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PAPER

Unsymmetrical tetrasubstituted ureas from tertiary carbamoylimidazole: activation by $AlMe_3$†

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An efficient and general method for the synthesis of unsymmetrical tetrasubstituted ureas from carbamoylimidazole is described. The conversion is achieved by the concurrent quarternization of the imidazole nitrogen and activation of amines with $AlMe_3$.

Introduction

The diverse applications of substituted urea functionalities are well known and they have been described in the literature as plant growth regulators, pesticides, herbicides, dyes, detergent additives, corrosion inhibitors, *etc*.[1,2a,b] In addition, ureas find numerous applications in the field of organocatalysis,[2c,d] medicines as tranquilizers, antidiabetics, anticonvulsants, as inhibitor of HIV-1 protease, tachykinin NK1 selective antagonist, *etc.*[3–7a,b] (Fig. 1). Di/trisubstituted ureas are often transformed to tetrasubstituted ureas and are of interests to medicinal chemists in establishing the hydrogen bond donor–acceptor requirements of the molecules for the binding of molecules to the receptors of interest.[7c] Numerous methodologies for the synthesis of mono, di and tri substituted ureas have been reported in literature.[8,9] A SciFinder search reveals more than 13 000 literature reports related to the synthesis of tetrasubstituted ureas. Notwithstanding this, the synthesis of various unsymmetrical tetrasubstituted ureas still remains a challenge to synthetic and medicinal chemists in that, most of the methods lack general applicability. The use of phosgene and triphosgene in the preparation of ureas has been limited to a great extent owing to their toxicity and the instability of the carbamoylchloride.[10] This is especially true for large scale synthesis.

The synthesis of di, tri-substituted ureas from protected carbamates using $AlMe_3$ was explored in detail by Clapham and Janda *et al*.[11a,b] Though this method is suitable for the synthesis of a limited class of unsymmetrical tetrasubstituted ureas, it suffers from the disadvantage of the need to use excess of the aliphatic amine (3.0 equiv) to react with carbamates. Katritzky *et al*. reported the synthesis of trisubstituted and tetrasubstituted ureas by using 1,1′-carbonylbisbenzotriazole (Scheme 1).[12]

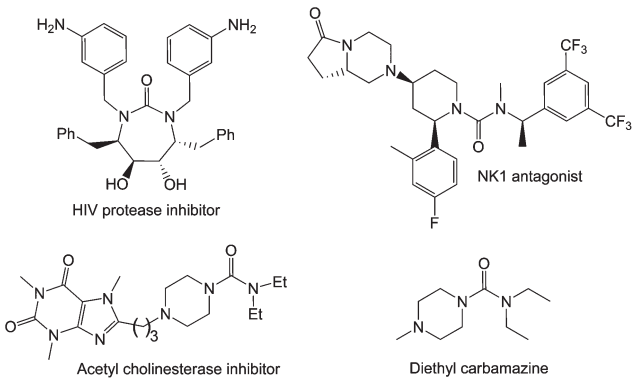

Fig. 1 Biologically potent molecules.

However, the commercial availability of 1,1′-carbonylbisbenzotriazole coupled with longer reaction time limits the scope of this method.

Carbonylations using Pd, W, Ru, Co, Ni, Mn, and $W(CO)_6$ catalysts have been studied as a substitute to phosgene based chemistry. These methods, in addition to the low yielding results, are limited to the synthesis of aliphatic/cyclic ureas.[13,14] Carbonylation using sulphur and selenium is strictly limited to the preparation of cyclic and or aromatic di-substituted ureas, whereas aliphatic amines only yielded di or tetrasubstituted symmetrical ureas.[15] Carbonylation of lithium amides leads to mixture of products including products of self coupling.[16]

Microwave assisted synthesis of tetrasubstituted ureas was reported by Tomkinson and Bridgeman by reacting 4-nitrophenyl carbamates with secondary amines. This method finds its application limited to aliphatic amines.[11c] Tetrasubstituted ureas were prepared from Mitsunobu's reagent by Chaturvedi *et al.*, but no unsymmetric aromatic tetrasubstituted ureas could be obtained by this method, thus restricting this method for aliphatic and symmetrical ureas exclusively.[17] *N*-Alkylation of ureas using base and Pd/Cu catalyzed carboamination of di or tri substituted ureas were reported. This method is applicable only if the preformed urea is available.[18–20]

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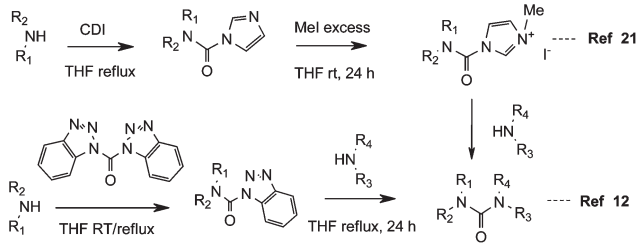
†Electronic supplementary information (ESI) available: ^1H NMR and ^{13}C NMR spectra of all compounds. See DOI: 10.1039/c2ob25412c



Scheme 1 Reported synthesis of tetrasubstituted ureas.

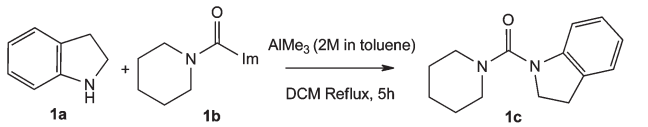
Results and discussion

Carbamoylimidazoles prepared by reacting secondary amines with CDI are less reactive and very stable towards nucleophiles. For many decades, the stable nature of carbamoylimidazole prepared from secondary amine was an impediment to chemists in the synthesis of tetrasubstituted ureas. In 1999, Batey *et al.* overcame this difficulty by quaternising the imidazole nitrogen with excess MeI thereby improving its reactivity and proving a viable route for preparing ureas and/thio ureas.[21] This method suffers from the disadvantage of the need to use a suspected carcinogen, *viz.*, MeI, which is a very reactive electrophile capable of reacting with other nucleophiles and quaternising other tertiary nitrogens in the molecule. Moreover the preparation of aromatic ureas from aromatic amines requires the use of a strong base like *n*-BuLi for the deprotonation of the aromatic amines. As a part of one of our research programmes to synthesize a large number of unsymmetrical tetrasubstituted ureas, we scouted for methods for the synthesis of unsymmetrical tetrasubstituted ureas from carbamoylimidazole without prequaternising with MeI. Activation by suitable Lewis acid appeared to be an attractive option and we envisioned that the unique properties (Lewis acid and organometallic behavior) of $AlMe_3$[22,23] would facilitate this transformation by coordinating with the imidazole nitrogen, thereby enhancing the electrophilicity of the urea carbonyl group and also enhancing the nucleophilicity of the amine by converting it to the *N*-aryldimethylaluminium-amide.

We commenced our study by carrying out a reaction with indoline **1a** (1.2 equiv), carbamoylimidazole **1b** (1.0 equiv) and one equivalent of $AlMe_3$ in dry dichloromethane under a nitrogen atmosphere. While no reaction was observed at ambient temperature, upon heating the reaction mixture to 55 °C (oil bath temperature) for 5 h product formation to the extent of 4% was observed as monitored by HPLC. A few parallel reactions were performed under the same reaction conditions by varying the equivalents of $AlMe_3$ (1.5 equiv, 2.0 equiv, 2.5 equiv). It was observed that maximum conversion to the desired product *viz.*, urea **1c** (89% conversion by HPLC) occurred with 2.5 equiv of $AlMe_3$ (Table 1). This urea was earlier reported[24] as unstable but in our hands this compound was found to be quite stable and was obtained in a yield of 72%.

After having optimized the reaction conditions, this methodology was successfully extended to a large number of secondary amines (**1a–17a**) and carbamoylimidazoles (**1b–12b**) as listed in Table 2. Indoline **1a** was reacted with seven different carbamoylimidazoles (**1b–7b**) to afford the ureas (**1c–7c**) in good yield (69–89%) with the exception of **7c** where the reaction time was

Table 1 Optimization of $AlMe_3$[a]



Entry	$AlMe_3$ (equiv)	% Conversion (by HPLC)[b]
1	1.0	4
2	1.5	16
3	2.0	65
4	2.5	89 (72)[c]

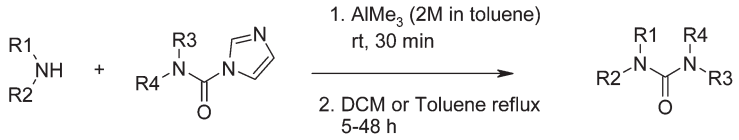
[a] Reaction conditions: amine (1.2 mmol), carbamoylimidazole (1.0 mmol), time 5 h, DCM solvent, oil bath temperature 55 °C. [b] Conversion determined by HPLC and based on **1b**. [c] Isolated yield.

deliberately reduced from 5 h to 3.5 h to avoid the destruction of the OTBS group. It is noted that the nature of carbamoylimidazole has little or no effect in the seven transformations above. In the cases of weakly nucleophilic amines, the reaction in refluxing dichloromethane was sluggish but proceeded satisfactorily under toluene reflux. The compound **8c** was prepared by two different routes. In the first reaction (entry 8), diphenylamine **2a** was taken as a nucleophile and refluxed with carbamoylimidazole **8b** and $AlMe_3$ in toluene for 16 h leading to formation of the product **8c** in 89% yield. In the second approach (entry 9) there was no reaction when dibenzyl amine (**3a**) reacted with carbamoylimidazole **9b** under the above conditions even after 16 h. Dibenzylamine and $AlMe_3$ were heated in refluxing toluene for 24 h and then reacted with carbamoylimidazole (**9b**) for additional 24 h affording the urea **8c** in 69% yield. Dibenzylamine despite being an aliphatic amine required longer reaction time which is attributed to $Bn_2NH{\cdot}AlMe_3$ adduct formation.[25] Similarly urea **9c** was prepared by two routes, one reacting dibenzylamine with carbamoylimidazole **10b** (entry 10) and the other employing morpholine (entry 11) as nucleophile and reacting it with carbamoylimidazole **8b**. The latter route furnished higher yield of the product **9c**. The findings from the above study clearly reveal that the success of this methodology primarily depends on the ease of formation of the aluminium–amide complex from the reaction of the amine with $AlMe_3$.

The nature of carbamoylimidazole has little or no effect in facilitating this transformation. Carbamoylimidazole **4b** was reacted successfully with different amines of varying nucleophilicity (**5a–10a**) to furnish the corresponding tetrasubstituted ureas (entries 12–17, Table 2). Less reactive amines like *p*-chloro (**5a**) and *p*-cyano (**6a**) *N*-methyl anilines also underwent this reaction to give the corresponding ureas in good yields by this method. As expected, the combined mesomeric effect of an additional phenyl group and that of the *p*-cyanophenyl group accounts for the less reactivity of the diphenylamine **7a** which afforded the urea **12c** in low yield (15%, entry 14).

Tertiary amines bearing *N*-benzyl group are known to undergo debenzylation when treated with phosgene or triphosgene and hence this unsolicited side reaction limits the scope of this method in the preparation of ureas.[26] With our new method, we were able to synthesize the *N*-benzyl urea **2c** in 81% yield without any side reactions. For the synthesis of the urea **19c**,

Table 2 Diversity of substrates[a]



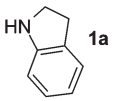
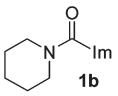
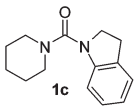
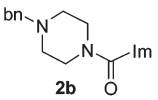
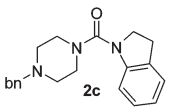
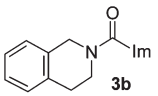
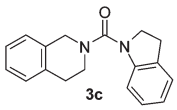
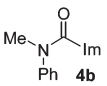
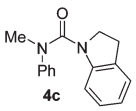
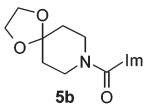
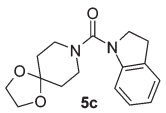
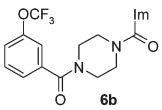
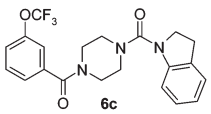
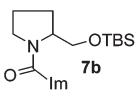
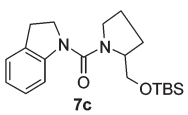
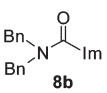
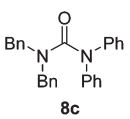
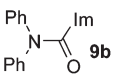
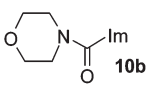
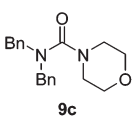
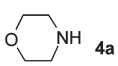
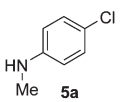
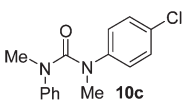
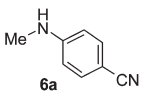
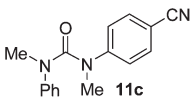
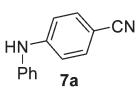
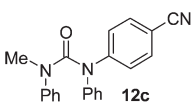
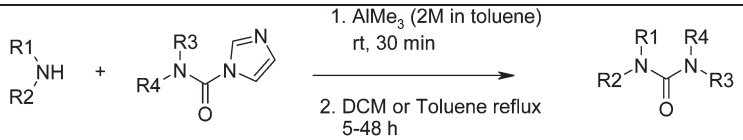
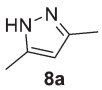
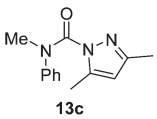
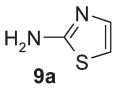
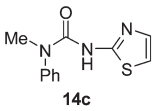
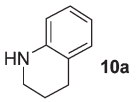
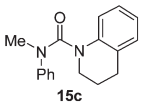
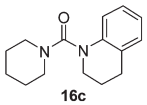
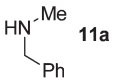
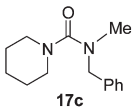
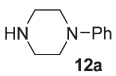
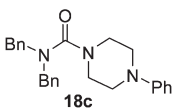
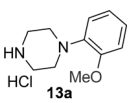
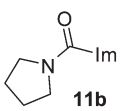
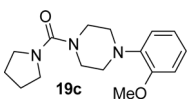
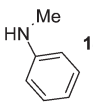
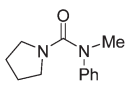
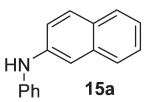
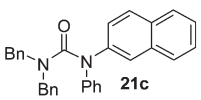
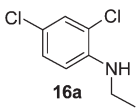
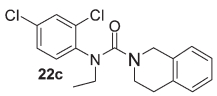
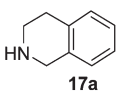
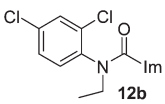
Entry	Amine	Carbamoylimidazole	Time (h)	Product	Yield[b] (%)
1	 **1a**	 **1b**	5	 **1c**	72[c]
2	**1a**	 **2b**	5	 **2c**	81[c]
3	**1a**	 **3b**	5	 **3c**	88[c]
4	**1a**	 **4b**	5	 **4c**	89[c]
5	**1a**	 **5b**	5	 **5c**	89[c]
6	**1a**	 **6b**	5	 **6c**	86[c]
7	**1a**	 **7b**	3.5	 **7c**	69[c]
8	 **2a**	 **8b**	16	 **8c**	89[d]
9	 **3a**	 **9b**	48	**8c**	69[de]
10	**3a**	 **10b**	48	 **9c**	62[de]
11	 **4a**	**8b**	5	**9c**	82[d]
12	 **5a**	**4b**	24	 **10c**	70[d]
13	 **6a**	**4b**	22	 **11c**	59[d]
14	 **7a**	**4b**	48	 **12c**	15[d]

Table 2 *(Contd.)*

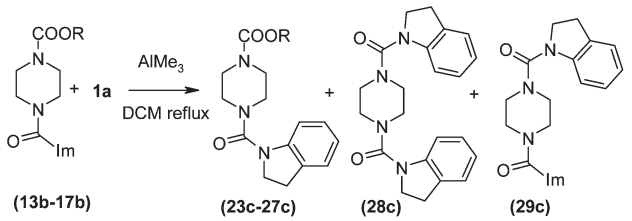


Entry	Amine	Carbamoylimidazole	Time (h)	Product	Yield[b] (%)
15	 **8a**	**4b**	48	 **13c**	53[d]
16	 **9a**	**4b**	16	 **14c**	79[d]
17	 **10a**	**4b**	16	 **15c**	86[d]
18	**10a**	**1b**	16	 **16c**	80[d]
19	 **11a**	**1b**	18	 **17c**	82[d]
20	 **12a**	**8b**	7	 **18c**	81[d]
21	 **13a**	 **11b**	7	 **19c**	78[df]
22	 **14a**	**11b**	16	 **20c**	77[d]
23	 **15a**	**8b**	19	 **21c**	74[d]
24	 **16a**	**3b**	48	 **22c**	NR[de]
25	 **17a**	 **12b**	16	**22c**	78[d]

[a] Reaction conditions: amine (1.2 mmol), carbamoylimidazole (1.0 mmol), $AlMe_3$ (2.5 mmol) 2 M in toluene. [b] Isolated yield. [c] DCM solvent, oil bath temperature 55 °C. [d] Toluene solvent, oil bath temperature 108 °C. [e] Amine and $AlMe_3$ were complexed for 24 h under reflux, cooled and then carbamoyl imidazole was added, and refluxed for additional 24 h. [f] $AlMe_3$(4.0 equiv) was used.

commercially available amine hydrochloride salt (**13a**) itself could be used and conversion to the aluminium amide was achieved by taking excess of $AlMe_3$ (4.0 equiv). The reactions were equally facile with heterocyclic amines like 3,5-dimethylpyrazole (**8a**) and 2-aminothiazole (**9a**) to afford ureas **13c** (53%) and **14c** (79%). The weakly nucleophilic 2,4-dichlorophenyl ethylamine (**16a**) failed to react under these conditions. By incorporating the less nucleophilic amine **16a** in the carbamoylimidazole and using the more reactive amine **17a** as nucleophile, the desired urea (**22c**) was prepared without any difficulty (entry

Table 3 Chemoselectivity over carbamates



Entry	R (**b**)	(Urea)[a] (%)	**28c**[a] (%)	**29c**
1	*t*-butyl (**13b**)	87 (**23c**)	0	0
2	Benzyl (**14b**)	81 (**24c**)	8	0
3	Ph (**15b**)	80 (**25c**)	8	0
4	Et (**16b**)	80 (**26c**)	9	0
5	Me (**17b**)	81 (**27c**)	7	0

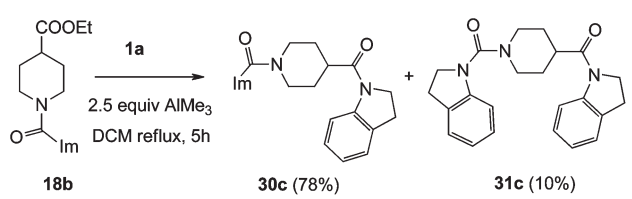
[a] Isolated yield.

24 and **25**, Table 2). Sensitive functional groups such as –OTBS (**7c**, 69%), ketal (**5c**, 89%) are also well tolerated in the above mentioned conditions. All the reactions were monitored by TLC and products were purified by silica gel column chromatography.

Since carbamates are known to react with amine in the presence of $AlMe_3$[11a] to form ureas, it was of interest to investigate the compatibility of the carbamate functional group appended to the carbamoylimidazole and examine the chemoselectivity of the reaction of substrates such as **13b–17b** towards this reaction. Indoline **1a** (1.1 mmol) when subjected to coupling reaction with **15b** (1.0 mmol), 2.5 equiv of $AlMe_3$ in 4 mL of dichloromethane for 5 h at 50 °C led to the selective formation of product **25c** in 80% yield, retaining the carbamate group. The bisurea **28c** was formed in very minor amount, *viz*., 8% (entry 3, Table 3). There was no evidence for the formation of the product **29c** arising out of selective monocoupling at the carbamate.

Similar chemoselectivity was observed in a few other cases investigated (Table 3). However in the case of *N*-Boc containing carbamoylimidazole **13b**, we observed almost complete selectivity in favour of mono urea **23c** (entry 1, Table 3). The *N*-Boc group was found to be quite stable under this condition. Analysis of the reaction by LCMS did not detect the formation of product **29c**.

Finally we examined the relative reactivities of an amine towards an aliphatic ester and a carbamoylimidazole in this trimethyl aluminium-mediated reaction. As anticipated, the ester functionality (Scheme 2) exhibited higher reactivity compared to the carbamoylimidazole carbonyl. Our limited study reveals that the order of reactivity towards amine in presence of $AlMe_3$ is aliphatic ester > *tert*-carbamoylimidazole > *tert*-carbamate.



Scheme 2 Chemoselectivity between ester and carbamoylimidazole.

Conclusions

In conclusion we have developed a general and efficient method for synthesizing a variety of unsymmetrical tetrasubstituted ureas from diverse amines and carbamoylimidazoles, based on the activation by $AlMe_3$. Commercially available cheaper and safer carbamoylimidazole was utilized as carbonyl source in place of toxic phosgene/triphosgene and carbon monoxide. Our method tolerates a wide range of functional groups like –OMe, Cl, CN, OTBS, ketal, amide, OCF_3, *tert*-*N*-benzyl, *N*-Boc, *N*-Cbz, and other carbamates. Various amines—aliphatic, alicyclic, aromatic, heterocyclic, poor and hindered—were found to be effective. Our method complements the existing methods of synthesis of tetrasubstituted urea. We believe that the aluminium–amide complexes which can be conveniently generated *in situ* with $AlMe_3$ have tremendous potential and could be very useful as efficient nucleophiles in reactions with diverse electrophiles.

Experimental

^1H NMR and ^{13}C NMR spectra were determined in 300 and 75 MHz NMR spectrometers with reference to TMS as an internal standard using solvents $CDCl_3$ or DMSO-d_6. High resolution mass spectrometry measurements were performed through positive electronspray ionization on a Bruker Daltonics instrument. HPLC conditions: HPLC Waters. Column: ASCENTIS C18, (50 × 4.6 mm I.D.) 2.7 μm; **A**: acetonitrile; **B**: 0.01 M NH_4OAc + 0.5% TEA, pH 5.0 with AcOH; (T/B%: 0/80, 6/20, 7/80, 10/80) with flow of 1 ml min^{-1} and Conc: 0.2 mg ml^{-1}. LCMS was done on Waters Acquity using Waters BEH C18 column of dimension (50 mm × 2.1 mm) 1.7 μm with solvent composition on Thermo LCMS Advantage with 5 mM ammonium acetate as buffer. Melting points were determined by open capillary method and are uncorrected. IR data were recorded on a Perkin Elmer FTIR. All reagents were purchased from commercial suppliers and used without further purification unless noted. $AlMe_3$ (2 M solution in toluene) was purchased from Aldrich. CH_2Cl_2 was dried with calcium chloride and distilled freshly. Toluene was dried over sodium, distilled and stored over molecular sieves. All reactions were conducted under an atmosphere of nitrogen. The products were purified with flash chromatography on silica gel (100–200 mesh).

General procedure (1) for synthesis of monosubstituted piperazinecarbamates (piperazine starting materials used in Table 3)

Step-1: A solution of mono Boc protected piperazine (5.0 mmol) and pyridine (5.25 mmol) in DCM (30 ml) was cooled to 0 °C. Chloroformate (5.25 mmol) was added slowly and stirred at RT for 1 h. The reaction was monitored by TLC. After completion of the reaction, reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with cold 1 N HCl (25 mL) and then with H_2O (150 mL). The CH_2Cl_2 layer was dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure. The crude product was taken to the next step as such without purification.

Step-2: The crude product (4.5 mmol) from step-1 was dissolved in CH_2Cl_2 (20 mL) cooled to 0 °C, and TFA (12 mmol) was added slowly, stirred and warmed to room temperature. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The crude product obtained was dissolved in CH_2Cl_2 (60 mL) and basified with cold aq. NH_3 (5–10 mL) and then washed with water. The CH_2Cl_2 layer was dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to get Boc deprotected monosubstituted piperazinecarbamates.

General procedure (2) for the preparation of carbamoylimidazoles 3b, 4b, 7b, 8b and 11b

To a solution of amine (10.0 mmol) in dry THF (100 mL) was slowly added carbonyldiimidazole (CDI) (12.0 mmol) under nitrogen atmosphere and the solution was refluxed for 20–24 h. The reaction was monitored by TLC. After completion of the reaction, the mixture was concentrated under reduced pressure. The residue was extracted with CH_2Cl_2 (200 mL), washed with water and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography.

Spectral data of carbamoylimidazole (3b, 4b, 7b, 8b and 11b)

(3,4-Dihydro-1H-isoquinolin-2-yl)-imidazol-1-yl-methanone (3b). Prepared by general procedure **2**. R_f = 0.6 (hexane–EtOAc, 1 : 4); mp 89–90 °C, (lit.[20b] 82–83 °C); IR (KBr): 3353, 3099, 2898, 1969, 1681, 1429, 1301, 1240, 1105, 1078, 752 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.93 (s, 1H), 7.27–7.17 (m, 4H), 7.12–7.08 (m, 2H), 4.74 (s, 2H), 3.81 (t, 2H, J = 6 Hz), 3.00 (t, 2H, J = 6 Hz); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 151.0, 136.8, 133.7, 131.7, 129.8, 128.8, 127.3, 126.8, 126.3, 117.9, 48.4, 44.5, 28.5; LCMS (M + 1): 227.87.

***N*-Methyl-*N*-phenyl-imidazole-1-carboxamide (4b).**[21b] Prepared by general procedure **2**. R_f = 0.5 (hexane–EtOAc, 2 : 3); Light brown solid, IR (KBr): 3384, 3128, 2946, 2587, 2358, 1988, 1958, 1699, 1596, 1423, 1383, 1340, 1294, 1212, 1073, 1038, 901, 777, 751 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.55 (s, 1H), 7.37–7.32 (m, 3H), 7.13–7.09 (m, 2H), 6.84–6.78 (m, 2H), 3.48 (s, 3H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 150.2, 142.9, 137.7, 130.2, 128.9, 128.0, 125.9, 118.4, 40.1; LCMS (M + 1): 202.08.

[2-[[*tert*-Butyl(dimethyl)silyl]oxymethyl]pyrrolidin-1-yl]-imidazol-1-yl-methanone (7b). Prepared by general procedure **2**. R_f = 0.5 (DCM–MeOH, 4.5 : 0.5). Yellow sticky mass. The compound could not be obtained in a very pure form. But it showed satisfactory ^1H and ^{13}C NMR spectra. HRMS data also complies. IR (KBr): 3118, 2954, 2929, 2856, 1757, 1693, 1471, 1406, 1257, 1215, 1105, 838 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.97 (s, 1H), 7.31 (s, 1H), 7.06 (s, 1H), 4.26–4.24 (m, 1H), 3.91–3.86 (m, 1H), 3.68–3.52 (m, 3.7H), 2.11–1.99 (m, 3.8H), 1.84–1.79 (m, 1H), 0.87 (s, 9H), 0.07–0.02 (m, 6H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 149.6, 136.7, 129.3, 117.7, 62.1, 60.4, 50.9, 27.0, 25.8, 25.7, 25.3, 18.1, −5.4, −5.5; ESI-HRMS: m/z calcd for $C_{15}H_{28}N_3O_2Si$ [M + H]: 310.1947, found: 310.1972.

***N*,*N*-Dibenzylimidazole-1-carboxamide (8b).** Prepared by the general procedure **2**. R_f = 0.5 (hexane–EtOAc, 1 : 4). Off white solid, mp 62–64 °C; IR(KBr): 3363, 3155, 3120, 2927, 1967, 1693, 1496, 1427 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.96 (s, 1H), 7.44–7.36 (m, 6H), 7.35–7.26 (m, 5H), 7.04 (s, 1H), 4.6 (s, 4H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 152.4, 137.0, 135.1, 129.9, 129.1, 128.2, 127.5, 117.9, 50.7; ESI-HRMS: m/z calcd for $C_{18}H_{18}N_3O$ [M + H]: 292.1444, found: 292.1435.

Imidazol-1-yl-pyrrolidin-1-yl-methanone (11b). Prepared by the general procedure **2**. Waxy solid, mp 52–53 °C (lit.[27] 50–52 °C); IR (KBr): 3335, 3137, 2976, 2881, 2565, 2308, 2141, 1947, 1699, 1414, 1339, 1158, 1098, 1037, 1012, 935, 919, 848, 727 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.98 (s, 1H), 7.32 (s, 1H), 7.03 (s, 1H), 3.61–3.56 (m, 4H), 1.97–1.93 (m, 4H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 149.6, 136.7, 129.3, 117.6, 48.8, 25.5.

General procedure (3) for the preparation of carbamoylimidazoles (1b, 2b, 5b, 6b, 10b, 13b–18b)

CDI (5.5 mol) was added portion-wise to the solution of amine (5.0 mmol) in dry CH_2Cl_2 (50 mL) under nitrogen. The reaction mixture was stirred at RT for 12 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with water (2 × 150 mL). The organic layer was dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure afforded the crude carbamoylimidazole which was purified by column chromatography.

Spectral data of carbamoylimidazoles (1b, 2b, 5b, 6b, 10b, 13b–18b)

Imidazol-1-yl-piperidin-1-yl-methanone (1b). Prepared by the general procedure **3**. R_f = 0.3 (EtOAc). Off white solid, mp 63–64 °C; IR (KBr): 3112, 2943, 2886, 1932, 1677, 1427, 1284 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.84 (s, 1H), 7.19–7.18 (m, 1H), 7.08–7.07 (m, 1H), 3.55–3.51 (m, 4H), 1.69–1.64 (m, 6H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 150.8, 136.8, 129.5, 117.9, 47.5, 25.7, 24.1; ESI-HRMS: m/z calcd for $C_9H_{14}N_3O$ [M + H]:180.1131, found: 180.1127.

(4-Benzylpiperazin-1-yl)-imidazol-1-yl-methanone (2b). Prepared by the general procedure **3**. R_f = 0.5 (DCM–MeOH, 4.5 : 0.5). Off white solid, mp 62 °C; IR (KBr): 3340, 3132, 3031, 2817, 1356, 1954, 1679, 1436, 1281, 1251, 994, 900, 699 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.79 (s, 1H), 7.23–7.19 (m, 5H), 7.11(s, 1H), 6.99 (s, 1H), 3.52–3.47 (m, 4H), 3.46 (s, 2H), 2.43–2.35 (m, 4H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 150.6, 137.2, 136.8, 129.6,129.0, 128.4, 127.4, 117.9, 62.6, 52.5, 46.4; ESI-HRMS: m/z calcd for $C_{15}H_{19}N_4O$ [M + H]: 271.1553, found: 271.1555.

1,4-Bioxa-8-azaspiro[4.5]decan-8-yl(imidazol-1-yl) methanone (5b). Prepared by the general procedure **3**. White solid, mp

123 °C, (lit.[21b] 121–123 °C); IR (KBr): 3377, 3133, 2956, 2891, 2679, 1935, 1698, 1428, 1249, 1104, 942, 913, 764 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.82 (s, 1H), 7.15 (s, 1H), 7.03 (s, 1H), 3.94 (s, 4H), 3.64–3.61 (m, 4H), 1.75–1.71 (m, 4H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 150.7, 136.8, 129.6, 117.9, 106.2, 64.5, 44.6, 34.9; ESI-HRMS: *m/z* calcd for $C_{11}H_{16}N_3O_3$ [M + H] is 238.1186, found: 238.1179.

Imidazol-1-yl-[4-(3-trifluoromethoxy-benzoyl) piperazin-1-yl] methanone (6b). Prepared by the general procedure. R_f = 0.3 (DCM–MeOH, 4.75 : 0.25). White solid, mp 93–95 °C; IR (KBr): 3353, 3162, 3111, 2917, 2869, 2418, 1811, 1678, 1652, 1597, 1365, 1279, 1221, 993, 753 cm^{-1}; ^1H NMR (300 MHz, TMS, DMSO-d_6): δ 7.78 (s, 1H), 7.41–7.35 (m, 1H), 7.26–7.19 (m, 3H), 7.11 (s, 1H), 6.97 (s, 1H), 3.68–3.54 (br, 8H); ^{13}C NMR (75 MHz, TMS, DMSO-d_6): δ 168.9, 150.9, 148.6, 138.1, 137.5, 131.1, 129.2, 126.5, 125.6 (OCF_3), 122.6, 122.2 (OCF_3), 120.2, 119.1, 118.8 (OCF_3), 115.4 (OCF_3, J_{C-F} = 262.5 Hz), 46.8, 45.9, 41.6; ESI-HRMS: *m/z* calcd for $C_{16}H_{16}F_3N_4O_3$ [M + H]: 369.1169, found: 369.1160.

4-(1H-Imidazol-1-ylcarbonyl) morpholine (10b). Prepared by general procedure **2**. R_f = 0.2 (EtOAc); White solid, mp 80–81 °C, (lit.[21b] 83–84 °C); IR (KBr): 3126, 3106, 2972, 2960, 2874, 1943, 1676, 1645, 1545, 1476, 1440, 1363, 1303 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.86 (s, 1H), 7.18 (s, 1H), 7.08 (s, 1H), 3.76–3.73 (m, 4H), 3.63–3.60 (m, 4H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 150.8, 136.8, 129.9, 117.7, 66.4, 46.7; LCMS (M + 1):182.08.

4-(Imidazole-1-carbonyl) piperazine-1-carboxylic acid *tert*-butyl ester (13b). Prepared by general procedure **3**. R_f = 0.3 (EtOAc). White solid, mp 106–108 °C; IR(KBr): 3110, 2995, 2929, 2864, 2506, 2112, 1677, 1420, 1367, 1248, 1167, 1130, 1033 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.87 (s, 1H), 7.19 (d, 1H, J = 1.2 Hz), 7.11 (d, 1H, J = 1.2 Hz), 3.60–3.51 (m, 8H), 1.48 (s, 9H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 154.4, 151.0, 136.9, 130.0, 117.8, 80.8, 46.3, 43.3, 28.3; ESI-HRMS: *m/z* calcd for $C_{13}H_{21}N_4O_3$ [M + H]: 281.1608, found: 281.1600.

4-(Imidazole-1-carbonyl) piperazine-1-carboxylic acid benzyl ester (14b). Prepared by general procedure **3**. R_f = 0.3 (EtOAc). Sticky mass; IR (KBr): 3116, 2927, 2867, 1694, 1496, 1453, 1429, 1363, 1283, 1076, 997, 750 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.88 (s, 1H), 7.43–7.30 (m, 5H), 7.19 (s, 1H), 7.11 (s, 1H), 5.16 (s, 2H), 3.67–3.53 (m, 8H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 154.9, 150.9, 136.8, 136.0, 129.9, 128.6, 128.3, 128.1, 117.8, 67.7, 46.2, 43.4; ESI-HRMS: *m/z* calcd for $C_{16}H_{19}N_4O_3$ [M + H]: 315.1452, found: 315.1446.

4-(Imidazole-1-carbonyl) piperazine-1-carboxylic acid phenyl ester (15b). Prepared by the general procedure **3**. R_f = 0.3 (EtOAc). White solid, mp 135 °C; IR(KBr): 3362, 3129, 3066, 3042, 3000, 2925, 2876, 2376, 2035, 1975, 1904, 1880, 1802, 1712, 1590, 1417, 1240, 1198, 1101, 1027, 1027, 961, 900 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.9 (s, 1H), 7.40–7.34 (m, 2H), 7.27–7.22 (m, 2H), 7.19–7.08 (m, 3H), 3.69–3.68 (m, 8H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 153.5, 151.1, 151.0, 136.9, 130.1, 129.4, 125.7, 121.5, 117.8, 46.2, 44.1, 43.6; ESI-HRMS: *m/z* calcd for $C_{15}H_{17}N_4O_3$ [M + H]: 301.1295, found: 301.1306.

4-(Imidazole-1-carbonyl) piperazine-1-carboxylic acid ethyl ester (16b). Prepared by general procedure **3**. R_f = 0. 3 (EtOAc). Colorless, viscous; IR (KBr): 3118, 2979, 2866, 1728, 1693, 1429, 1315, 1276, 1315, 1276, 1174, 1101, 1068, 1041, 989, 752 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.88 (s, 1H), 7.19 (s, 1H), 7.11 (s, 1H), 4.16 (q, 2H, J = 7.1 Hz), 3.65–3.55 (m, 8H), 1.27 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 155.2, 151.1, 136.9, 130.0, 117.8, 61.9, 46.2, 43.3, 14.6; ESI-HRMS: *m/z* calcd for $C_{11}H_{17}N_4O_3$ [M + H]: 253.1295, found: 253.1310.

4-(Imidazole-1-carbonyl) piperazine-1-carboxylic acid methyl ester (17b). Prepared by general procedure **3**. R_f = 0.3 (EtOAc); White solid, mp 86–88 °C; IR(KBr): 3380, 3131, 2913, 2869, 2690, 2057, 1988, 1926, 1694, 1438, 1292, 1251, 1127, 1081, 997 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.89 (s, 1H), 7.22 (s, 1H), 7.15 (s, 1H), 3.75 (s, 3H), 3.62–3.52 (m, 8H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 155.5, 151.0, 136.8, 130.0, 117.8, 53.4, 46.2, 43.4; ESI-HRMS: *m/z* calcd for $C_{10}H_{15}N_4O_3$ [M + H]: 239.1139, found: 239.1141.

1-(Imidazole-1-carbonyl) piperidine-4-carboxylic acid ethyl ester (18b). Prepared by the general procedure **3**. R_f = 0.3 (EtOAc). Colourless, sticky; IR (KBr): 2977, 2864, 2607, 1901, 1739, 1712, 1643, 1622, 1465, 1452 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.86 (s, 1H), 7.29 (s, 1H), 7.09 (s, 1H), 4.18 (q, 2H, J = 7.2 Hz), 4.03–3.97 (m, 2H), 3.25–3.16 (m, 2H), 2.65–2.57 (m, 1H), 2.06–1.97 (m, 2H), 1.87–1.76 (m, 2 H), 1.28 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 173.6, 151.9, 136.8, 129.7, 117.9, 60.9, 45.8, 40.8, 27.9, 14.3; ESI-HRMS: *m/z* calcd for $C_{12}H_{18}N_3O_3$ [M + H]: 252.1343, found: 252.1333.

***N,N*-Diphenylimidazole-1-carboxamide (9b).**[28] CAS no [2875–79–8]: To a solution of diphenylamine (1.69 g, 10.0 mmol), DBU (1.83 g, 12 mmol) in dry acetonitrile (60 mL) was added carbonyldiimidazole (**CDI**) (1.95 g, 12.0 mmol) under nitrogen atmosphere and refluxed for 48 h. The reaction did not go to completion. Volatiles were distilled out under reduced pressure.

The residue was extracted with CH_2Cl_2 (200 mL), washed with water and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and crude product was purified by column chromatography to get white solid. Yield 58%; R_f = 0.35 (hexane–EtOAc, 3 : 2); white solid; mp 119–120 °C; IR (KBr): 3161, 3050, 3038, 1702, 1693, 1592, 1491, 1487, 1389 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$) δ 7.73 (s, 1H), 7.42–7.35 (m, 4H), 7.33–7.27 (m, 2H), 7.22–7.16 (m, 4H), 7.01–7.0 (m, 1H), 6.90–6.86 (m, 1H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$) δ 150.1, 142.4, 137.9, 129.8, 129.3, 127.5, 126.5, 118.4. LCMS (M + 1) −264.0.

Imidazole-1-carboxylic acid (2,4-dichloro-phenyl) ethyl amide (12b). Solution of 2,4-dichloro *N*-ethylaniline (800 mg, 4.21 mmol) in dry THF under argon atmosphere was cooled to −45 °C and 1.6 M solution of *n*-BuLi in hexane (2.9 mL, 4.63 mmol) was slowly added. After a period of 15 min, a solution of CDI (820 mg, 5.05 mmol) in dry THF was slowly added drop-wise. The reaction mixture was left at RT overnight (16 h), then cooled to 0 °C and quenched with NH_4Cl solution

(5 mL) and evaporated under reduced pressure. The residue was extracted with CH_2Cl_2 (100 mL) and washed with water (50 ml). The CH_2Cl_2 layer was separated and dried over anhydrous Na_2SO_4. The CH_2Cl_2 was evaporated under reduced pressure. The crude was purified by column chromatography (20% EtOAc/hexane) to obtain the pure product in 57% yield. White solid, mp 63–65 °C; IR(KBr): 3385, 3117, 2925, 2584, 2298, 1928, 1698, 1542, 1496, 1299, 995, 806 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.60 (s, 1H), 7.50 (d, 1H, J = 2.1 Hz), 7.33–7.28 (m, 1H), 7.18–7.15 (m, 1H), 6.9–6.85 (m, 2H), 3.94–3.79 (br, 2H), 1.26 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 149.9, 137.3, 137.2, 135.2, 133.5, 131.1, 130.4, 129.3, 128.9, 118.0, 47.0, 12.1; ESI-HRMS: m/z calcd for $C_{12}H_{12}Cl_2N_3O$ [M + H]: 284.0352, found: 284.0366.

General procedure (4) for the preparation of ureas 1c–22c (Table 2)

In a dry two necked flask, under nitrogen atmosphere amine **A** (3.6 mmol) and carbamoylimidazole **B** (3.0 mmol), were taken and added dry dichloromethane (10 mL) or toluene (10 mL) and cooled to 0 °C. To this solution was added 2 M solution of $AlMe_3$ in toluene (3.75 mL, 7.5 mmol). The reaction mixture was stirred at room temperature for 30 min and heated to 55 °C or 108 °C (oil bath temperature) for the specified time. The reaction mixture was cooled to 0 °C, quenched with saturated $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 or ethyl acetate. The organic extract was dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate/hexane).

Spectral data of ureas (1c–22c)

Indolin-1-yl (1-piperidyl)methanone (1c).[24] Prepared by general procedure **4**. Brown, sticky; R_f = 0.35 (hexane–EtOAc, 4 : 1); Following general procedure **4** (DCM, 5 h) tetrasubstituted urea **15c** was synthesized in 72% yield. The colourless sticky mass turned brown after 24 h. IR (KBr): 2935, 2852, 1893, 1650, 1604, 1483, 1404, 1255, 1022, 750 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.17–7.10 (m, 2H), 7.01–6.99 (m, 1H), 6.89–6.84 (m, 1H), 3.91 (t, 2H, J = 8.4 Hz), 3.34–3.32 (m, 4H), 3.01 (t, 2H, J = 8.4 Hz), 1.63–1.61 (m, 6H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 159.5, 144.3, 131.4, 126.9, 124.8, 121.3, 112.8, 50.3, 47.4, 27.9, 25.8, 24.5; ESI-HRMS: m/z calcd for $C_{14}H_{19}N_2O$ [M + H]: 231.1497, found: 231.1509. HPLC (220 nm): 4.521 min, 98.9%.

(4-Benzylpiperazin-1-yl)-indolin-1-yl-methanone (2c). Prepared by general procedure **4**. Brown, sticky; R_f = 0.3 (hexane–EtOAc, 3 : 2); IR (KBr): 3029, 2919, 2867, 2810, 2782, 2768, 1652, 1483, 1404, 1311, 1054, 1002, 786, 759 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.36–7.28 (m, 5H), 7.19–7.13 (m, 2H), 7.07–7.04 (m, 1H), 6.93–6.88 (m, 1H), 3.94 (t, 2H, J = 8.1 Hz), 3.57 (s, 2H), 3.43 (br, 4H), 3.03 (t, 2H, J = 8.1 Hz), 2.54 (br, 4H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 159.3, 143.9, 137.7, 131.6, 129.2, 128.3, 127.2, 127.0, 124.9, 121.6, 112.9, 63.1, 52.9, 50.4, 46.4, 27.9; ESI-HRMS: m/z calcd for $C_{20}H_{24}N_3O$ [M + H]: 322.1914, found: 322. 1905.

3,4-Dihydro-1H-isoquinolin-2-yl (indolin-1-yl) methanone (3c). Prepared by general procedure **4**. Brown solid, R_f = 0.4 (hexane–EtOAc, 4 : 1); mp 95–97 °C; IR (KBr): 3267, 3066, 2945, 2562, 2866, 1963, 1909, 1866, 1643, 1477, 1419, 1355, 1259. 972, 926 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.22–7.15 (m, 4H), 7.13–7.10 (m, 1H), 7.09–7.05 (m, 1H), 7.03–7.01 (m, 1H), 6.93–6.88 (m, 1H), 4.56 (s, 2H), 3.96 (t, 2H, J = 8.1 Hz), 3.68 (t, 2H, J = 5.7 Hz), 3.08–2.98 (m, 4H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 159.4, 144.0, 134.4, 133.4, 131.5, 128.9, 127.1, 126.3, 126.2, 124.9, 121.5, 113.2, 50.4, 48.5, 43.8, 28.4, 28.0; ESI-HRMS: m/z calcd for $C_{18}H_{19}N_2O$ [M + H]: 279.1497, found: 279.1494.

***N*-Methyl-*N*-phenyl indoline-1-carboxamide (4c).** Prepared by general procedure **4**. Dark brown solid, R_f = 0.4 (hexane–EtOAc, 4 : 1); mp 105–106 °C; IR (KBr): 3290, 3035, 2970, 2931, 2858, 2106, 1963, 1882, 1751, 1650, 1596, 1485, 1419, 1380, 1342, 1114, 948 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.69 (d, 1H, J = 8.1 Hz), 7.36–7.26 (m, 2H), 7.19–7.15 (m, 4H), 7.09–7.07 (m, 1H), 6.93–6.90 (m, 1H), 3.38–3.33 (m, 5H), 2.89 (t, 2H, J = 8.7 Hz); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 158.2, 145.4, 144.0, 130.9, 129.5, 127.1, 125.3, 124.8, 124.4, 122.3, 116.1, 49.8, 39.4, 28.5; ESI-HRMS: m/z calcd for $C_{16}H_{17}N_2O$ [M + H^+]: 253.1335, found: 253.1341.

1,4-Dioxa-8-azaspiro[4.5]decan-8-yl (indolin-1-yl) methanone (5c). Prepared by general procedure **4**. Brown, sticky; R_f = 0.3 (hexane–EtOAc, 3 : 2); IR (KBr): 2959, 2929, 2882, 1651, 1613, 1604, 1481, 1408, 1361, 1243, 1097, 911,752 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.18–7.10 (m, 2H), 6.99 (d, 1H, J = 8.1 Hz), 6.91–6.86 (m, 1H), 3.98 (s, 4H), 3.92 (t, 2H, J = 8.4 Hz), 3.50–3.46 (m, 4H), 3.02 (t, 2H, J = 8.1 Hz), 1.79–1.76 (m, 4H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 159.1, 144.1, 131.5, 127.0, 124.9, 121.5, 112.8, 107.1, 64.4, 50.3, 44.5, 35.0, 27.9; ESI-HRMS: m/z calcd for $C_{16}H_{21}N_2O_3$ [M + H^+]: 289.1547, found: 289.1551.

Tetrasubstituted urea (6c). Prepared by the general procedure **4**. Brown solid, R_f = 0.3 (hexane–EtOAc, 1 : 1); mp 113 °C; IR (KBr): 3253, 3075, 3035, 2882, 2901, 2866, 1945, 1902, 1641, 1548, 1412, 1357, 1260, 1085, 989 cm^{-1}; ^1H NMR (300 MHz, TMS, DMSO-d_6): δ 7.63–7.58 (m, 1H), 7.49–7.46 (m, 3H), 7.21–7.18 (m, 1H), 7.15–7.10 (m, 2H), 6.9–6.86 (m, 1H), 3.85 (t, 2H, J = 8.1 Hz), 3.7–3.31(m, 8H), 3.0 (t, 2H, J = 8.1 Hz); ^{13}C NMR (75 MHz, TMS, DMSO-d_6): δ 167.4, 158.5, 148.1, 143.7, 137.9, 131.4, 130.7, 126.8, 126.0, 125.0 (OCF_3) 124.9, 122.1, 121.7 (OCF_3), 121.5, 119.7, 118.2 (OCF_3), 114.9 (OCF_3, J_{C-F} = 255.1 Hz), 113.4, 50.0, 46.8, 45.5, 40.3, 27.5; ESI-HRMS: m/z calcd for $C_{21}H_{21}F_3N_3O_3$ [M + H]: 420.1530, found: 420.1522.

Tetrasubstituted urea (7c). Prepared by the general procedure **4**. Brown solid, R_f = 0.6 (hexane–EtOAc, 4 : 1); mp 88 °C; IR (KBr): 3274, 2954, 2931, 1858, 1944, 1899, 1639, 1598, 1477, 1400, 1257, 1083, 840 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.16–7.10 (m, 3H), 6.89–6.85 (m, 1H), 4.30–4.27 (m, 1H), 3.99–3.92 (m, 1H), 3.86–3.66 (m, 3H), 3.43–3.32 (m, 2H), 3.07–2.96 (m, 2H), 2.03–1.94 (m, 3H), 1.76–1.72 (m, 2H), 0.91 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 158.2, 144.3, 131.4, 126.9, 124.7, 121.3, 114.2, 63.6,

58.9, 50.2, 50.0, 29.7, 28.3, 27.4, 25.9, 25.5, 18.2, −5.3, −5.4; ESI-HRMS: *m/z* calcd for $C_{20}H_{32}N_2NaO_2Si$ [M + Na]: 383.2125, found: 383.2116.

1,1-Dibenzyl 3,3-diphenyl urea (8c). Prepared by general procedure **4**. Off white solid, R_f = 0.6 (hexane–EtOAc, 4 : 1); mp 128–130 °C; IR (KBr): 3269, 3028, 2854, 1951, 1622, 1604, 1569, 1496, 1367, 1309, 1263.1076, 1027, 991 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.42–6.84 (m, 20H), 4.67–4.52 (m, 4H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 171.9, 142.7, 142.3, 137.0, 129.7, 129.2, 128.0, 127.9, 124.7, 121.8, 120.3, 119.0, 118.1, 52.4, 47.1; ESI-HRMS: *m/z* calcd for $C_{27}H_{25}N_2O$ [M + H]: 393.1961, found: 393.1949.

***N,N*-Dibenzylmorpholine-4-carboxamide (9c).** In a dry two necked flask, under nitrogen atmosphere, dibenzylamine (3.6 mmol) and dry toluene (10 mL) were taken and cooled to 0 °C, 2 M solution of $AlMe_3$ in toluene (3.75 mL, 7.5 mmol) was added. The mixture was heated to 110 °C (oil bath temperature) for 24 h. The reaction mixture was cooled to 0 °C, and carbamoylimidazole **10b** (3.0 mmol) was added and the mixture was heated to 110 °C for 24 h. The reaction mixture was cooled to 0 °C, quenched with saturated $NaHCO_3$ (5 mL) and extracted with ethyl acetate. The organic extract was dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography (20–25% EtOAc/hexane). White solid, mp 106–108 °C; IR (KBr): 3363, 3129, 2875, 2692, 2586, 2373, 2230, 2036, 1976, 1955, 1904, 1802, 1712, 1590, 1417, 1371, 1240, 1198, 1072, 996 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.36–7.25 (m, 6H), 7.24–7.15 (m, 4H), 4.31 (s, 4H), 3.71–3.68 (m, 4H), 3.34–3.31 (m, 4H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 164.8, 137.2, 128.6, 127.8, 127.4, 66.6, 50.6, 47.7; ESI-HRMS: *m/z* calcd for $C_{19}H_{22}N_2O_2Na$ [M + Na]: 333.1573, found: 333.1570.

1-(4-Chlorophenyl)-1, 3-dimethyl-3-phenyl urea (10c). Prepared by general procedure **4**. Yellow solid, R_f = 0.5 (hexane–EtOAc, 3 : 2); mp 166–169 °C; IR(KBr): 3274, 3089, 3055, 3035, 2931, 2588, 2310, 1743, 1647, 1589, 1492, 1434, 1361, 1118 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.10–6.97 (m, 5H), 6.80–6.79 (m, 2H), 6.77–6.69 (m, 2H), 3.19 (s, 3H), 3.15 (s, 3H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 161.0, 145.4, 144.1, 130.2, 128.7, 128.6, 126.9, 125.8, 125.1, 39.3, 39.2; ESI-HRMS: *m/z* calcd for $C_{15}H_{15}ClN_2ONa$ [M + Na^+]: 297.0765, found: 297.0762.

1-(4-Cyanophenyl)-1,3-dimethyl-3-phenyl urea (11c). Prepared by the general procedure **4**. Light yellow solid, R_f = 0.3 (hexane–EtOAc, 4 : 1); mp 162 °C; IR (KBr): 3120, 3047, 2933, 2225, 2001, 1886, 1755, 1650, 1600, 1583, 1510, 1436, 1361, 1118, 1074, 948 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.34–7.32 (m, 2H), 7.11–7.06 (m, 2H), 6.99–6.95 (m, 1H), 6.92–6.89 (m, 2H), 6.82–6.80 (m, 2H), 3.26 (s, 3H), 3.16 (s, 3H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 160.4, 149.6, 145.0, 133.0, 129.3, 125.9, 125.8, 124.1, 119.1, 107.1, 39.5, 38.4; ESI-HRMS: *m/z* calcd for $C_{16}H_{15}N_3ONa$ [M + Na]: 288.1107, found: 288.1113.

1-(4-Cyanophenyl)3-methyl-1,3-diphenyl urea (12c). Prepared by general procedure **4**. Yellow, sticky; R_f = 0.3 (hexane–EtOAc, 4 : 1); IR (KBr): 3111, 3099, 2899, 2579, 2397, 2212, 1969, 1930, 1892, 1809, 1685, 1429, 1302, 1240, 1077, 1053, 979, 904, 752 cm^{-1}. ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.46–7.43 (m, 2H), 7.25–6.96 (m, 8H), 6.81–6.73 (m, 4H), 3.32 (s, 3H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 159.7, 148.9, 144.2, 142.5, 133.1, 129.6, 129.3, 126.8, 126.5, 126.4, 126.2, 123.9, 119.3, 106.8, 39.5. ESI-HRMS: *m/z* calcd for $C_{21}H_{18}N_3O$ [M + H]: 328.1444, found: 328.1430.

***N*-Methyl-*N*-phenyl-3,5-dimethylpyrazole-1-carboxamide (13c).** Prepared by general procedure **4**. Off white solid, R_f = 0.5 (hexanes–EtOAc, 4 : 1); mp 82–84 °C; IR (KBr): 3373, 3107, 3064, 2925, 2376, 1976, 1884, 1807, 1693, 1596, 1566, 1379, 1107 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.28–7.23 (m, 2H), 7.17–7.10 (m, 1H), 7.05–7.02 (m, 2H), 5.76 (s, 1H), 3.48 (s, 3H), 2.41 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 153.2, 149.9, 144.7, 143.0, 129.3, 126.5, 125.4, 108.4, 39.9, 13.7, 12.7; ESI-HRMS: *m/z* calcd for $C_{13}H_{15}N_3ONa$ [M + Na]: 252.1107, found: 252.1119.

1-Methyl-1-phenyl-3-thiazol-2-yl-urea (14c). Prepared by general procedure **4**. White solid, R_f = 0.4 (hexane–EtOAc, 3 : 2); mp 139–142 °C; IR(KBr): 3098, 2938, 2331, 2166, 1955, 1886, 1664, 1590, 1529, 1494, 1340, 1284, 1166, 1088, 1072 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.90–7.82 (br, 1H), 7.51–7.38 (m, 3H), 7.33–7.30 (m, 2H), 7.26–7.25 (m, 1H), 6.85 (d, 1H, *J* = 3.6 Hz), 3.37 (s, 3H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 160.2, 152.9, 141.3, 137.1, 130.6, 128.7, 127.4, 112.6, 37.5; ESI-HRMS: *m/z* calcd for $C_{11}H_{12}N_3OS$ [M + H]: 234.0696, found: 234.0688.

***N*-Methyl-*N*-phenyl-3,4-dihydroquinoline-1(2*H*) carboxamide (15c).** Prepared by general procedure **4**. Yellow, viscous; R_f = 0.4 (hexane–EtOAc, 4 : 1); IR (KBr): 3060, 3035, 2937, 2883, 1942, 1658, 1595, 1581, 1492, 1454, 1359, 1269, 1116, 750 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.28–7.26 (m, 3H), 7.17–7.04 (m, 4H), 6.96–6.91 (m, 1H), 6.83–6.82 (m, 1H), 3.39 (t, 2H, *J* = 6.1 Hz), 3.33 (s, 3H), 2.59 (t, 2H, *J* = 6.6 Hz), 1.89–1.85 (m, 2H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 160.2, 145.3, 139.4, 128.9, 128.5, 128.4, 126.0, 124.9, 124.2, 122.3, 121.8, 45.9, 38.8, 26.7, 23.2; ESI-HRMS: *m/z* calcd for $C_{17}H_{19}N_2O$[M + H]: 267.1497, found: 267.1503.

3,4-Dihydro-2H-quinolin-1-yl (1-piperidyl) methanone (16c). Prepared by general procedure **4**. Brown, sticky; R_f = 0.35 (hexane–EtOAc, 4 : 1); IR(KBr): 2935, 2854, 1647, 1604, 1577, 1492, 1413, 1253, 1027, 989, 752 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.09–7.06 (m, 2H), 7.01 (d, 1H, *J* = 1.2 Hz), 6.88 (t, 1H, *J* = 1.2 Hz), 3.58 (t, 2H, *J* = 6.1 Hz), 3.28–3.25 (m, 4H), 2.77 (t, 2H, *J* = 6.1 Hz), 1.98–1.94 (m, 2H), 1.56–1.50 (m, 6H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 160.3, 141.1, 129.0, 127.3, 126.3, 121.6, 119.5, 46.8, 45.6, 27.0, 25.6, 24.5, 23.4; ESI-HRMS: *m/z* calcd for $C_{15}H_{21}N_2O$ [M + H^+]: 245.1654, found: 245.1650.

***N*-Benzyl-*N*-methyl-piperidine-1-carboxamide (17c).** Prepared by general procedure **4**. Colourless, sticky; R_f = 0.6 (hexane–EtOAc, 3 : 2); IR(KBr): 3473, 2933, 2852, 1643, 1485, 1442, 1396, 1244, 1128, 1027, 918, 779, 730, 700 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.27–7.14 (m, 5H), 4.29 (s, 2H), 3.14–3.08 (m, 4H), 2.64 (s, 3H), 1.56–1.49 (m, 6H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 165.2, 138.0, 128.5, 127.6, 127.1,

54.0, 47.9, 36.5, 25.7, 24.7; ESI-HRMS: *m/z* calcd for $C_{14}H_{20}N_2ONa$ [M + Na^+]: 255.1468, found: 255.1473.

4-Phenylpiperazine-1-carboxylicacid dibenzylamide (18c). Prepared by general procedure **4**. White solid, R_f = 0.35 (hexane–EtOAc, 3 : 2); mp 143 °C; IR (KBr): 3228, 3039, 2923, 2815, 2692, 1959, 1704, 1620, 1596, 1581, 1473, 1365, 1234, 1215, 1164, 1072, 1018, 933 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.39–7.18 (m, 12H), 6.97–6.87 (m, 3H), 4.37 (s, 4H), 3.55–3.45 (m, 4H), 3.27–3.17 (m, 4H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 164.7, 151.1, 137.3, 129.1, 128.6, 127.8, 127.4, 120.2, 116.4, 50.6, 49.2, 47.2; ESI-HRMS: *m/z* calcd for $C_{25}H_{28}N_3O$ [M + H]: 386.2227, found: 386.2224.

1-(2-Methoxyphenyl)-4-(pyrrolidin-1-ylcarbonyl) piperazine (19c). Prepared by the general procedure **4**. R_f = 0.35 (hexane–EtOAc, 3 : 2). Light brown, sticky; IR (KBr): 2948, 2873, 1635, 1500, 1413, 1240, 1027, 1006, 748 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.04–7.0 (m, 1H), 6.98–6.86 (m, 3H), 3.87 (s, 3H), 3.48 (t, 4H, J = 4.8 Hz), 3.39–3.35 (m, 4H), 3.05 (t, 4H, J = 4.8 Hz), 1.88–1.78 (m, 4H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 162.7, 152.2, 141.1, 123.2, 120.9, 118.3, 111.2, 55.3, 50.7, 48.4, 46.2, 25.3; ESI-HRMS: *m/z* calcd for $C_{16}H_{24}N_3O_2$ [M + H^+]: 290.1863, found: 290.1873.

***N*-Methyl-*N*-phenylpyrrolidine-1-carboxamide (20c).** Prepared by general procedure **4**. R_f = 0.5 (hexane–EtOAc, 2 : 3). Yellow solid, mp 63 °C (lit.[20b] 64–66 °C); IR (KBr): 3256, 3058, 2878, 2597, 1987, 1902, 1814, 1596, 1425, 967, 758, 703 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.34–7.29 (m, 2H), 7.13–7.08 (m, 3H), 3.22 (s, 3H), 3.05 (t, 4H, J = 6.6 Hz), 1.70–1.65 (m, 4H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 159.9, 146.4, 129.3, 125.0, 124.5, 47.8, 39.6, 25.3; ESI-HRMS: *m/z* calcd for $C_{12}H_{16}N_2ONa$ [M + Na^+]: 227.1155, found: 227.1164.

1,1-Dibenzyl 3-naphthalen-2-yl-3-phenyl urea (21c). Prepared by general procedure **4**. R_f = 0.6 (hexane–EtOAc, 4 : 1). Brown solid, mp 140–142 °C; IR (KBr): 3331, 3051, 3027, 2941, 2903, 2528, 1964, 1933, 1821, 1701, 1599, 1493, 1448, 1302, 1272, 1234, 1180, 1082, 995, 978 cm^{-1}; ^1H NMR (300 MHz, TMS, DMSO-d_6): δ 7.70–7.86 (m, 2H), 7.79 (s, 1H), 7.60 (d, 1H, J = 8.1 Hz), 7.51–7.45 (m, 2H), 7.42–7.29 (m, 6H), 7.24–7.19 (m, 2H), 7.13–7.00 (m, 5H), 6.92 (d, 2H, J = 7.2 Hz), 6.85 (t, 1H, J = 3.3 Hz), 4.71 (q, 2H, J = 14.7 Hz), 4.27 (d, 1H, J = 15.6 Hz), 4.07 (d, 1H, J = 15.6 Hz); ^{13}C NMR (75 MHz, TMS, DMSO-d_6): δ 169.3, 144.4, 137.6, 137.4, 136.2, 131.2, 130.1, 129.7, 129.5, 129.0, 128.7, 128.1, 127.7, 127.6, 124.8, 123.9, 123.3, 121.6, 120.4, 117.1, 51.5, 46.8; ESI-HRMS: *m/z* calcd for $C_{31}H_{27}N_2O$ [M + H]: 443.2118, found: 443.2117.

Tetrasubstituted urea (22c). Prepared by general procedure **4**. R_f = 0.4 (hexane–EtOAc, 4 : 1). Light yellow, sticky; IR (KBr): 3384, 3109, 2923, 2584, 2298, 1928, 1688, 1532, 1445, 1078, 1105, 995, 806, 656, 497 cm^{-1}; ^1H NMR (300 MHz, TMS, $CDCl_3$): δ 7.49 (d, 1H, J = 7 Hz), 7.28–7.22 (m, 1H), 7.20 (d, 1H, J = 7 Hz), 7.14–7.07 (m, 2H), 7.07–7.02 (m, 1H), 7.00–6.97 (m, 1H), 4.28 (s, 2H), 3.63 (q, 2H, J = 7.2 Hz), 3.35 (t, 2H, J = 5.8 Hz), 2.55 (t, 2H, J = 5.8 Hz), 1.16 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 160.8, 140.7, 134.6, 133.5, 132.6, 132.2, 130.6, 130.2, 128.5, 128.1, 126.4, 126.2, 126.1, 47.5, 45.5, 43.7, 28.4, 13.7; ESI-HRMS: *m/z* calcd for $C_{18}H_{19}Cl_2N_2O$ [M + H^+]: 349.0869, found: 349.0867.

General procedure (5) for the preparation of ureas 23c–31c

$AlMe_3$ (3.75 mL, 7.5 mmol) was added to a solution of indoline (3.3 mmol), carbamoylimidazole (3.0 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at RT for 30 min and heated to reflux for 5 h. Then cooled to 0 °C and quenched with $NaHCO_3$ solution. Then extracted with CH_2Cl_2 and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography.

***tert*-Butyl 4-(indoline-1-carbonyl) piperazine-1-carboxylate (23c).** Prepared by the general procedure **5**. Yield 83%; R_f = 0.35 (hexane–EtOAc = 4 : 1). Light brown solid; mp 106–108 °C; IR (KBr): 3295, 2973, 2903, 2866, 2671, 2412, 2228, 2125, 2064, 2022, 1933, 1897, 1689, 1408, 1247, 1173, 1115, 985 cm^{-1}; ^1H NMR (300 MHz, TMS, DMSO-d_6): δ 7.21–7.06 (m, 3H), 6.90–6.85 (m, 1H), 3.84 (t, 2H, J = 8.1 Hz), 3.39–3.23 (m, 8H), 2.99 (t, 2H, J = 8.1 Hz), 1.4 (s, 9H); ^{13}C NMR (75 MHz, TMS, DMSO-d_6): δ 159.1, 154.4, 144.3, 131.9, 127.3, 125.3, 121.9, 113.9, 79.6, 50.5, 46.1, 43.8, 28.5, 28.0; ESI-HRMS: *m/z* calcd for $C_{18}H_{25}N_3O_3Na$ [M + Na]: 354.1788, found: 354.1777.

Benzyl 4-(indoline-1-carbonyl)piperazine-1-carboxylate (24c). Prepared by general procedure **5**. Yield 81%; R_f = 0.5 (hexane–EtOAc, 3 : 2). Brown sticky mass; IR (KBr): 3031, 2897, 2858, 1694, 1604, 1393, 1285, 1236, 1152, 1116, 1088, 997 cm^{-1}; ^1H NMR (300 MHz, TMS, DMSO-d_6): δ 7.37–7.30 (m, 5H), 7.20–7.17 (m, 1H), 7.10–7.05 (m, 2H), 6.89–6.84 (m, 1H), 5.1 (s, 2H), 3.84 (t, 2H, J = 8.1 Hz), 3.47–3.26 (m, 8H), 2.98 (t, 2H, J = 8.1 Hz); ^{13}C NMR (75 MHz, TMS, DMSO-d_6): δ 159.1, 154.9, 144.2, 137.2, 131.9, 128.9, 128.3, 128.0, 127.3, 125.3, 121.9, 113.9, 66.8, 50.4, 46.0, 43.7, 28.0; ESI-HRMS: *m/z* calcd for $C_{21}H_{23}N_3O_3Na$ [M + Na]: 388.1632, found: 388.1623.

Phenyl 4-(indoline-1-carbonyl)piperazine-1-carboxylate (25c). Prepared by general procedure **5**.Yield 85%; R_f = 0.5 (hexane–EtOAc, 3 : 2). Light brown solid, mp 135 °C; IR (KBr): 3279, 3012, 2925, 2687, 2411, 2411, 2070, 2038, 1940, 1789, 1709, 1636, 1599, 1419, 1330, 1261, 1206, 1330, 1261, 1104, 1062, 998 cm^{-1}; ^1H NMR (300 MHz, TMS, DMSO-d_6): δ 7.42–7.37 (m, 2H), 7.25–7.09 (m, 6H), 6.92–6.86 (m, 1H), 3.87 (t, 2H, J = 8.1 Hz), 3.67–3.33 (m, 8H), 3.02 (t, 2H, J = 8.1 Hz); ^{13}C NMR (75 MHz, TMS, DMSO-d_6): δ 159.1, 153.5, 151.6, 144.2, 131.9, 129.7, 127.4, 125.7, 125.4, 122.3, 122.0, 113.9, 50.5, 45.9, 44.4, 43.8, 28.0; ESI-HRMS: *m/z* calcd for $C_{20}H_{22}N_3O_3$ [M + H]: 352.1656, found: 352.1645.

Ethyl 4-(indoline-1-carbonyl) piperazine-1-carboxylate (26c). Prepared by general procedure **5**. Yield 80%; R_f = 0.4 (hexane–EtOAc, 3 : 2). Light brown solid, mp 97–99 °C; IR(KBr): 3372, 2975, 2893, 2852, 2675, 1954, 1913, 1705, 1644, 1600, 1469, 1411, 1283, 1246, 1167, 1121, 1074, 991 cm^{-1}; ^1H NMR (300 MHz, TMS, DMSO-d_6): δ 7.21–7.05 (m, 3H), 6.9–6.85 (m, 1H), 4.07 (q, 2H, J = 7.2 Hz), 3.85 (t, 2H, J = 8.1 Hz), 3.44–3.26 (m, 8H), 2.99 (t, 2H, J = 8.1 Hz), 1.20 (t, 3H, J =

8.1 Hz); ^{13}C NMR (75 MHz, TMS, DMSO-d_6): δ 159.1, 155.1, 144.2, 131.9, 127.3, 125.3, 121.9, 113.9, 61.3, 50.5, 46.0, 43.4, 28.0, 15.0; ESI-HRMS: *m/z* calcd for $C_{16}H_{22}N_3O_3$ [M + H]: 304.1656, found: 304.1661.

Methyl 4-(indoline-1-carbonyl)piperazine-1-carboxylate (27c). Prepared by general procedure **5**. Yield 81%; R_f = 0.4 (hexane–EtOAc, 3 : 2). Light brown solid, mp 105 °C; IR (KBr): 3386, 3009, 2895, 2855, 2732, 2677, 2492, 2409, 2206, 2057, 1950, 1914, 1877, 1713, 1642, 1599, 1409, 1283, 1247, 1124, 988, 762 cm^{-1}; ^{1}H NMR (300 MHz, TMS, $CDCl_3$): δ 7.21–7.13 (m, 2H), 7.06–7.03 (m, 1H), 6.95–6.90 (m, 1H), 3.95 (t, 2H, *J* = 8.1 Hz), 3.74 (s, 3H), 3.58–3.55 (m, 4H), 3.40–3.36 (m, 4H), 3.05 (t, 2H, *J* = 8.1 Hz); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 159.2, 155.8, 143.5, 131.7, 127.1, 125.1, 121.9, 112.9, 52.8, 50.4, 46.3, 43.6, 27.8; ESI-HRMS: *m/z* calcd for $C_{15}H_{19}N_3NaO_3$ [M + Na]: 312.1319, found: 312.1316.

[4-(Indoline-1-carbonyl)piperazin-1-yl]-indolin-1-yl-methanone (28c). Prepared by general procedure **5**; R_f = 0.5 (hexane–EtOAc, 1 : 4); Light brown solid, mp 252 °C; IR (KBr): 3118, 3043, 3014, 2928, 2899, 2854, 2668, 1941, 1899, 1856, 1707, 1642, 1600, 1483, 1396, 1272, 1237, 1160, 992 cm^{-1}; ^{1}H NMR (300 MHz, TMS, $CDCl_3$): δ 7.05–7.24 (m, 6H), 6.88–6.99 (m, 2H), 3.95 (t, 4H, *J* = 8.3 Hz), 3.47 (s, 8H), 3.04 (t, 4H, *J* = 8.3 Hz); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 159.3, 143.4, 131.7, 127.1, 125.1, 121.9, 112.9, 50.3, 46.3, 27.8; ESI-HRMS: *m/z* calcd for $C_{22}H_{25}N_4O_2$ [M + H]: 377.1972, found: 377.1968.

[1-(Imidazole-1-carbonyl)-4-piperidyl]-indolin-1-yl-methanone (30c). Prepared by general procedure **5**. Yield 78%; R_f = 0.3 (EtOAc). Light brown solid, mp 203 °C; IR (KBr): 3350, 3295, 3140, 3115, 3019, 2962, 2878, 2582, 2109, 1901, 1868, 1678, 1598, 1460, 1421, 1324, 1276, 1231, 1181, 1036, 995 cm^{-1}; ^{1}H NMR (300 MHz, TMS, $CDCl_3$): δ 8.22 (d, 1H), 7.88 (s, 1H), 7.01–7.33 (m, 5H), 4.23–4.08 (m, 4H), 3.26–3.14 (m, 4H), 2.86–2.77 (m, 1H), 2.03–1.91 (m, 4H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 170.8, 149.9, 141.8, 135.9, 130.1, 128.8, 126.7, 123.6, 123.1, 116.9, 116.3, 46.9, 44.8, 39.8, 27.0, 26.9; ESI-HRMS: *m/z* calcd for $C_{18}H_{21}N_4O_2$[M + H]: 325.1659, found: 325.1657.

[1-(Indoline-1-carbonyl)-4-piperidyl]-indolin-1-yl-methanone (31c). Prepared by general procedure **5**. Yield 10%; R_f = 0.35 (hexane–EtOAc, 1 : 4). Light brown solid, mp 210–212 °C; IR (KBr): 3294, 3141, 2962, 1934, 1901, 1677, 1654, 1598, 1485, 1421, 1230, 1182, 748 cm^{-1}; ^{1}H NMR (300 MHz, TMS, $CDCl_3$): δ 8.5 (m, 1H), 7.25–7.00 (m, 6H), 6.93–6.86 (m, 1H), 4.2 (t, 2H, *J* = 8.1 Hz), 3.96–3.90 (m, 4H), 3.26–3.23 (m, 2H), 3.1–2.9 (m, 4H), 2.72–2.64 (m, 1H), 2.10–1.78 (m, 4H); ^{13}C NMR (75 MHz, TMS, $CDCl_3$): δ 172.8, 159.6, 143.9, 143.0, 131.6, 131.1, 127.6, 127.1, 124.9, 124.6, 123.9, 121.6, 117.4, 112.9, 50.4, 47.9, 46.0, 41.7, 29.7, 28.1, 27.9; ESI-HRMS: *m/z* calcd for $C_{23}H_{26}N_3O_2$ [M + H]: 376.2020, found: 376.2011.

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