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Water mediated, environmentally friendly, step-wise, tandem & one-pot syntheses of 2-(1*H*-benzo[*d*]imidazole-2-yl)-*N*-arylbenzamides†

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Water mediated and environmentally friendly, step-wise, tandem & one-pot syntheses of 2-(1*H*-benzo[*d*]imidazole-2-yl)-*N*-arylbenzamide derivatives have been developed by simply combining phthalic anhydride, anilines and phenylenediammonium dihydrogenphosphate. This reaction has an easy workup, provides excellent yields, and uses water as the solvent which is considered to be relatively environmentally benign.

Introduction

The development of efficient, economical & environmentally friendly syntheses is an important challenge in modern organic syntheses.[1] In many synthetic organic processes, solvents represent a severe pollution problem. Thus, the replacement of hazardous solvents with relatively green solvents or the altogether elimination of use of hazardous solvents in chemical processes has been one of the key achievements of green chemistry.[2] Based on the principles of green chemistry, a green solvent should meet numerous criteria such as low toxicity, non-volatility, non-mutagenicity, non-flammability and widespread availability among others.[3] In the past decade, water,[4] glycerol,[5] polyethylene glycol,[6] ionic liquids[7] have been used as green solvents in organic reactions. Among all the green solvents, water is the safest, cheapest & non-toxic media-free from economic & environmental problems.[8] As a result, serious efforts are being made to develop water as a solvent for most of the organic syntheses and processes wherever possible.

There are currently a number of synthetic methodologies available for the synthesis of 2-substituted benzimidazole. Generally, two protocols are commonly followed for the synthesis of 2-substituted benzimidazole. The first route is coupling of 1,2-phenylenediamines with carboxylic acids or their derivatives,[9] and the second route is condensation of 1,2-phenylenediamines with aldehydes followed by oxidative cyclodehydrogenation.[10] But, these protocols fail to meet the requirement of green chemistry due to long reaction time, low yields, the use of toxic solvents & catalysts. Recently, Bahrami *et al.* reported[11] green method for synthesis of simple 2-arylbenzimidazole by reaction of 1,2-phenylenediamine with benzaldehyde in water in the presence of sodium dodecylsulfate (SDS) as a catalyst, ammonium persulfate [$(NH_4)_2S_2O_8$] as a promoter. In 1921, Bistrzycki *et al.* reported[12] the preparation of 2-(1*H*-benzo[*d*]-imidazole-2-yl)-*N*-phenylbezamide by the condensation of 1-(CO)-2-benzoylene benzimidazole with aniline. On the other hand, benzimidazole derivatives bear versatile pharmacological properties[13] based on their presence in both clinical medicines[14] and compounds of broad biological functions.[15] In addition, the treatment potency of benzimidazoles in diseases such as ischemia-reperfusion injury,[16] hypertension,[17] obesity[18] *etc.* have been recently reported.

Keeping the above results in mind and in continuation of our earlier work,[19] we now wish to report our synthetic studies on reactions of phthalic anhydride **1** with anilines and with *o*-phenylenediammonium dihydrogenphosphate **4**. To the best of our knowledge, this is probably first report to prepare 2-(1*H*-benzo[*d*]-imidazole-2-yl)-*N*-arylbenzamide derivatives in water.

Results and discussion

As illustrated in Scheme 1, phthalic anhydride **1** was reacted with aniline **2a** to form 2-(arylcarbamoyl)benzoic acid **3a** in the presence of 5% aq. H_3PO_4 at RT for 10 min (Table 1, entry 1). **3a** was then reacted with *o*-phenylenediammonium dihydrogenphosphate **4** (ref. 20) in refluxing water for 90 min resulting in the formation of 2-(1*H*-benzo[*d*]imidazole-2-yl)-*N*-phenylbenzamide **5a** (Table 2, entry 1). The structure of the product was assigned on the basis of its spectral properties -IR, NMR & mass spectra (for details, please see the Experimental section). **5a** could also be prepared by the tandem method

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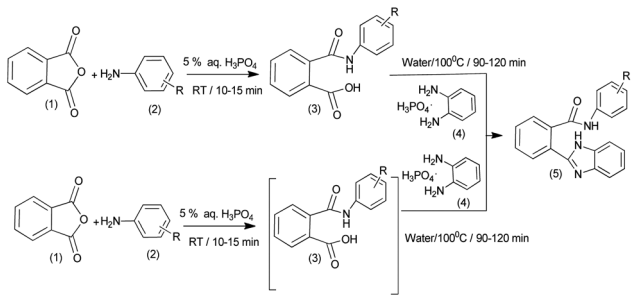


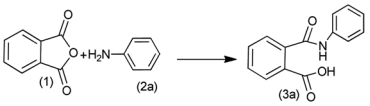
Scheme 1 Synthesis of **5a–5l** by step-wise & tandem reaction in water.

involving the sequences ($\mathbf{1} + \mathbf{2a} \rightarrow \mathbf{3a} \xrightarrow{4} \mathbf{5a}$) (Scheme 1). In this tandem reaction, **1** was treated with **2a** in the presence of 5% aq. H_3PO_4 at RT for 10 min until the disappearance of **1** was found on TLC. To the same reaction mixture **4** was added and then the reaction mixture refluxed for 90 min until the disappearance of **3a** took place. The mixture was then processed to obtain **5a** identical with the same product obtained earlier in the step-wise route (Scheme 1).

The reaction of **1** with **2a** was examined by treating **1** (1 mmol) with aniline **2a** (1 mmol) in the presence of different acid catalysts with different amounts in water to form **3a** (Table 1).

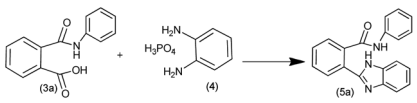
However, reaction with 5% aq. H_3PO_4 as catalyst at RT for 10 min in water, unlike other acid catalysts HCl, H_2SO_4, boric acid gave reasonably high yield (91%) of the product **3a** (Table 1, entry 1). The reaction of **3a** (1 mmol) with **4** (1 mmol) was also optimized by doing a series of experiments in the presence of different solvents and ionic liquids at different temperatures (Table 2). However, it is greatly notable that the reaction of **3a** with **4** at 100 °C for 90 min in water, unlike in other solvents such as glycerol, PEG-600, ethylene glycol, DMF, ionic liquids [bmim][Br], [bmim][OH] and PPA gave reasonably high yield (88%) of the product **5a** (Table 2, entry 1).

Table 1 Effect of acid catalyst on reaction of **1** with **2a** in water yielding **3a**



Entry	Catalyst	% of catalyst (10 ml)	Time/min	**3a** (%)
1	H_3PO_4	5	10	91
2	H_3PO_4	10	10	87
3	H_3PO_4	15	10	81
4	H_2SO_4	5	15	80
5	H_2SO_4	10	15	86
6	H_2SO_4	15	15	82
7	HCl	5	15	77
8	HCl	10	15	83
9	HCl	15	15	79
10	Boric acid	5	15	81
11	Boric acid	10	15	79
12	Boric acid	15	15	75

Table 2 Effect of solvent & temperature on reaction of **3a** with **4** yielding **5a**

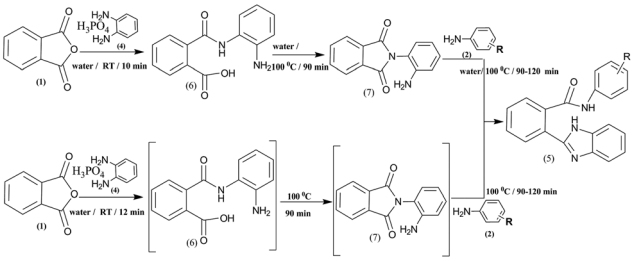


Entry	Solvent	Temp./°C	Time/min	**5a** (%)
1	H_2O	100	90	88
2	Glycerol	50	240	82
3	Glycerol	100	120	88
4	Glycerol	120	120	84
5	H_2O	RT	300	—
6	H_2O	50	200	76
7	PEG-600	50	300	72
8	PEG-600	100	150	72
9	Ethyleneglycol	50	240	68
10	Ethyleneglycol	100	150	63
11	DMF	50	300	35
12	DMF	100	240	40
13	[bmim][Br]	50	120	75
14	[bmim][Br]	80	90	79
15	[bmim][OH]	50	120	36
16	[bmim][OH]	80	90	49
17	PPA	100	90	60

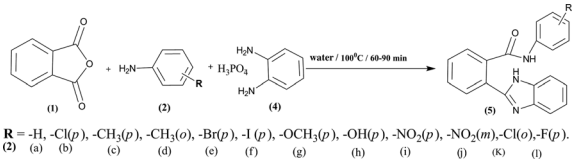
Using the above-stated optimised conditions, in both, the step-wise & tandem reactions, **5a–5l** have been prepared by the condensation of phthalic anhydride **1** with anilines **2a–2l** in the presence of 5% aq. H_3PO_4 to form 2-(arylcarbamoyl)benzoic acids **3a–3l** as intermediates at RT for 10–15 min. Thereafter, **3a–3l** were condensed with **4** at reflux for 90–120 min in water with good yield and no side products were detected. Their structures have been established on the basis of spectra such as IR, NMR & H. R. mass spectra (Scheme 1) (Tables 3[22,23], 4 & 6, included in ESI†).

Alternative synthesis of 5a–5l

As illustrated in Scheme 2, **1** was reacted with **4** in water at RT for 10 min to form 2-((2-aminophenyl)carbamoyl)benzoic acid **6.** The product was characterized by comparison of its physical data with that of the same product reported[21] earlier. **6** was converted into 2-(2-aminophenyl)isoindoline-1,3-dione **7** in the presence of 5% aq. H_3PO_4 in refluxing water for 90 min



Scheme 2 Alternative synthesis of **5a–5l** by step-wise & tandem reaction in water.



Scheme 3 Synthesis of **5a–5l** by one pot synthesis in water.

(Scheme 2). The product was characterized by comparison of its physical data with that of same product reported[21] earlier. **7** was then reacted with **2a–2l** in refluxing water for 90 min resulting in the formation of **5a–5l**. **5a–5l** could also be prepared by tandem method involving the sequence ($\mathbf{1}+\mathbf{4}\rightarrow\mathbf{7}\xrightarrow{\mathbf{2a}}\mathbf{5a}$) (Scheme 2). In the tandem reaction, **1** was treated with **4** in the presence of 5% aq. H_3PO_4 at RT for 10 min. The completion of reaction was checked by TLC until the disappearance of **1** took place. To the resulting mixture, **2a–2l** was added and the whole thing refluxed for 90–120 min giving **5a–5l** and on processing the mixture no side products were detected. Structure of the final product was established by its comparison with authentic sample prepared earlier in step-wise route shown in Scheme 1. (Scheme 2) (Tables 5 & 6, included in ESI†).

One-pot synthesis of 5a–5l

Encouraged by above results, the title compounds **5a–5l** could also be prepared in one-pot by heating a mixture of **1**, **2a–2l** and **4** (Scheme 3) in water at 100 °C for 60–90 min in good yield and no side products were detected. Structures of the products have been established by comparison with authentic samples which were prepared in step wise fashion in Scheme 1. (Scheme 3) (Table 6, included in ESI†).

Conclusion

In summary, practical and green synthetic methods have been developed for the synthesis of **5a–5l** in water through step wise fashion, tandem reaction and one-pot, three-component synthesis. Of all the methods discussed, one-pot, three-component synthesis (Scheme 3) appears to be the better, less time and efficient method of products obtained, compared to the other two methods. Significant rate acceleration of the reaction in water observed and compared to commonly use of green solvents & ionic liquids. Through this reaction, variety of **5a–5l** synthesized in water with good yield.

Experimental section

Melting points are uncorrected and were determined in open capillary tubes in sulphuric acid bath. TLC was run on silica gel-G and visualization was done using iodine or UV light. IR spectra were recorded using Perkin-Elmer 1000 instrument in KBr pellets. ^{1}H NMR spectra were recorded in DMSO-d_6 using TMS as internal standard using 400 MHz spectrometer. Mass spectra were recorded on Agilent-LCMS instrument. Starting materials **1** & **2** were obtained from commercial sources and used as such. **4** has been prepared by literature method.[13]

General procedures for preparation of 3

A mixture of **1** (10 mM) and **2** (10 mM) was stirred at RT for 10–15 min in the presence of 5% aq. H_3PO_4 (20 ml). At the end of this period, reaction mixture was neutralized with 5% Na_2CO_3 solution. Further, a colourless solid separated out from the reaction mass which was collected by filtration. The isolated solid was washed with water (10 ml) and dried. The product was recrystallized from a suitable solvent to obtain **3**.

General procedure for preparation of 5 from 3 & 4

A mixture of **3** (10 mM), **4** (10 mM) and water (20 ml) was refluxed at 100 °C for 90–120 min. At the end of this period, reaction mixture was neutralized with 5% Na_2CO_3 solution. Further, a colourless solid separated out from the reaction mass which was collected by filtration. The isolated solid was washed with water (10 ml) and dried. The crude product was recrystallized from a suitable solvent to obtain **5**.

General procedure for preparation of 5 by tandem reaction ($\mathbf{1}+\mathbf{2}\rightarrow\mathbf{3}\xrightarrow{\mathbf{4}}\mathbf{5}$)

A mixture of **1** (10 mM), **2** (10 mM) and 5% aq. H_3PO_4 (20 ml) was stirred at RT for 10–15 min when colourless solid separated out from reaction mixture. Then, to this solution **4** (10 mM) was added and the mixture refluxed at 100 °C for 90–120 min. At the end of this period, reaction mixture was neutralized with 5% Na_2CO_3 solution. Further, a colourless solid separated out from the reaction mass which was collected by filtration. The isolated solid was washed with water (10 ml) and dried. The crude product was recrystallized from a suitable solvent to obtain **5**.

2-(1*H*-Benzo[*d*]imidazole-2-yl)-*N*-phenylbenzamide (5a)

M.P. = >250 °C; IR (KBr): 3052–3450 cm^{-1} (broad, medium, –NH– group), 1700 cm^{-1} (sharp, strong, –CO– of amide group); ^{1}H NMR δ_H (400 MHz; DMSO-d_6; Me_4Si): 7.05–7.91 (m, 13H, Ar–H), 10.43 (s, 1H, –CO–NH, D_2O exchangeable), 12.69 (s, 1H, –NH, D_2O exchangeable); ^{13}C NMR δ_C (400 MHz; DMSO-d_6): 115.3, 120.2, 121.8, 123.2, 127.3, 128.5, 128.9, 129.0, 129.0, 130.5, 130.7, 133.2, 135.6, 137.6, 138.7, 150.9, 151.0, 167.6; HRMS calcd for $C_{20}H_{15}N_3O$ $[M + H]^+$: 314.04235, found: 314.04268.

2-(1*H*-Benzo[*d*]imidazole-2-yl)-*N*-(4-chlorophenyl)benzamide (5b)

M.P. = >250 °C; IR (KBr): 3030–3354 cm^{-1} (broad, medium, –NH– group), 1690 cm^{-1} (sharp, strong, –CO– of amide group); ^{1}H NMR δ_H (400 MHz; DMSO-d_6; Me_4Si): 7.04–7.91 (m, 12H, Ar–H), 10.54 (s, 1H, –CO–NH, D_2O exchangeable), 12.58 (s, 1H, –NH, D_2O exchangeable); ^{13}C NMR δ_C (400 MHz; DMSO-d_6): 114.3, 121.5, 121.8, 124.2, 127.3, 128.3, 128.5, 129.9, 129.9, 130.7, 131.9, 134.1, 136.7, 138.5, 139.6, 151.4, 152.0, 169.8; HRMS calcd for $C_{20}H_{14}ClN_3O$ $[M + H]^+$: 348.32353, found: 348.32329.

2-(1*H*-Benzo[*d*]imidazole-2-yl)-*N*-(4-methylphenyl)benzamide (5c)

M.P. = >250 °C; IR (KBr): 3038–3353 cm^{-1} (broad, medium, –NH– group), 1651 cm^{-1} (sharp, strong, –CO– of amide group); ^1H NMR δ_H (400 MHz; DMSO-d_6; Me_4Si): 2.25 (s, 3H, CH_3), 7.09–7.91 (m, 12H, Ar–H), 10.34 (s, 1H, –CO–NH, D_2O exchangeable), 11.62 (s, 1H, –NH, D_2O exchangeable); ^{13}C NMR δ_C (400 MHz; DMSO-d_6): 20.4, 115.0, 120.0, 121.9, 123.3, 127.2, 128.5, 128.8, 129.3, 129.5, 130.0, 130.8, 132.3, 136.8, 137.5, 138.9, 150.7, 151.1, 168.6; HRMS calcd for $C_{21}H_{17}N_3O$ $[M + H]^+$: 328.03145, found: 328.03111.

2-(1*H*-Benzo[*d*]imidazole-2-yl)-*N*-(2-methylphenyl)benzamide (5d)

M.P. = >250 °C; IR (KBr): 3035–3355 cm^{-1} (broad, medium, –NH– group), 1694 cm^{-1} (sharp, strong, –CO– of amide group); ^1H NMR δ_H (400 MHz; DMSO-d_6; Me_4Si): 2.44 (s, 3H, CH_3), 7.21–7.95 (m, 12H, Ar–H), 10.43 (s, 1H, –CO–NH, D_2O exchangeable), 11.66 (s, 1H, –NH, D_2O exchangeable); ^{13}C NMR δ_C (400 MHz; DMSO-d_6): 21.0, 114.9, 120.0, 121.8, 122.3, 127.4, 128.7, 128.8, 129.5, 129.5, 130.2, 130.8, 132.4, 136.8, 137.9, 138.9, 150.7, 151.1, 168.6; HRMS calcd for $C_{21}H_{17}N_3O$ $[M + H]^+$: 328.32356, found: 328.32329.

2-(1*H*-Benzo[*d*]imidazole-2-yl)-*N*-(4-bromophenyl)benzamide (5e)

M.P. = >250 °C; IR (KBr): 3034–3360 cm^{-1} (broad, medium, –NH– group), 1689 cm^{-1} (sharp, strong, –CO– of amide group); ^1H NMR δ_H (400 MHz; DMSO-d_6; Me_4Si): 7.04–7.90 (m, 12H, Ar–H), 10.30 (s, 1H, –CO–NH, D_2O exchangeable), 12.25 (s, 1H, –NH, D_2O exchangeable); ^{13}C NMR δ_C (400 MHz; DMSO-d_6): 114.3, 121.2, 121.8, 123.2, 127.3, 128.5, 128.9, 129.0, 129.1, 130.5, 130.7, 133.2, 135.7, 137.3, 138.6, 150.9, 151.0, 169.7; HRMS calcd for $C_{20}H_{14}BrN_3O$ $[M + H]^+$: 392.32356, found: 392.32387.

2-(1*H*-Benzo[*d*]imidazole-2-yl)-*N*-(4-iodophenyl)benzamide (5f)

M.P. = 240–242 °C; IR (KBr): 3030–3350 cm^{-1} (broad, medium, –NH– group), 1690 cm^{-1} (sharp, strong, –CO– of amide group); ^1H NMR δ_H (400 MHz; DMSO-d_6; Me_4Si): δ 7.04–7.90 (m, 12H, Ar–H), 10.30 (s, 1H, –CO–NH, D_2O exchangeable), 12.29 (s, 1H, –NH, D_2O exchangeable); ^{13}C NMR δ_C (400 MHz; DMSO-d_6): 114.3, 121.5, 121.8, 123.1, 127.3, 128.3, 128.5, 129.0, 129.1, 130.5, 130.9, 133.2, 135.7, 137.5, 138.7, 150.9, 151.1, 169.6; HRMS calcd for $C_{20}H_{14}IN_3O$ $[M + H]^+$: 440.32300, found: 440.32329.

2-(1*H*-Benzo[*d*]imidazole-2-yl)-*N*-(4-methoxyphenyl) benzamide (5g)

M.P. = >250 °C; IR (KBr): 3040–3383 cm^{-1} (broad, medium, –NH– group), 1692 cm^{-1} (sharp, strong, –CO– of amide group); ^1H NMR δ_H (400 MHz; DMSO-d_6; Me_4Si): 3.35 (s, 3H, CH_3), 7.22–7.99 (m, 12H, Ar–H), 10.48 (s, 1H, –CO–NH, D_2O exchangeable), 11.48 (s, 1H, –NH, D_2O exchangeable); ^{13}C NMR δ_C (400 MHz; DMSO-d_6): 55.9, 118.3, 120.2, 121.5, 123.6, 127.5, 128.5, 128.9, 129.0, 129.2, 130.6, 130.8, 133.1, 136.5, 137.0, 138.9, 150.9, 151.1, 167.9; HRMS calcd for $C_{21}H_{17}N_3O_2$ $[M + H]^+$: 344.32466, found: 344.32497.

2-(1*H*-Benzo[*d*]imidazole-2-yl)-*N*-(4-hydroxyphenyl)benzamide (5h)

M.P. = >250 °C; IR (KBr): 3039–3353 cm^{-1} (broad, medium, –NH– group), 1632 cm^{-1} (sharp, strong, –CO– of amide group); ^1H NMR δ_H (400 MHz; DMSO-d_6; Me_4Si): 7.05–7.89 (m, 12H, Ar–H), 8.13 (s, 1H, –OH, D_2O exchangeable), 10.47 (s, 1H, –CO–NH, D_2O exchangeable), 12.66 (s, 1H, –NH, D_2O exchangeable); ^{13}C NMR δ_C (400 MHz; DMSO-d_6): 115.2, 120.2, 121.8, 123.3, 127.6, 128.5, 128.9, 129.0, 129.0, 130.6, 130.7, 133.1, 135.6, 137.5, 138.9, 150.9, 151.0, 167.5; HRMS calcd for $C_{20}H_{15}N_3O_2$ $[M + H]^+$: 330.23416, found: 330.23456.

2-(1*H*-Benzo[*d*]imidazole-2-yl)-*N*-(4-nitrophenyl)benzamide (5i)

M.P. = >250 °C; IR (KBr): 3033–3373 cm^{-1} (broad, medium, –NH– group), 1692 cm^{-1} (sharp, strong, –CO– of amide group); ^1H NMR δ_H (400 MHz; DMSO-d_6; Me_4Si): 7.05–7.91 (m, 12H, Ar–H), 10.43 (s, 1H, –CO–NH, D_2O exchangeable), 12.69 (s, 1H, –NH, D_2O exchangeable); ^{13}C NMR δ_C (400 MHz; DMSO-d_6): 114.9, 120.0, 121.7, 122.3, 127.4, 128.5, 128.8, 129.5, 129.9, 130.2, 130.5, 132.5, 136.7, 137.9, 138.9, 150.6, 151.2, 168.5; HRMS calcd for $C_{20}H_{14}N_4O_3$ $[M + H]^+$: 359.85652, found: 359.85624.

2-(1*H*-Benzo[*d*]imidazole-2-yl)-*N*-(3-nitrophenyl)benzamide (5j)

M.P. = >250 °C; IR (KBr): 3039–3359 cm^{-1} (broad, medium, –NH– group), 1695 cm^{-1} (sharp, strong, –CO– of amide group); ^1H NMR δ_H (400 MHz; DMSO-d_6; Me_4Si): 7.05–7.96 (m, 12H, Ar–H), 10.43 (s, 1H, –CO–NH, D_2O exchangeable), 12.68 (s, 1H, –NH, D_2O exchangeable); ^{13}C NMR δ_C (400 MHz; DMSO-d_6): 114.9, 120.1, 121.7, 122.3, 127.4, 128.5, 128.8, 129.5, 129.8, 130.2, 130.5, 131.5, 136.7, 137.9, 138.9, 150.6, 151.3, 168.6; HRMS calcd for $C_{20}H_{14}N_4O_3$ $[M + H]^+$: 359.24516, found: 359.24567.

2-(1*H*-Benzo[*d*]imidazole-2-yl)-*N*-(2-chlorophenyl)benzamide (5k)

M.P. = >250 °C; IR (KBr): 3028–3350 cm^{-1} (broad, medium, –NH– group), 1682 cm^{-1} (sharp, strong, –CO– of amide group); ^1H NMR δ_H (400 MHz; DMSO-d_6; Me_4Si): δ 7.04–7.90 (m, 12H, Ar–H), 10.53 (s, 1H, –CO–NH, D_2O exchangeable), 12.59 (s, 1H, –NH, D_2O exchangeable); ^{13}C NMR δ_C (400 MHz; DMSO-d_6): 114.6, 121.5, 121.9, 124.2, 127.3, 128.0, 128.3, 129.5, 129.9, 130.9, 131.9, 134.1, 136.7, 138.6, 139.0, 151.6, 152.1, 169.8; HRMS calcd for $C_{20}H_{14}ClN_3O$ $[M + H]^+$: 348.42396, found: 348.42356.

2-(1*H*-Benzo[*d*]imidazole-2-yl)-*N*-(4-fluorophenyl)benzamide (5l)

M.P. = 235–236 °C; IR (KBr): 3040–3380 cm^{-1} (broad, medium, –NH– group), 1693 cm^{-1} (sharp, strong, –CO– of amide group); ^1H NMR δ_H (400 MHz; DMSO-d_6; Me_4Si): δ 7.04–7.95 (m, 12H, Ar–H), 10.31 (s, 1H, –CO–NH, D_2O exchangeable), 12.29 (s, 1H, –NH, D_2O exchangeable); ^{13}C NMR δ_C (400 MHz; DMSO-d_6): 115.3, 120.0, 121.9, 123.3, 127.3, 128.5, 128.7, 129.3, 129.5, 130.0, 130.9, 132.3, 136.8, 137.0, 138.7, 150.6, 151.5, 168.6; HRMS calcd for $C_{20}H_{14}FN_3O$ $[M + H]^+$: 332.56771, found: 332.56721.

General procedure for preparation of 6 from 1 & 4

A mixture of **1** (10 mM), **4** (10 mM) and H_2O (20 ml) was stirred at RT for 10–15 min. At the end of this period, reaction mixture was neutralized with 5% Na_2CO_3 solution. Further, a colourless solid separated out from the reaction mass which was collected by filtration. The isolated solid was washed with water (10 ml)

and dried. The product was recrystallized from a suitable solvent to obtain **6**.

2-((2-Aminophenyl)carbamoyl)benzoic acid 6. M. P = 165–167 °C [lit.,[21] 167–168 °C], yield = 90%.

Preparation of 7 from 6

6 (10 mM) and 5% aq. H_3PO_4 (20 ml) was refluxed at 100 °C for 90 min. At the end of this period, reaction mixture was neutralized with 5% Na_2CO_3 solution. Further, a colourless solid separated out from the reaction mass which was collected by filtration. The isolated solid was washed with water (10 ml) and dried. The crude product was recrystallized from a suitable solvent to obtain **7**.

2-(2-Aminophenyl)isoindoline-1,3-dione 7. M.P. = 205–206 °C [lit.,[21] 206–207 °C], yield = 90%.

General procedure for preparation of 5 from 7 & 2

A mixture of **7** (10 mM), **2** (10 mM) and 5% aq. H_3PO_4 (20 ml) was refluxed at 100 °C for 120–150 min. the end of this period, reaction mixture was neutralized with 5% Na_2CO_3 solution. Further, a colourless solid separated out from the reaction mass which was collected by filtration. The isolated solid was washed with hexane (10 ml) and dried. The product was recrystallized from a suitable solvent to obtain **5**.

General procedure for preparation of 5 by tandem reaction ($1 + 4 \rightarrow 7 \xrightarrow{2} 5$)

A mixture of **1** (10 mM), **4** (10 mM) and water (20 ml) was refluxed at 100 °C for 90 min. A colourless solid separated out from reaction mixture. Then, to this mixture at RT **2a–2l** (10 mM) was added and refluxed at 100 °C for 120–150 min. the end of this period, reaction mixture was neutralized with 5% Na_2CO_3 solution. Further, a colourless solid separated out from the reaction mass which was collected by filtration. The isolated solid was washed with water (10 ml) and dried. The product was recrystallized from suitable solvent to obtain **5**.

General procedure for preparation of 5 from 1, 3 & 4 by one-pot synthesis

A mixture of **1** (10 mM), **3a–3l** (10 mM), **4** (10 mM), and water (20 ml) was refluxed at 100 °C for 60–90 min. At the end of this period, reaction mixture was neutralized with 5% Na_2CO_3 solution. Further, a colourless solid separated out from the reaction mass which was collected by filtration. The isolated solid was washed with water (10 ml) and dried. The product was recrystallized from a suitable solvent to obtain **5a–5l**.

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