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Scalable, one-pot, microwave-accelerated tandem synthesis of unsymmetrical urea derivatives

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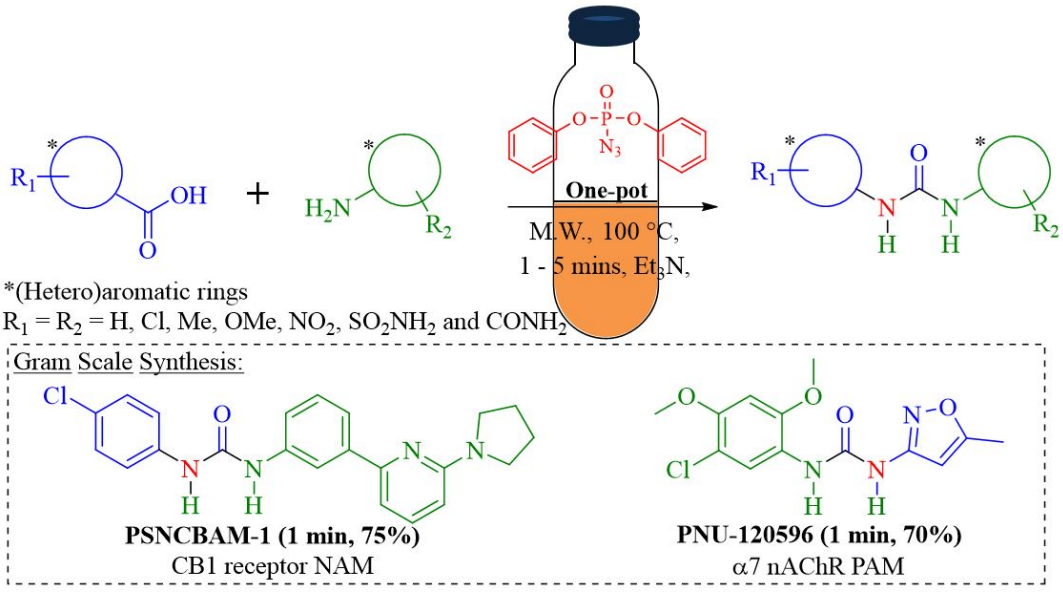

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ABSTRACT

We report a facile, microwave-accelerated, one-pot tandem synthesis of unsymmetrical ureas *via* Curtius rearrangement. In this method, one-pot microwave irradiation of commercially available (hetero)aromatic acids and amines in presence of diphenylphosphorylazide enabled extremely

rapid (1-5 mins) construction of an array of unsymmetrical ureas in good to excellent yields. We demonstrate the utility of our method in efficient, gram-scale synthesis of key biologically active compounds targeting the cannabinoid 1 and α7 nicotinic acetylcholine receptors.

INTRODUCTION

Considerable attention has been devoted to the synthesis of the urea scaffold as it is an important motif in many biologically active natural products,[1] pharmaceuticals,[2] agrochemicals[3] (e.g. Cumyluron as herbicide), material science[4] and as organocatalysts.[5] A large number of biologically

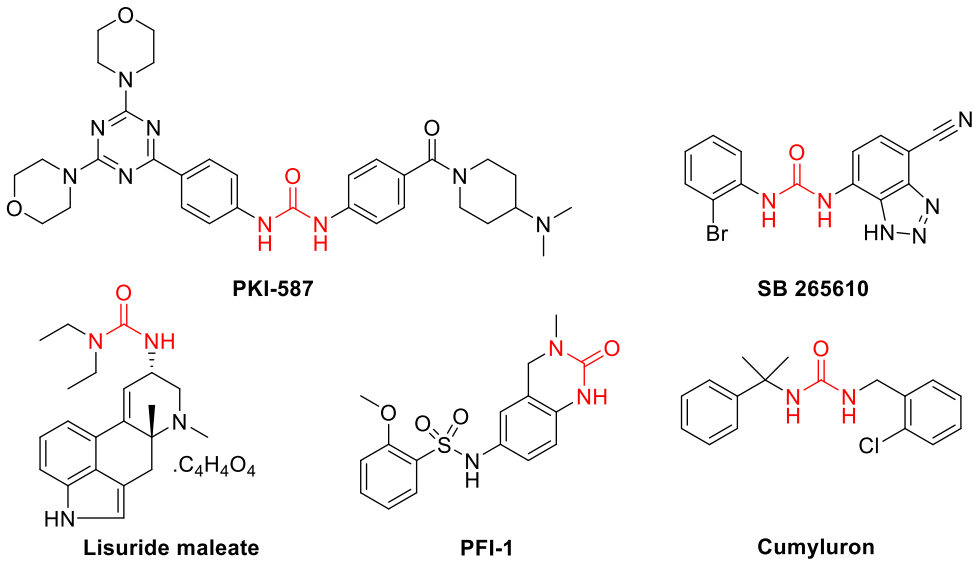


Fig. 1. Diverse biologically active compounds with urea backbone

important compounds like PKI-587, a potent kinase inhibitor[6] as anti- cancer agent; Lisuride maleate, an anti-Parkinson's agent working through agonism at the dopamine D2 and D4 receptors[7]; and PFI-1, a bromodomain-containing protein 4 inhibitor as an anti-cancer agent[8], have a urea skeleton (Fig. 1). Recent literature reports have cited use of the urea scaffold as lead

molecules in the G-protein coupled receptor (GPCR) superfamily, such as SB 265610, a potent CXCR2 chemokine receptor inhibitors that obstructs HIV replication[9](Fig. 1); cannabinoid 1 (CB1) receptor negative allosteric modulators (NAMs) like PSNCBAM-1 (6),[10] to treat obesity[10] and addiction[11]; as well as in the ligand-gated ion channel (LGIC) receptor system as positive allosteric modulators (PAMs) of the α7 nicotinic acetylcholine receptor (nAChR) like PNU-120596 (9),[12] to treat neurological disorders like pain[13] and Alzheimer's disease[14]. As these urea analogs have shown (pre)clinical utility in treating several medical conditions, rapid construction of novel libraries of a variety of urea derivatives still holds great demand. As a consequence, the development of an efficient method for the synthesis of urea scaffold is an important area of synthetic research.

Conventional approaches for urea synthesis involve the addition of an appropriate amine to isocyanates, which are moisture-sensitive, or the reaction of amines with triphosgene.[15] Alternative methods to synthesize unsymmetrical ureas include: (a) step-wise addition of amines to carbonyldiimidazole;[16] (b) zirconium(IV)-catalyzed exchange process from dialkyl carbonates and carbamates;[17] (c) direct carbonylation of primary amines using carbon monoxide;[18] (d) transition-metal-catalyzed reactions[19] and other miscellaneous urea formations reaction.[20] Carbamoyl chlorides and isocyanates have limited commercial availability, whereas phosgene and triphosgene are toxic and moisture sensitive, thereby setting limitations to such approaches. Isocyanates/acyl azides are unstable and therefore various methods have been developed to allow their *in situ* generation from carbamates,[17,21] carbamic acids,[22] hydroxamic acids,[16b] acetoacetanilides.[23] Such processes not only eliminate the need for isolation of potentially unstable isocyanates, but also decrease the amount of chemical waste generated. Urea derivatives

have also been obtained with sequential addition of amine to the isocyanate formed *in situ*, however with longer reaction time and in moderate yields.[24] In most of the above reported urea syntheses, multiple steps are required to obtain the desired urea and thus, a one-pot process that allows the direct conversion of carboxylic acids into urea is desirable.

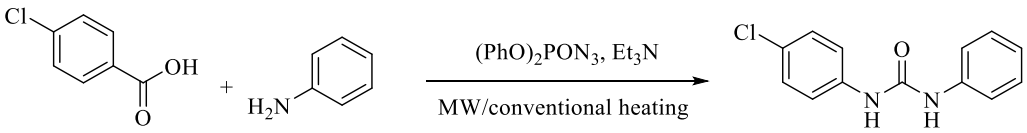
Our laboratory is actively engaged in the synthesis of urea derivatives as biologically important compounds, especially, the allosteric modulators of the CB1 and the α7 nAChR.[25] To expedite the lead optimization process of identification of 'druggable candidates', there is a need for the development of an efficient process for the synthesis of urea. Several methods that are accessible for the synthesis of urea scaffold are plagued with severe drawbacks including the number of steps for the synthesis, high reaction time, moderate yields, limited substrate scope, and use of toxic, unstable, explosive (phosgene, inorganic azides) and bio-hazardous metallic reagents. In this letter, we describe the one-pot, super-accelerated synthesis of urea which is facile and versatile on gram scale.

RESULT AND DISCUSSION

Although one-pot synthesis of carbamates and isocyanates is reported,[24, 26] to the best of our knowledge, there is no report on a one-pot tandem (one-step, non-sequential) synthesis of unsymmetrical ureas using an acid and an amine. Initially we attempted a one-pot urea formation reaction under conventional reflux conditions (Scheme 1) using 4-chlorobenzoic acid (1; 1.0 eq.), aniline (2; 1.0 eq.), triethylamine (TEA, 3.0 eq.) and diphenylphosphorylazide (DPPA; 1.2 eq.)[27] as a source of azide in toluene which reached completion in 3 h in good yield (70 %). With this unprecedented observation, we wanted to optimize reaction conditions to improve yield and reduce the reaction time. It has been well demonstrated that microwave-assisted synthesis is an

important tool in organic and medicinal chemistry for enhancing the rate of reactions, improving reaction yields, and reducing thermal degradation byproducts.[25g,28]

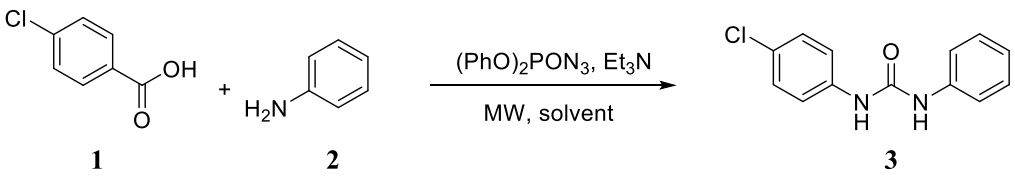
Scheme 1. General scheme for one-pot urea formation



In our preliminary investigation, all the above reaction ingredients were added to a microwave vial and irradiated at 100 °C, for 15 minutes. The desired urea was obtained in 55 % yield with some amine unreacted (Table 1, entry 1). This yield was lower than that of the prototype conventional reflux reaction. As this urea formation is a series of three tandem reactions in one-pot: (a) acid to acid azide; (b) acid azide to isocyanate; and (c) isothiocyanate to urea; we observed that if the aromatic acid and amine are reacted with equal stoichiometry, some unconsumed amine remains in the reactions, reducing the overall yield. It was observed that with the increase in the amount of acid, the amount of unreacted amine reduced and the yield increased. Thus, 1.5 eq. of acid was found to be necessary for the highest yield (95 %) and any further increase in the quantity of acid did not lead to any increase in yield (Table 1, entries 1-4) and was used for the further optimization. Interestingly, we observed that gradually decreasing the reaction time from 15 min to 1 min did not show any noticeable decrease in the yield (Table 1, entries 5-7). We also examined the temperature of microwave irradiation which indicated that gradually decreasing the temperature of the microwave irradiation from 100 °C to 25 °C (rt) increased the amount of unreacted starting materials (Table 1, entries 8-9) suggesting that 100 °C

temperature is crucial for the complete consumption of acid. The next step in this optimization protocol was to attempt a variety of aprotic

Table 1. Optimization of urea formation under microwave irradiation



1 **2** **3**

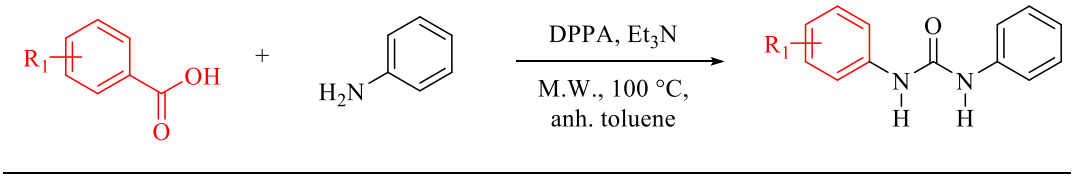
Entry	Time (min)	Temp (°C)	Solvent	Acid: Amine	Isolated yield (%)
1	15	100	Toluene	1.0:1.	55[a]
2	15	100	Toluene	1.2:1	82
3	15	100	Toluene	1.5:1	95
4	15	100	Toluene	2.0:1	90
5	10	100	Toluene	1.5:1	93
6	5	100	Toluene	1.5:1	92
7	**1**	**100**	**Toluene**	**1.5:1**	**95**
8	1	25	Toluene	1.5:1	50[b]
9	1	75	Toluene	1.5:1	72
10	1	100	THF	1.5:1	87
11	1	100	DMSO	1.5:1	91

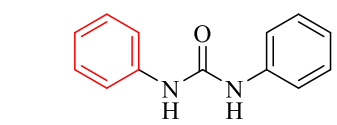
solvents to form the reaction mixture. When high boiling and very polar solvent like dimethyl sulfoxide (DMSO), and low boiling solvent like tetrahydrofuran (THF) were used, good conversion to urea was observed but the yield was lower when compared to toluene as solvent (entries 3, 10-11).

After establishing the optimum reaction conditions (Table 1, entry 7), we turned our attention towards exploring various aromatic acids to examine the scope of the method (Table 2). We evaluated the electronic requirement of this reaction, and relatively electronically neutral, rich and deficient aromatic carboxylic acids yielded corresponding ureas in good to excellent yields (88%

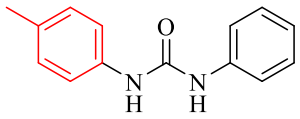
Table 2. Scope of (hetero)aromatic acids for the synthesis of urea

a = 17% aniline recovered; b = 85% conversion

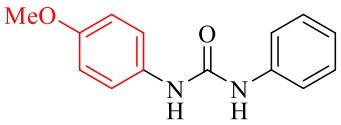




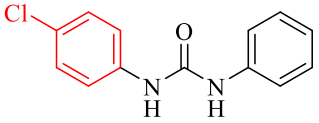
2a, 96% (1 min)



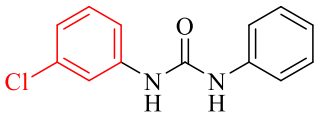
2b, 94% (1 min)



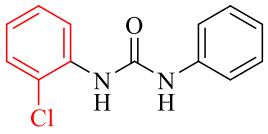
2c, 95% (1 min)



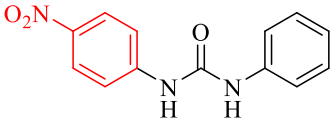
2d, 93% (1 min)



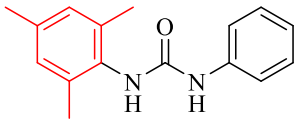
2e, 96% (1 min)



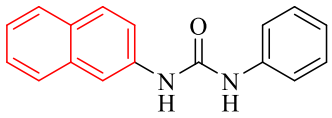
2f, 99% (1 min)



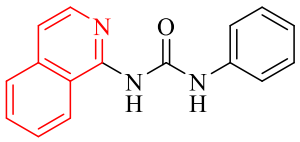
2g, 88% (1 min)



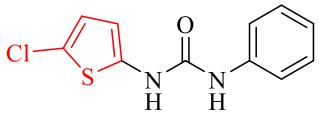
2h, 99% (1 min)



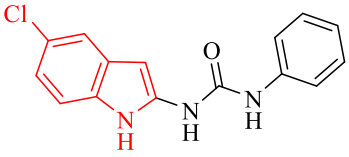
2i, 67% (1 min)



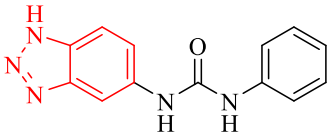
2j, 45% (2 min)



2k, 55% (1 min)



2l, 55% (1 min)



2m, 83% (3 min)

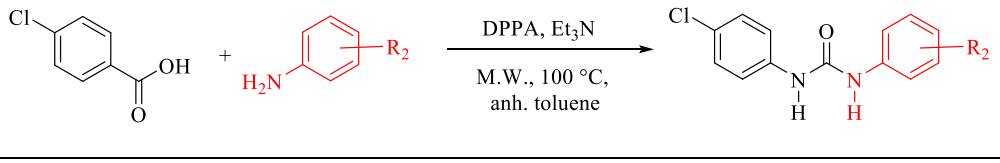
to 99%) in a short time (1 min) (2a-2h). This indicates that the rate and yield of the reaction was not much influenced by the electronic properties of the substituents on the aromatic acid. Also, the reaction proceeded with similar efficiency for o, m and p-chloro substitution on benzoic acid (2d-2f). The reaction with relatively sterically hindered acid as well as polycyclic aromatic acid

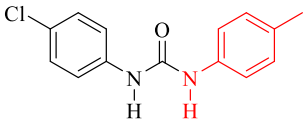
also occurred smoothly in short time (**2h**, **2i**). More importantly a wide range of heterocyclic acids with a thiophene, indole and isoquinoline core furnished the corresponding ureas in good yields (45-55%) in relatively short time (1-3 min) (**2j-2l**). It is noteworthy that the triazole moiety, which introduces one more amine to compete in the urea formation, was compatible for this method (**2m**). Impressively, majority of the product was isolated with analytical purity by filtration post workup when washed with cold dichloromethane, and the remaining minor fraction was isolated by silica gel column chromatography. This method is not effective for phenyl acetic acid in which case we isolated only amide compound.[29]

To further explore the scope of this reaction, a wide range of amines (Table 3) were used with 4-chlorobenzoic acid under optimized reaction condition. Electron rich as well as deficient amines demonstrated equal efficiency for the urea formation reaction (**3a, 3b**). Urea synthesis also occurred smoothly and in short time with naphthalene amine in good yield (**3c**). It is worth noting that several heterocyclic amines like pyridine, triazole, thiazole and 5-benzotriazole (**3f-3i**) as well as aliphatic/alicyclic amines (**3d**, **3e**) worked well with our method to yield corresponding urea derivatives in moderate to excellent yields (68-95%) in a short time (1-5 min). The urea formation reaction was found to be effective with the presence of an array of different functional groups such as amide and sulfonamide (**3j-3k)**. Interestingly, when we attempted this reaction with secondary amines it observed that in addition to the ureas, some quantity of amides were formed and their proportion depended on the nucleophilicity of the amine. However, amide formation with such secondary amines could be completely avoided by sequential addition of amine to the microwaved mixture of acid, TEA and DPPA followed by

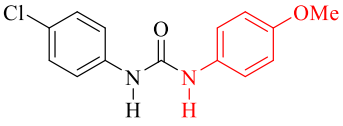
microwave exposure for a minute. The simplicity and mildness of this method makes it a versatile and useful transformation with potential for large scale applications up to gram scales.

Table 3. Scope of (hetero)aromatic amines for the synthesis of urea

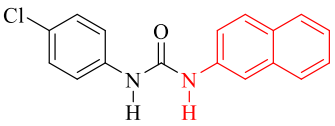




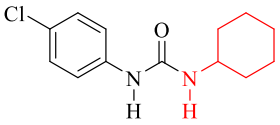
3a, 89% (1 min)



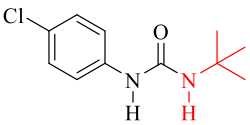
3b, 95% (1 min)



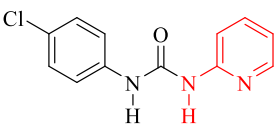
3c, 79% (2 min)



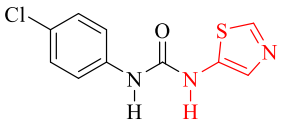
3d, 93% (2 min)



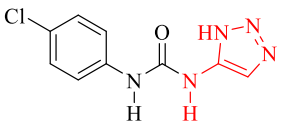
3e, 92% (1 min)



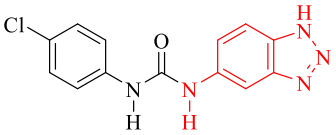
3f, 73% (1 min)



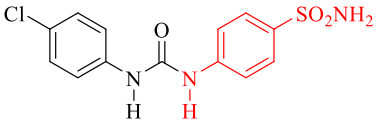
3g, 92% (5 min)



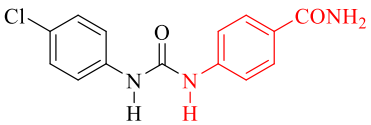
3h, 87% (5 min)



3i, 68% (5 min)



3j, 75% (5 min)

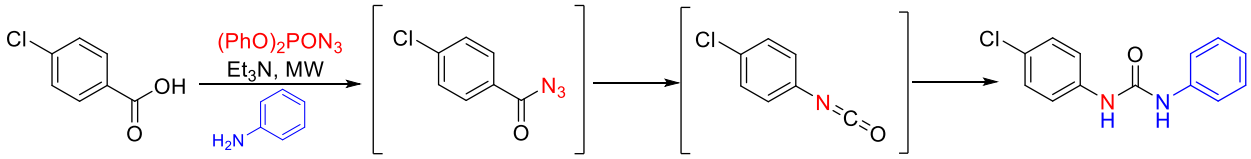


3k, 79% (5 min)

Having determined the effect of electronic and steric nature of the substituents on yield and time of reaction through a variety of (hetero)aromatic and polycyclic acids and amines, this study

revealed the versatility of this synthetic approach and diverse ureas could be obtained in excellent to good yields without the need for purification and in short duration of time. Based on previous literature report,[29] we have postulated a plausible mechanism for the one-pot, microwave-assisted unsymmetrical urea formation (Scheme 2).

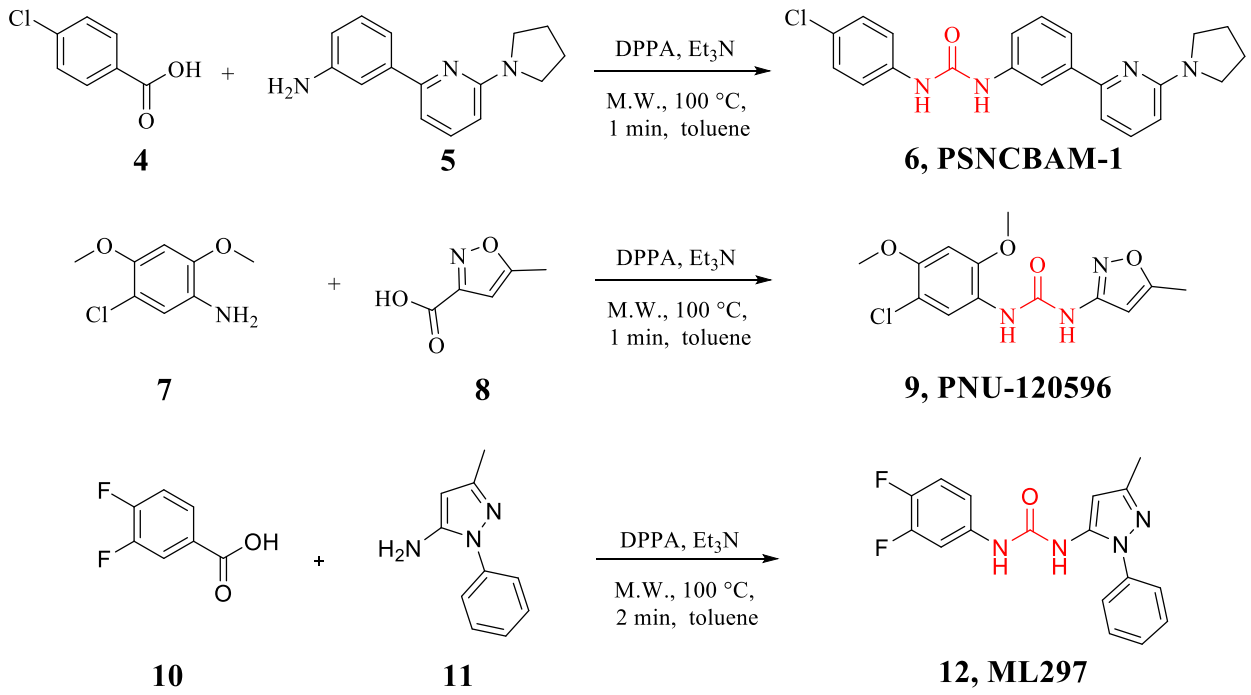
Scheme 2. Plausible mechanism for the "one-pot" urea formation reaction.



Our next focus was on expanding the utility of our one-pot methodology in rapid and concise synthesis of biologically important molecules. In receptor pharmacology and medicinal chemistry, allosterism is a recent concept that is attracting significant attention due to several therapeutic advantages it provides over the orthosteric site targeting.[25a-f, 30] As a drug discovery lab with an interest in capitalizing the medical benefits of allosteric modulators of the CB1 receptor as well as the α7 nAChR, we chose two distinct receptor ligands PSNCBAM-1[10] and PNU-120596[14] targeting these receptor allosteric sites, respectively. PSNCBAM-1 has shown to have hypophagic effects in rodent models and is a promising strategy for treating obesity and addiction through the CB1 receptor.[10] Under our optimized conditions, the reaction between 4-chlorobenzoic acid (**4**) and the tricyclic amine (**5**) led to the synthesis of PSNCBAM-1 (**6**) in excellent yield (75 %). This was superior to the earlier reports in terms of reaction time and yield.[31] PNU-120596 and other Type II PAMs of the α7 nAChR have been proven to be neuroprotective in an in vivo model and hold the promise in the treatment of neuropathic pain and Alzheimer's disease.[14] Reaction between 5-chloro-2, 4-dimethoxy aniline (**7**) and 5-methylisoxazol acid (**8**) under our optimized conditions led to the construction of PNU-120596

(**9**) in excellent yield (70%) in 1 min. We have also efficiently synthesized ML297 (**12**), an antagonist of the GIRK receptor[32] in good yield from corresponding acid (**10**) and amine (**11**) using this methodology in 2 min (Scheme 2).

Scheme 3. Gram-scale synthesis of PSNCBAM-1, PNU-120596 and ML297



CONCLUSION

We have developed a convenient, efficient and one-pot route for the super-accelerated synthesis of wide array unsymmetrical ureas through Curtius rearrangement in excellent yields using readily available aromatic acids and amines. This novel protocol allows the synthesis of a variety of biologically important ureas on gram-scale and in a short duration of time, and will prove to be valuable in the iterative design of structural analogs to rapidly construct compound libraries.

EXPERIMENTAL SECTION

All commercial chemicals and solvents were purchased from standard commercial sources as reagent grade and unless otherwise specified were used without further purification. Biotage Initiator microwave system was used for the synthesis of a few of the intermediates of the final covalent probes. Reaction progress was monitored by thin-layer chromatography (TLC) using commercially prepared silica gel 60 F254 glass plates. Compounds were visualized under ultraviolet (UV) light or by staining with iodine, phosphomolybdic acid,or p-anisaldehyde reagent. Flash column chromatography was carried out on an auto-flash purification unit using pre-packed columns from Reveleris, Biotage and Luknova. Solvents used include hexanes, ethyl acetate, acetone, methanol and dichloromethane. Characterization of compounds and their purity were established by a combination of HPLC, TLC, mass spectrometry and NMR analyses. NMR spectra were recorded in DMSO-d6, chloroform-d or methanol-d4, on NMR spectrometer (^{1}H NMR at 500 MHz and ^{13}C NMR at 125 MHz). Chemical shifts were recorded in parts per million (δ) relative to tetramethylsilane (TMS; 0.00 ppm) or solvent peaks as the internal reference. Multiplicities are indicated as br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sept (septet) or m (multiplet). Coupling constants (*J*) are reported in hertz (Hz). All test compounds were greater than 95% pure as determined by LC/MS analysis performed with dual-wavelength UV−visible detector and Quadrupole mass spectrometer (electrospray ionization). HRMS was done on a MALDI-TOF-MS in a negative ion mode with a delay time of 150 ns. Each sample well was surveyed to find a “sweet spot”, and then, 400 laser pulses were averaged to generate a spectrum. MS/MS was performed with a medium pressure of air and a mass resolution window of 400 with the metastable-ion suppressor on.

General Procedure: To a microwave vial was added a suspension of the carboxylic acid, the amine, diphenyl phosphorylazide (DPPA) and triethyl amine (TEA) in anh. toluene and the

reaction was irradiated in a Biotage Microwave Synthesizer for 1 – 5 min at 100 °C (surface sensor). The reaction mixture was poured in water and extracted with dichloromethane/ethyl acetate (3 x 50 mL). The combined organic layer was washed with water (20 ml), brine (20 ml), dried over Na_2SO_4 and evaporated under vacuum. The crude residue was purified by silica gel column chromatography (EtOAc:Hexane) to yield the desired urea. Refer to individual compounds for details.

1,3-diphenylurea (2a)[33]**:** Compound was synthesized according to the general procedure using benzoic acid (393 mg, 3.22 mmol), aniline (200 mg, 2.14 mmol), DPPA (707 mg, 2.58 mmol) and TEA (648 mg, 6.42 mmol) to give a white solid; ^{1}H NMR (500 MHz, DMSO-*d6*) δ (s, 2H), 7.45 (dd, *J* = 9.0 Hz, 1.0 Hz, 4H), 7.28 (dd, *J* = 8.5 Hz, 7.5 Hz, 4H), 6.97 (tt, *J* = 7.5 Hz, 1.0 Hz, 2H); MS-ESI (m/z): 213 $[M+H]^+$.

1-(4-methylphenyl)-3-phenylurea (2b)[34]**:** Compound was synthesized according to the general procedure using 4-methylbenzoic acid (345 mg, 3.22 mmol), aniline (200 mg, 2.14 mmol), DPPA (485 mg, 2.56 mmol) and TEA (445 mg, 6.42 mmol) to give a white solid to give a white solid; ^{1}H NMR (500 MHz, DMSO-d6): δ 8.57 (s, 1H), 8.50 (s, 1H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 7.25 (t, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.94 (t, *J* = 7.5 Hz, 1H), 2.23 (s, 3H); MS-ESI (m/z): 227 $[M+H]^+$

1-(4-methoxyphenyl)-3-phenylurea (2c)[34]**:** Compound was synthesized according to the general procedure using 4-methoxybenzoic acid (490 mg, 3.22 mmol), aniline (200 mg, 2.14 mmol), DPPA (707 mg, 2.56 mmol) and TEA (648 mg, 6.42 mmol) to give a white solid.; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.56 (s, 1H), 8.45 (s, 1H), 7.43 (dd, *J* = 8.5 Hz, 1.0 Hz, 2H), 7.35

(d, *J* = 9.0 Hz, 2H), 7.26 (dd, *J* = 8.5 Hz, 7.5 Hz, 2H), 6.95 (tt, *J* = 7.5 Hz, 1.0 Hz, 1H), 6.87 (d, *J* = 9.0 Hz, 2H), 3.71 (s, 3H); MS-ESI (m/z): 243 $[M+H]^+$.

1-(4-chlorophenyl)-3-phenylurea (2d)[35]**:** Compound was synthesized according to the general procedure using 4-chlorobenzoic acid (502 mg, 3.21 mmol), aniline (200 mg, 2.14 mmol), DPPA (706 mg, 2.56 mmol) and TEA (6.48 mg, 6.42 mmol) to give a white solid.; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.80 (s, 1H), 8.69 (s, 1H), 7.48 (d, *J* = 9.0 Hz, 2H), 7.44 (dd, *J* = 8.5 Hz, 1.0 Hz, 2H), 7.32 (d, *J* = 9.0 Hz, 2H), 7.28 (dd, *J* = 8.5 Hz, 7.5 Hz, 2H), 6.97 (tt, *J* = 7.5 Hz, 1.0 Hz, 1H) ; MS-ESI (m/z): 247 $[M+H]^+$.

1-(3-chlorophenyl)-3-phenylurea (2e)[36]**:** Compound was synthesized according to the general procedure using 3-chlorobenzoic acid (502 mg, 3.21 mmol), aniline (200 mg, 2.14 mmol), DPPA (706 mg, 2.56 mmol) and TEA (6.48 mg, 6.42 mmol) to give a white solid.; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.92 (s, 1H), 8.78 (s, 1H), 7.71 (t, *J* = 2.0 Hz, 1H), 7.45 (dd, *J* = 7.0 Hz, 1.5 Hz, 2H), 7.31 – 7.26 (m, 4H), 7.03 – 6.96 (m, 2H); MS-ESI (m/z): 247 $[M+H]^+$.

1-(2-chlorophenyl)-3-phenylurea (2f)[37] **:** Compound was synthesized according to the general procedure using 2-chlorobenzoic acid (502 mg, 3.21 mmol), aniline (200 mg, 2.14 mmol), DPPA (706 mg, 2.56 mmol) and TEA (6.48 mg, 6.42 mmol) to give a white solid.; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.42 (s, 1H), 8.32 (s, 1H), 8.17 (dd, *J* = 8.5 Hz, 2.0 Hz, 1H), 7.47 (dd, *J* = 8.5 Hz, 1.0 Hz, 1H), 7.46 (dd, *J* = 8.0 Hz, 1.5 Hz, 1H), 7.33 – 7.27 (m, 3H), 7.06 – 7.01 (m, 1H), 6.99 (tt, *J* = 7.0 Hz, 1.0 Hz, 1H); MS-ESI (m/z): 247 $[M+H]^+$.

1-(4-nitrophenyl)-3-phenylurea (2g)[34]**:** Compound was synthesized according to the general procedure using 4-nitrobenzoic acid (538 mg, 3.22 mmol), aniline (200 mg, 2.14 mmol), DPPA (707 mg, 2.64 mmol) and TEA (648 mg, 6.42 mmol) to give a white solid.; ^{1}H NMR (500 MHz,

DMSO-*d6*) δ 9.45 (s, 1H), 8.32 (s, 1H), 8.20 (d, *J* = 9.5 Hz, 2H), 7.70 (d, *J* = 9.5 Hz, 2H), 7.48 (dd, *J* = 7.5 Hz, 1.0 Hz, 2H), 7.31 (td, *J* = 7.5 Hz, 1.5 Hz, 2H), 7.02 (tt, *J* = 7.5 Hz, 1.0 Hz, 1H); MS-ESI (m/z): 258 $[M+H]^+$.

1-mesityl-3-phenylurea (2h)[24a]**:** Compound was synthesized according to the general procedure using 2,4,6-trimethylbenzoic acid (528 mg, 3.22 mmol), aniline (200 mg, 2.14 mmol), DPPA (707 mg, 2.58 mmol) and TEA (648 mg, 6.42 mmol) to give a white solid.; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.66 (s, 1H), 7.60 (s, 1H), 7.44 (dd, *J* = 8.5 Hz, 1.0 Hz, 2H), 7.24 (t, *J* = 8.0 Hz, 2H), 6.92 (tt, *J* = 9.0 Hz, 1.0 Hz, 1H), 6.88 (s, 2H), 2.23 (s, 3H), 2.16 (s, 6H); MS-ESI (m/z): 255 $[M+H]^+$.

1-(naphthalen-2-yl)-3-phenylurea (2i)[38]**:** Compound was synthesized according to the general procedure using 2-naphthalinic acid (469 mg, 2.99 mmol), aniline (200 mg, 2.14 mmol), DPPA (659 mg, 2.58 mmol) and TEA (605 mg, 6.42 mmol) to give a white solid.; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.94 (s, 1H), 8.91 (s, 1H), 8.10 (s, 1H), 7.84 (d, *J* = 9.0 Hz, 1H), 7.82 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.49 (dd, *J* = 8.5 Hz, 2.0 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.40 – 7.30 (m, 3H); MS-ESI (m/z): 263 $[M+H]^+$.

1-(isoquinolin-3-yl)-3-phenylurea (2j)[39]**:** Compound was synthesized according to the general procedure using isoquinolinic acid (340 mg, 2.17 mmol), aniline (200 mg, 2.14 mmol), DPPA (497 mg, 2.58 mmol) and TEA (439 mg, 6.42 mmol) to give a white solid; mp 227-231 ^{0}C; ^{1}H NMR (500 MHz, DMSO-*d6*) ^{1}H NMR (500 MHz, DMSO-*d6*) δ 12.60 (s, 1H), 9.95 (s, 1H), 8.70 (d, *J*=8.5 Hz, 1H), 8.22 (d, *J*=6.0 Hz, 1H),7.94 (d, *J*=8.0 Hz, 1H), 7.82-7.79 (m, 1H), 7.68-7.67 (m, 1H), 7.49 (d, *J*=5.5 Hz, 1H), 7.38-7.35 (m, 2H), 7.08 (t, *J*=7.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO *d6*): δ 152.54, 151.44, 139.85, 138.75, 138.33, 131.14, 128.93, 127.36, 127.10, 123.92,

123.82, 119.58, 118.33, 115.48; MS-ESI (m/z): 264 $[M+H]^+$; HRMS *m/z* $[M + H]^+$ calcd for $C_{16}H_{13}N_3O$ 264.1131, found 264.1124.

1-(5-chlorothiophen-2-yl)-3-phenylurea (2k): Compound was synthesized according to the general procedure using 5-chlorothiophene carboxylic acid (522 mg, 3.22 mmol), aniline (200 mg, 2.14 mmol), DPPA (707 mg, 2.56 mmol) and TEA (648 mg, 6.42 mmol) to give a white solid; mp 174-177 ^{0}C; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.83 (s, 1H), 8.82 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.29 (t, *J* = 8.0 Hz, 2H), 7.00 (t, *J* = 8.0 Hz, 1H), 6.81 (d, *J* = 4.5 Hz, 1H), 6.37 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO *d6*): δ 151.7, 139.1, 139.0, 128.0, 123.3, 122.4, 118.6, 118.0, 107.4; MS-ESI (m/z): 253 $[M+H]^+$; HRMS *m/z* [M + H]+ calcd for $C_{11}H_9ClN_2OS$ 253.0197, found 253.0201.

1-(1*H*-indol-2-yl)-3-phenylurea (2l): Compound was synthesized according to the general procedure using 5-chloroindole carboxylic acid (630 mg, 3.22 mmol), aniline (200 mg, 2.14 mmol), DPPA (707 mg, 2.56 mmol) and TEA (648 mg, 6.42 mmol) to give an off-white solid; mp 185-188 ^{0}C; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 11.96 (s, 1H), 9.26 (s, 1H), 8.91 (s, 1H), 7.50 (d, *J* = 7.5 Hz, 2H), 7.35-7.29 (m, 4H), 7.00 (t, *J* = 7.0 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.01 (s, 1H); ^{13}C NMR (DMSO d6, 125 MHz): 151.8, 139.2, 137.5, 131.2, 129.1, 128.9, 123.6, 122.2, 118.6, 118.4, 117.0, 112.2; MS-ESI (m/z): 286 $[M+H]^+$; HRMS *m/z* [M + H]+ calcd for $C_{15}H_{12}ClN_3O$ 286.0742, found 286.0727.

1-(1*H*-benzo[d][1,2,3]triazol-5-yl)-3-phenylurea (2m): Compound was synthesized according to the general procedure using 1*H*-benzo[d][1,2,3]triazol carboxylic acid (525 mg, 3.22 mmol), aniline (200 mg, 2.14 mmol), DPPA (707 mg, 2.56 mmol) and TEA (648 mg, 6.42 mmol) to give a white solid; mp 348-352 ^{0}C; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.01 (s, 1H), 8.75 (s, 1H), 8.16

(s, 1H), 7.90 (s, 1H), 7.48 (d, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.18 (s, 1H), 6.99 (t, *J* = 7.5 Hz, 1H) ^{13}C NMR (125 MHz, DMSO-*d6*): δ 152.72, 139.56, 128.86, 122.07, 118.42; MS-ESI (m/z): 254 $[M+H]^+$; HRMS *m/z* [M + H]+ calcd for $C_{13}H_{11}N_5O$ 254.1036, found 254.1046.

1-(4-chlorophenyl)-3-(p-tolyl)urea (3a)[40]: Compound was synthesized according to the general procedure using 4-chlorobenzoic acid (438 mg, 2.80 mmol), p-toluidine (200 mg, 1.87 mmol), DPPA (615 mg, 2.24 mmol) and TEA (566 mg, 5.60 mmol) to give a white solid; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.79 (s, 1H), 8.62 (s, 1H), 7.48 (d, *J* = 9.0 Hz, 2H), 7.36 – 7.29 (m, 4H), 7.09 (d, *J* = 8.5 Hz, 2H), 2.25 (s, 3H); MS-ESI (m/z): 261 $[M+H]^+$.

1-(4-chlorophenyl)-3-(4-methoxyphenyl)urea (3b)[41]: Compound was synthesized according to the general procedure using 4-chlorobenzoic acid (381 mg, 2.44 mmol), 4-methoxyaniline (200 mg, 1.63 mmol), DPPA (537 mg, 1.95 mmol) and TEA (492 mg, 4.88 mmol) to give a white solid; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.77 (s, 1H), 8.54 (s, 1H), 7.47 (d, *J* = 9.0 Hz, 2H), 7.35 (d, *J* = 9.0 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 3.71 (s, 3H); MS-ESI (m/z): 277 $[M+H]^+$.

1-(4-chlorophenyl)-3-(naphthalen-2-yl)urea (3c)[42]: Compound was synthesized according to the general procedure using 4-chlorobenzoic acid (345 mg, 2.20 mmol), 2-naphthylamine (200 mg, 1.47 mmol), DPPA (485 mg, 1.76 mmol) and TEA (445 mg, 4.41 mmol) to give a white solid. ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.94 (s, 1H), 8.91 (s, 1H), 8.10 (s, 1H), 7.84 (d, *J* = 9.0 Hz, 1H), 7.82 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.49 (dd, *J* = 8.5 Hz, 2.0 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.40 – 7.30 (m, 3H); MS-ESI (m/z): 297 $[M+H]^+$.

1-(4-chlorophenyl)-3-cyclohexylurea (3d)[43]: Compound was synthesized according to the general procedure using 4-chlorobenzoic acid (473 mg, 3.02 mmol), cyclohexylamine (200 mg,

2.02 mmol), DPPA (666 mg, 2.42 mmol) and TEA (610 mg, 6.05 mmol) to give a white solid; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.50 (s, 1H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 2H), 6.15 (d, *J* = 7.5 Hz, 1H), 3.51 – 3.38 (m, 1H), 1.83 – 1.74 (m, 2H), 1.69 – 1.59 (m, 2H), 1.56 – 1.47 (m, 1H), 1.35 – 1.24 (m, 2H), 1.20 – 1.09 (m, 3H); MS-ESI (m/z): 253 $[M+H]^{+}$.

1-(tert-butyl)-3-(4-chlorophenyl)urea (3e)[44]: Compound was synthesized according to the general procedure using 4-chlorobenzoic acid (473 mg, 3.02 mmol), tert-butyl amine (200 mg, 2.02 mmol), DPPA (666 mg, 2.42 mmol) and TEA (610 mg, 6.05 mmol) to give a white solid. ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.36 (s, 1H), 7.37 (d, *J* = 9.0 Hz, 2H), 7.23 (d, *J* = 9.0 Hz, 2H), 6.00 (s, 1H), 1.28 (s, 9H); MS-ESI (m/z): 227 $[M+H]^{+}$.

1-(4-chlorophenyl)-3-(pyridin-2-yl)urea (3f)[45]: Compound was synthesized according to the general procedure using 4-chlorobenzoic acid (499 mg, 3.19 mmol), 2-aminopyridine (200 mg, 2.12 mmol), DPPA (700 mg, 2.54 mmol) and TEA (642 mg, 6.36 mmol) to give a white solid; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 10.66 (s, 1H), 9.51 (s, 1H), 8.28 (ddd, *J* = 5.5 Hz, 2.0 Hz, 1.0 Hz, 1H), 7.75 (tdd, *J* = 7.0 Hz, 2.0 Hz, 1.0 Hz, 1H), 7.57 (d, *J* = 9.0 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 1H), 7.36 (d, *J* = 9.5 Hz, 2H), 7.01 (ddd, *J* = 7.5 Hz, 5.0 Hz, 1.0 Hz, 1H); MS-ESI (m/z): 248 $[M+H]^{+}$.

1-(4-chlorophenyl)-3-(thiazol-5-yl)urea (3g): Compound was synthesized according to the general procedure using 4-chlorobenzoic acid (469 mg, 2.99 mmol), thiazol-5-amine (200 mg, 1.77 mmol), DPPA (659 mg, 2.39 mmol) and TEA (605 mg, 5.99 mmol) to give a white solid; mp 250-254 ^{0}C; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 10.67 (s, 1H), 9.10 (s, 1H), 7.53 (d, *J* = 9.0 Hz, 2H), 7.39 (d, *J* = 3.5 Hz, 1H), 7.37 (d, *J* = 9.0 Hz, 2H), 7.12 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR

(125 MHz, DMSO d6): δ 159.7, 151.9, 137.8, 136.8, 128.8, 126.3, 120.2, 112.4; MS-ESI (m/z): 254 $[M+H]^+$; HRMS *m/z* [M + H]+ calcd for $C_{10}H_8ClN_3OS$ 254.0149, found 254.0152.

1-(4-chlorophenyl)-3-(1*H*-1,2,3-triazol-4-yl)urea (3h): Compound was synthesized according to the general procedure using 4-chlorobenzoic acid (558 mg, 3.56 mmol), 1*H*-1,2,3-triazol-4-amine (200 mg, 2.38 mmol), DPPA (768 mg, 2.86 mmol) and TEA (721 mg, 7.14 mmol) to give a white solid; mp 319-322 ^{0}C; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 10.30 (s, 1H), 7.73 (d, *J* = 9.0 Hz, 2H), 7.67 (s, 1H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.35 (s, 2H); ^{13}C NMR (125 MHz, DMSO d6): δ 157.0, 150.1, 149.0, 136.3, 128.5, 128.1, 122.6; MS-ESI (m/z): 238 $[M+H]^+$; HRMS *m/z* [M + H]+ calcd for $C_9H_8ClN_5O$ 238.0490, found 238.0482.

1-(1*H*-benzo[d][1,2,3]triazol-5-yl)-3-(4-chlorophenyl)urea (3i): Compound was synthesized according to the general procedure using 4-chlorobenzoic acid (350 mg, 2.24 mmol), 1*H*-benzo[d][1,2,3]triazol-5-amine (200 mg, 1.49 mmol), DPPA (489 mg, 1.78 mmol) and TEA (448 mg, 4.40 mmol) to give a white solid; mp 340-343 ^{0}C; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.07 (s, 1H), 8.93 (s, 1H), 8.14 (d, *J* = 2.0 Hz, 1H), 7.88 (d, *J* = 9.0 Hz, 1H), 7.51 (d, *J* = 9.0 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 1H), 7.29 – 7.15 (m, 1H); ^{13}C NMR (125 MHz, DMSO-*d6*): δ 152.6, 138.6, 128.7, 125.6, 119.9; MS-ESI (m/z): 288 $[M+H]^+$; HRMS *m/z* [M + H]+ calcd for $C_{13}H_{10}ClN_5O$ 288.0647, found 288.0660.

4-(3-(4-chlorophenyl)ureido)benzenesulfonamide (3j): Compound was synthesized according to the general procedure using 4-chlorobenzoic acid (272 mg, 1.74 mmol), sulfanilamide (200 mg, 1.16 mmol), DPPA (383 mg, 1.39 mmol) and TEA (352 mg, 3.48 mmol) to give a white solid; mp 244-247 ^{0}C; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.10 (s, 1H), 8.94 (s, 1H), 7.73 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 7.21 (s,

2H); ^{13}C NMR (125 MHz, DMSO-*d6*): 152.2, 142.7, 137.0, 128.7, 126.8, 125.8, 120.0, 117.6; MS-ESI (m/z): 326 $[M+H]^+$; HRMS *m/z* [M + H]+ calcd for $C_{13}H_{12}ClN_3O_3S$ 326.0361, found 326.0360.

4-(3-(4-chlorophenyl)ureido)benzamide (3k): Compound was synthesized according to the general procedure using 4-chlorobenzoic acid (345 mg, 2.20 mmol), 4-aminobenzamide (200 mg, 1.47 mmol), DPPA (485 mg, 1.76 mmol) and TEA (445 mg, 4.41 mmol) to give a white solid; mp 288-291 ^{0}C; ^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.01 (s, 1H), 8.96 (s, 1H), 7.83 (d, *J* = 9.0 Hz, 3H), 7.51 (t, *J* = 9.0 Hz, 4H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.21 (s, 1H); ^{13}C NMR (125 MHz, DMSO-*d6*): 167.7, 152.3, 142.4, 138.5, 128.7, 128.6, 127.5, 125.7, 119.9, 117.2; MS-ESI (m/z): 290 $[M+H]^+$; HRMS *m/z* [M + H]+ calcd for $C_{14}H_{12}ClN_3O_2$ 290.0691, found 290.0681.

1-(4-chlorophenyl)-3-{3-[6-(pyrrolidin-1-yl)pyridin-2-yl]phenyl}urea(6)[10]: Compound was synthesized according to the general procedure using 4-chlorobenzoic acid (1.24 g, 7.35 mmol), 3-(6-(pyrrolidin-1-yl)pyridin-2-yl)aniline (1 g, 4.90 mmol), DPPA (1.87 g, 7.99 mmol) and TEA (1.80 g, 15.99 mmol) to give a white solid. ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.82 (d, *J* = 12.00 Hz, 2H), 8.08 (s, 1H), 7.43−7.71 (m, 5H), 7.23−7.40 (m, 3H), 7.06 (d, *J* = 7.5 Hz, 1H), 6.42 (d, *J* = 8.5 Hz, 1H), 3.48 (br s, 4H), 1.97 (br s, 4H); MS-ESI (m/z): 393 $[M+H]^+$.

1-(5-chloro-2,4-dimethoxyphenyl)-3-(5-methylisoxazol-3-yl)urea(9)[14]: Compound was synthesized according to the general procedure using 4-methyloxazole carboxylic acid (934 mg, 7.35 mmol), 5-chloro-2,4-dimethoxyaniline (920 mg, 4.90 mmol), DPPA (2.20 g, 7.99 mmol) and TEA (1.60 g, 15.99 mmol) to give a white solid. ^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.90 (s, 1H), 8.60 (s, 1H), 8.11 (s, 1H), 6.87 (s, 1H), 6.48 (s, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 2.35 (s, 3H); MS-ESI (m/z): 312 $[M+H]^+$.

1-(3,4-difluorophenyl)-3-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)urea(12)[32]: Compound was synthesized according to the general procedure using 3,4-difluorobenzoic acid (1.368 gm, 8.66 mmol), 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (1 gm, 5.78 mmol), DPPA (1.908 gm, 6.92 mmol) and TEA (2.60 g, 26.0 mmol) to give a white solid. ^{1}H NMR (500 MHz, DMSO-*d6*) δ 9.48 (s, 1H), 8.80 (s, 1H), 7.92-7.90 (m, 1H), 7.88-7.80 (m, 4H), 7.73-7.69 (m, 1H), 7.63 (q, J = 10.0 Hz, 1H), 7.38-7.36 (m, 1H), 6.58 (s, 1H), 2.19 (s, 3H). MS-ESI (m/z): 331 $[M+H]^{+}$.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. ^{1}H and ^{13}C spectra and characterization of all new compounds is included.

AUTHOR CONTRIBUTIONS

‡These authors contributed equally.

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