.601 (4H, m). Mass spectrum (EI), *m/z* (*I* rel, %): 299.81 $[M]^+$ (100).

4.2.5 Procedure for the synthesis of 3-(4-methoxyphenyl)acrylic acid (**11a**).

To a stirred solution of malonic acid **10c** (1.84 g, 17.66 mmol) in pyridine (15 mL), piperidine (0.63 g, 7.40 mmol) and 4-methoxybenzaldehyde **10a** (2 g, 14.69 mmol) was added at room temperature. The resulting mixture was refluxed for 7 h at 70 °C temperature and progress of reaction was monitored by TLC. Upon completion of reaction, the mixture was quenched by slowly adding the conc. HCl at 0-5 °C temperature and solid white material was formed. Solid material was filtered through suction filtration and dried under vacuum to get white solid 3-(4-methoxyphenyl)acrylic acid **11a**. That was used directly for the next step. Yield 2.10 g (86%), white powder, mp: 173–175 °C, Rf: 0.7 (EtOAc– *n*-hexane, 3:7). LC-Mass spectrum (EI), *m/z* (*I* rel, %): 179.00 $[M+H]^+$ (100).

4.2.6 Procedure for the synthesis of 3-(4-bromophenyl)acrylic acid (**11b**).

To a stirred solution of malonic acid **10c** (2.03 g, 19.49 mmol) in pyridine (30 mL) and pipiridine (0.69 g, 8.10 mmol), 4-bromobenzaldehyde **10b** (3 g, 16.21 mmol) was added in reaction mixture. The resulting mixture was refluxed for 2 h at 70 °C temperature and progress of reaction was monitored by TLC. Upon completion of the reaction mixture was quenched by the conc. HCl at 0-5 °C temperature and solid material was formed. Solid material was filtered through the Buchner funnel and dried under vacuum to get white solid 3-(4-bromophenyl)acrylic acid **11b**. That was used directly for the next step. Yield 2.02 g (81%), white powder, mp: 260–262 °C, Rf: 0.7 (EtOAc– *n*-hexane, 3:7). LC-Mass spectrum (EI), *m/z* (*I* rel, %): 225.17 $[M-H]^+$ (100).

4.2.7 Procedure for the synthesis of 3-(4-methoxyphenyl)-1-morpholinoprop-2-en-1-one (**13a**).

Solution of 3-(4-methoxyphenyl)acrylic acid **11a** (0.3 g, 1.68 mmol) and HATU (0.96 g, 2.53 mmol) in THF (15 mL) at 0 °C was stirring for 10 min. DIPEA (0.652 g, 5.05 mmol) and morpholine **12a** (0.18 g, 2.02 mmol) were added in reaction mixture at 0-5 °C. Removed the ice bath, stirred the resulting mixture at room temperature for 1.5 h and progress of reaction was monitored by TLC. Upon completion of reaction, the reaction mixture was diluted with water (25 mL), extracted with ethyl acetate (25 mL × 2). The organic phases were combined, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to get crude product. It was purified by column chromatography using 100-200 mesh size silica gel, using 30% ethyl acetate in *n*-hexane as mobile phase to give desire yellow solid product as 3-(4-methoxyphenyl)-1-morpholinoprop-2-en-1-one **13a**. Yield 0.37 g (92%), yellow liquid, mp: 86–88 °C, Rf: 0.5 (EtOAc– *n*-hexane, 3:7). ^{1}H NMR spectrum, δ ppm (*J*, Hz): 7.71-7.67 (1H, d), 7.51-7.49 (2H, d), 6.93-6.91 (2H, d), 6.76-6.72 (1H, d), 3.86 (3H, s, OCH_3), 3.86-3.75 (8H, m). LC-Mass spectrum (EI), *m/z* (*I* rel, %): 248.13 $[M+H]^+$ (94.67).

4.2.8 Procedure for the synthesis of N-benzyl-3-(4-bromophenyl)acrylamide (**13b**).

Solution of 3-(4-bromophenyl)acrylic acid **11b** (0.5 g, 2.20 mmol) and HATU (1.255 g, 3.30 mmol) in THF (10 mL) were stirred at 0 °C for 10 min. DIPEA (0.85 g, 6.17 mmol) and phenylmethanamine **12b** (0.283g, 2.64 mmol) were added in the reaction mixture at 0-5 °C temperature. Removed the ice bath and stirred the resulting mixture for 1.5 h and progress of reaction was monitored by TLC. Upon completion of reaction, the reaction mixture was diluted with water (25 mL), extracted with ethyl acetate (25 mL × 2). The organic phases were combined, and dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to get the crude product. It was purified by column chromatography using 100-200 mesh size silica gel, using 40% ethyl acetate in *n*-hexane as mobile phase to give the desired product as *N*-benzyl-3-(4-bromophenyl)acrylamide **13b**. Yield 0.42 g (60%), pale yellow powder, mp: 280–282 °C, Rf: 0.6 (EtOAc– *n*-hexane, 3:7). ^{1}H NMR spectrum ($CDCl_3$), δ ppm (*J*, Hz):8.19-7.29 (9H, m), 6.43 (1H, d), 5.95 (1H, d), 4.62-4.60 (2H, d). LC-Mass spectrum (EI), *m/z* (*I* rel, %): 316.11 $[M]^+$ (100).

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