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Ammonium Chloride-Promoted Rapid Synthesis of Monosubstituted Ureas under Microwave Irradiation

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Abstract: Monosubstituted ureas are important scaffolds in organic chemistry. They appear in various biologically active compounds and serve as versatile precursors in synthesis. Monosubstituted ureas were originally prepared using toxic and hazardous phosgene equivalents. Modern methods include transamidation of urea and nucleophilic addition to cyanate salts, both of which suffer from a narrow substrate scope due to the need for a strong acid and prolonged reaction times. We hereby report that ammonium chloride can promote the reaction between amines and potassium cyanate to generate monosubstituted ureas in water. This method proceeds rapidly under microwave irradiation and tolerates a broad range of functional groups. Unlike previous strategies, it is compatible with other nucleophiles, acid-labile moieties and most of the common protecting groups. The products precipitate out of solution, allowing facile isolation without column chromatography.

Introduction

Urea derivatives find applications in many fields, including medicinal chemistry,[1] agricultural chemistry,[2] and organocatalysis.[3] In particular, monosubstituted ureas have been of interest for decades as precursors to various biologically active scaffolds, including hydantoins,[4] and pyrimidine derivatives.[5] They also serve as excellent substrates for Buchwald-Hartwig cross-coupling.[6]
Early syntheses of monosubstituted ureas relied on the use of phosgene equivalents such as phosgene itself, triphosgene, chlorosulfonyl isocyanate, and trimethylsilyl isocyanate.[7] These reagents are moisture sensitive, toxic, and hazardous, thereby challenging to handle and environmentally unfriendly. A more modern alternative uses transamidation of urea with amines; however, several drawbacks limit the scope of this reaction. Traditional transamidation proceeds in the presence of excess hydrochloric acid under prolonged heating or refluxing conditions, restricting the functional groups tolerated.[8a-8b] Although new modifications have been published, they typically employ transition metal catalysts and yield disubstituted ureas.[8c-8f] Other transamidation methods either use harsh acidic conditions[9a-9c] or involve two steps with low atom economy.[9d-9e] Hence, one-step methodologies that use milder reagents are lacking.

The use of potassium cyanate for the synthesis of monosubstituted ureas has recently gained popularity due to the accessibility of this reagent, minimal hazard, and low cost. Similar to transamidation, however, this method necessitates an acidic medium (*p*H <3) at high temperature (60°C to reflux) for prolonged periods (6-18 h), which dramatically restricts the scope of the reaction.[10] Several variants of this reaction have been reported (Scheme 1). De Luca and coworkers adapted the potassium cyanate strategy for use in a microwave reactor. [11a] Inaloo and coworkers reported a solvent-free synthesis of monosubstituted ureas with 4-dodecylbenzene sulfonic acid (DBSA) as the promoter.[11b] Mahajan and coworkers adapted the original method to a room temperature reaction by using excess hydrochloric acid. [11c] Despite the progress made, none of these methods overcome the issue of poor functional group tolerance. We envisaged to solve this problem with the selection of a less acidic reaction promoter.
Ammonium chloride is a ubiquitous inorganic salt with diverse applications in agriculture, medicine, and the food industry.[12] Often produced as a by-product in Solvay process,[12] its low production cost and innocuity make it an ideal reagent or catalyst in organic synthesis. For example, ammonium chloride has been reported to promote asymmetric hydrogenation[13a] and thiol-Michael addition.[13b] It has also been extensively employed as an effective catalyst in various heterocycle syntheses.[13c-13j] Although in most cases the reaction mechanism has yet to be elucidated, the role of ammonium chloride is presumably attributed to its mild acidity and hydrogen bonding ability. We envisioned that these properties might be conducive to promoting the synthesis of monosubstituted ureas.

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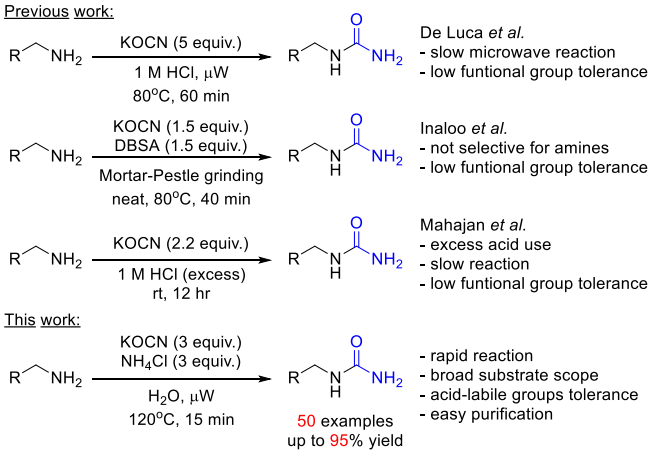
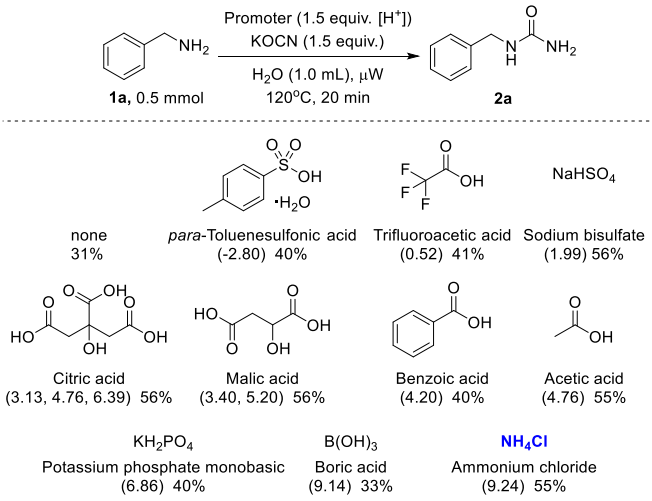


Scheme 1. The work presented here in the context of previous work. DBSA, 4-dodecylbenzene sulfonic acid.

Herein, we report a novel microwave-assisted methodology for the synthesis of monosubstituted ureas in water from the reaction of amines with potassium cyanate in the presence of ammonium chloride (Scheme 1). This method is simple, fast, and efficient with a large scope of substrates, including acid-labile functionalities and most of the common protecting groups.

Results and Discussion

With benzyl amine (**1a**) as a model substrate, ten reaction promoters were initially tested with varying acidity (Scheme 2, *p*Ka of the promoters shown in brackets). The initial reaction conditions consisted of microwave irradiation at 120°C for 20 minutes to produce *N*-benzylurea (**2a**) in the presence of potassium cyanate (1.5 equiv.) and the promoter in water (1.0 mL). The amount of promoter used was adjusted to provide 1.5 equivalent of proton in the reaction system. Upon reaction completion, cooling down the mixture to 0°C triggers precipitation of the desired product as a white solid. Simple filtration followed by a wash is sufficient to isolate the product in reasonable purity. Gratifyingly, all promoters tested were found to support clean formation of the monosubstituted urea **2a**. This corroborated our assumption that milder reagents could replace hydrochloric acid in this reaction. Surprisingly, there was no obvious correlation between the *p*K_a of the promoter and the yield. We therefore settled to employ the non-hazardous and inexpensive ammonium chloride in further optimization.



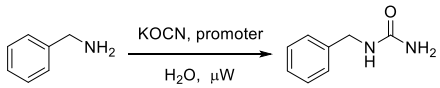
Scheme 2. Promoter screening. All yields are isolated yields. *p*K_a values of the promoters are indicated in parentheses.

Using ammonium chloride as the reaction promoter, the effect of reaction concentration was explored (Table 1, entries 1-3). Doubling the concentration of all reaction components (by reducing the solvent volume by half) increased the yield from 55% to 81%, whereas quadrupling the concentration was detrimental. We speculate that this concentration effect might be the result of a compromise between increased reactivity due to higher frequency of molecular collisions and decomposition of potassium cyanate.[14]

In an attempt to better understand the stoichiometry of the reaction, the number of equivalents of potassium cyanate and of ammonium chloride were varied (Table 1, entries 4-7). We observed that increasing only one of them to 3.0 equivalents was detrimental, whereas raising both to 2.0 equivalents was beneficial. Using 3.0 equivalents of each was even more promising, with a 91% yield. Such a trend is not expected if the promoter acts solely as a proton source. This is further supported by our mechanistic investigations (*vide infra*).

Reaction temperature and duration were optimized next (Table 1, entries 8-11). Our data reveal that although a reaction time of 5 minutes is inadequate, 15 minutes is sufficient to reach 92% yield at 120°C. Increasing the temperature to 130°C was not beneficial, whereas maintaining a temperature of 100°C for 30 minutes afforded a 92% yield of **2a**. Since shorter reaction times are desirable in microwave-assisted processes, most of the subsequent reactions were conducted at 120°C for 15 minutes. In addition, to validate the necessity of microwave irradiation, we ran a comparative reaction using conventional heating (Table 1, entries 12-13). Conventional heating under the optimal conditions resulted in only 64% yield instead of 92%, and extending the reaction time to 60 minutes did not significantly increase the yield. Hence, we believe that microwave irradiation is indispensable to achieve high yield.

Table 1. Optimization of reaction conditions



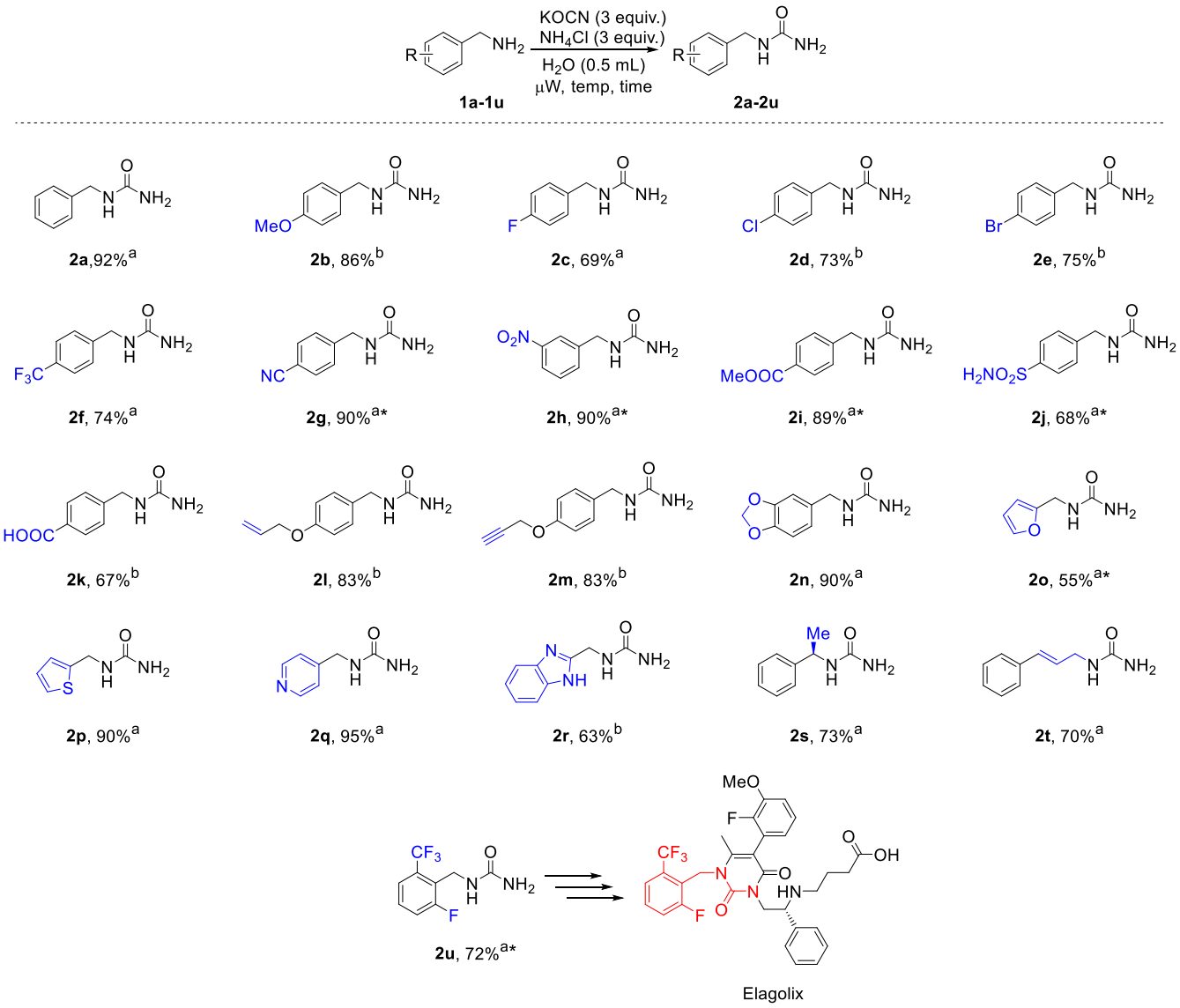
1a **2a**

Entry[a]	KOCN /equiv.	Promoter /equiv.	H_2O[b] /mL	Temp. /°C	Time /min	Yield[c] /%
1	1.5	NH_4Cl (1.5)	1.0	120	20	55
2	1.5	NH_4Cl (1.5)	0.5	120	20	81
3	1.5	NH_4Cl (1.5)	0.25	120	20	63
4	1.5	NH_4Cl (3.0)	0.5	120	20	53
5	3.0	NH_4Cl (1.5)	0.5	120	20	64
6	2.0	NH_4Cl (2.0)	0.5	120	20	80
7	3.0	NH_4Cl (3.0)	0.5	120	20	91
8	**3.0**	**NH_4Cl (3.0)**	**0.5**	**120**	**15**	**92**
9	3.0	NH_4Cl (3.0)	0.5	120	5	80
10	3.0	NH_4Cl (3.0)	0.5	100	30	92
11	3.0	NH_4Cl (3.0)	0.5	130	10	84
12	3.0	NH_4Cl (3.0)	0.5	120[d]	15	64
13	3.0	NH_4Cl (3.0)	0.5	120[d]	60	65

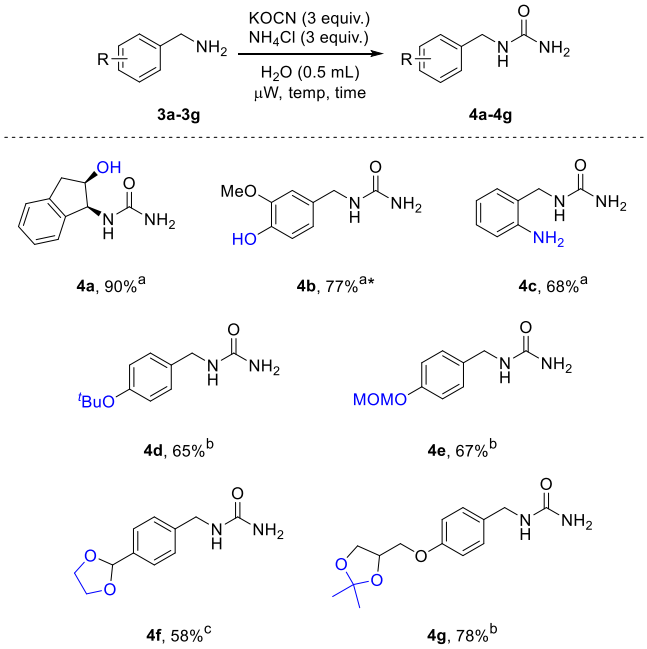
[a] All reactions were performed at 0.5 mmol scale, in a microwave reactor set to high-absorption level; [b] milli-Q water; [c] isolated yield; [d] conventional heating was used instead of microwave irradiation.

With optimized conditions in hand, the scope of the reaction was evaluated on amines containing a large variety of functional groups (Scheme 3). Most substrates showed excellent reactivity under the standard conditions. 4-Methoxy benzylamine (**1b**) gave the desired product **2b** in 86% yield. Halogens were well tolerated on the aromatic ring, as suggested by the yields of **2c**-**2e.**

Electron-withdrawing groups, such as trifluoromethyl, cyano, nitro, ester, sulfonamide, and a free carboxylic acid were all compatible with our method, affording the desired products **2f**-**2k** in good to excellent yields. Interestingly, the starting materials **1g**-**1j** were commercially available as hydrochloride salts and were used without conversion to the free amine, implying that our method is compatible with both free amines and amine salts. Terminal alkene and alkyne moieties were well tolerated, producing **2l** and **2m** in high yields. Piperonylamine (**1n**) was tested because of its methylenedioxy moiety that is prevalent in natural products. Compound **1n** was converted to the corresponding urea derivative **2n** in 90% yield. Substrates bearing a heterocyclic ring were also explored. With furfurylamine (**1o**), the starting amine itself decomposed to a brown mixture under microwave conditions. However, converting it to the corresponding hydrochloride salt had a stabilizing effect, and under these conditions, the product **2o** was isolated in 55% yield. Other heterocycles, such as thiophene, pyridine, and benzimidazole were well tolerated, affording the desired products **2p-2r** in good to excellent yields. Alpha-substitution of the amine did not significantly affect the reaction, as suggested by the production of **2s** in 73% yield. Allyl amines were also compatible with this methodology based on the transformation of cinnamyl amine (**1t**) to **2t** in 70% yield. Finally, product **2u**, derived from 2-fluoro-6-trifluoromethyl benzylamine in 72% yield using our method, is a key building block for the synthesis of elagolix, a drug used in the treatment of pain associated with endometriosis.[15] In contrast to the previously reported synthesis of **2u**[15] which was conducted in 2.5 M hydrochloric acid under reflux for 6 hours to give the desired product in 73% yield, our method requires only 15 minutes to reach the same yield without the use of a strong acid.



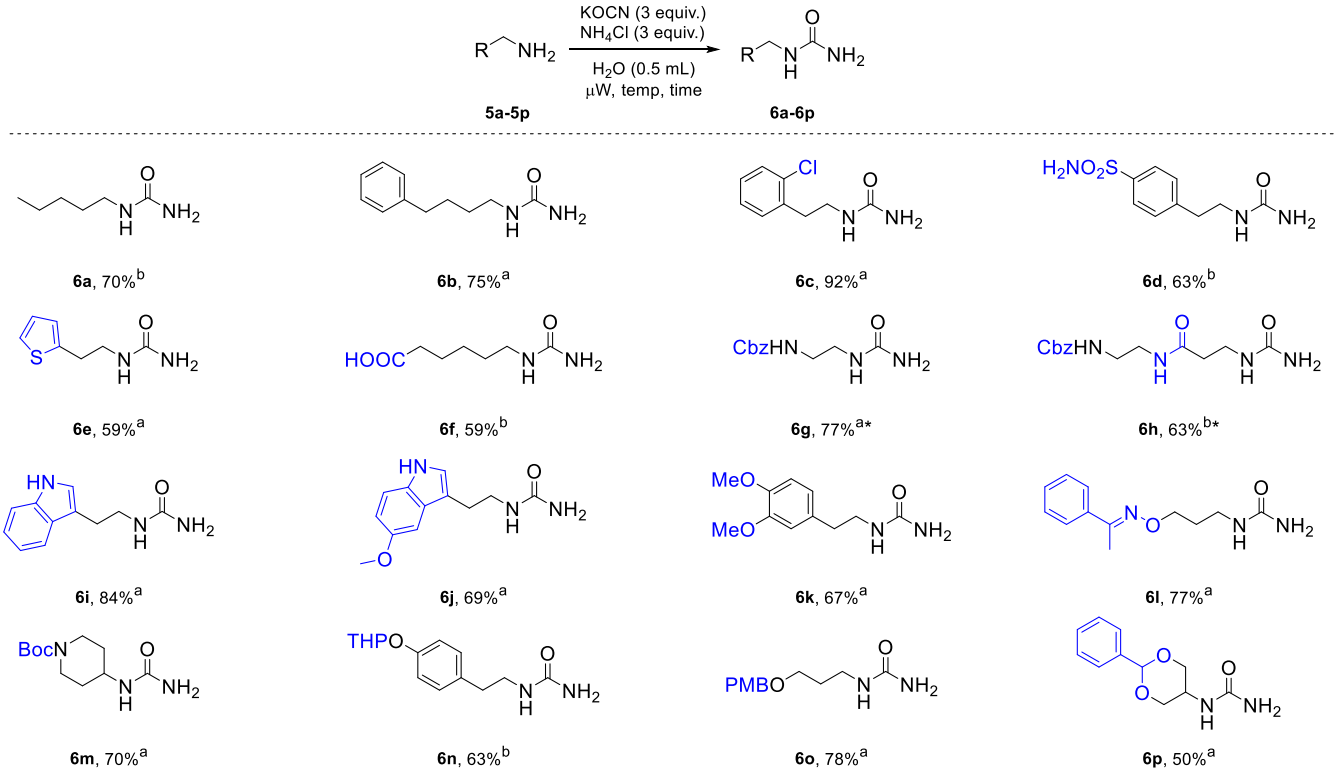
Scheme 3. Functional group tolerance of our method, reported as isolated yields. All reactions were performed at a 0.5 mmol scale, in a microwave reactor set to high-absorption level. Reaction conditions: [a]120°C, 15 min; [b]130°C, 10 min; the higher temperature is better for the more hydrophobic amines, likely due to increased solubility. *The corresponding amine hydrochloride salt was used as the starting material.



Scheme 4. Selectivity and protecting group tolerance of our method, reported as yields. All reactions were performed at a 0.5 mmol scale, in a microwave reactor set to high-absorption level. Reaction conditions: [a]120°C, 15 min; [b]130°C, 10 min; [c]80°C, 60 min. *The corresponding amine hydrochloride salt was used as the starting material.

To date, no single-step method for the synthesis of monosubstituted ureas have been reported that are compatible with the presence of other nucleophiles or acid-labile protecting groups.[11] Remarkably, as summarized in Scheme 4, our process is oblivious to other nucleophilic or acid-sensitive groups. Indeed, aminoindanol (**3a**) gave the desired urea product **4a** in 90% yield, without detectable formation of the corresponding carbamate. The phenol group of vinallyl amine (**3b**) remained unreacted during the formation of **4b**, and so did the aromatic amino group of **3c** in the synthesis of **4c**. A measurement of the reaction endpoint *p*H (see Experimental Section) showed that the solution was basic, indicating that acid-labile groups might be tolerated under our reaction conditions. Indeed, common acid-labile protecting groups were preserved under our conditions, including a phenolic *tert*-butyl group (see **4d**), a methoxymethyl ether (MOM, see **4e**), a 1,3-dioxolane (see **4f**), and an acetonide (see **4g**).

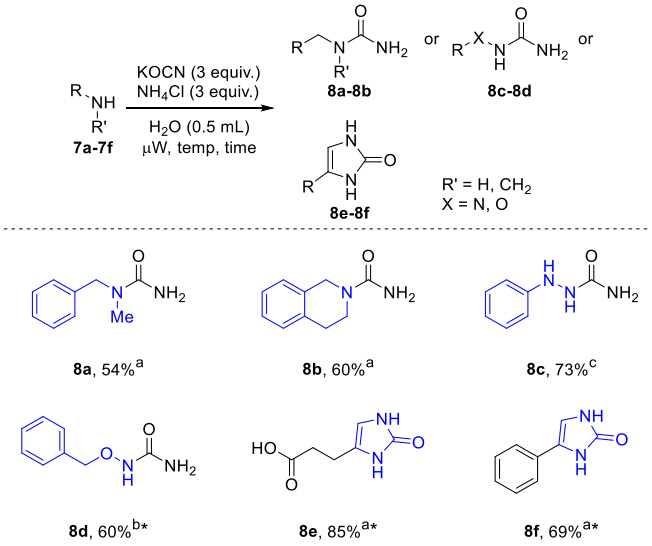
Encouraged by the robustness of our process, we extended the investigations beyond benzyl amines while still including assorted functionalities (Scheme 5). Simple alkyl amines such as 1-pentylamine and 4-phenyl-1-butylamine afforded product **6a** and **6b** in very good yields. Moieties such as a chlorine atom, sulfonamide, thiophene, and carboxylic acid were well tolerated in the context of alkyl amines, generating the desired products **6c**-**6f** in moderate to excellent yields. The presence of a carboxybenzyl (Cbz) protecting group and/or an amide in the substrate were not detrimental either, as demonstrated by the production of **6g** and **6h** in satisfactory yields. A series of biologically-relevant amines was examined next. Tryptamine (**5i**) was transformed into its urea derivative **6i** in 84% yield. Mexamine (**5j**) was also compatible with our conditions, affording the melatonin/serotonin analog **6j**. Lastly, homoveratrylamine (**5k**) was successfully transformed to the desired product **6k**, a precursor of dopamine urea.



Scheme 5. Expanding the substrate scope to non-benzyl amines. All reactions were performed at a 0.5 mmol scale, in a microwave reactor set to high-absorption level. Reaction conditions: [a]120°C, 15 min; [b]130°C, 10 min. *The corresponding amine hydrochloride salt was used as starting material

Additional acid-labile functional groups were next tested, again in the context of non-benzyl amines. An oxime-containing amine reacted to produce **6l** selectively, without detectable hydrolysis of the oxime. The *tert*-butyloxycarbonyl (Boc), tetrahydropyran (THP), *p*-methoxybenzyl (PMB), and benzylidene acetal protecting groups all survived the reaction conditions to afford the urea products **6m**-**6p** in moderate to good yield.

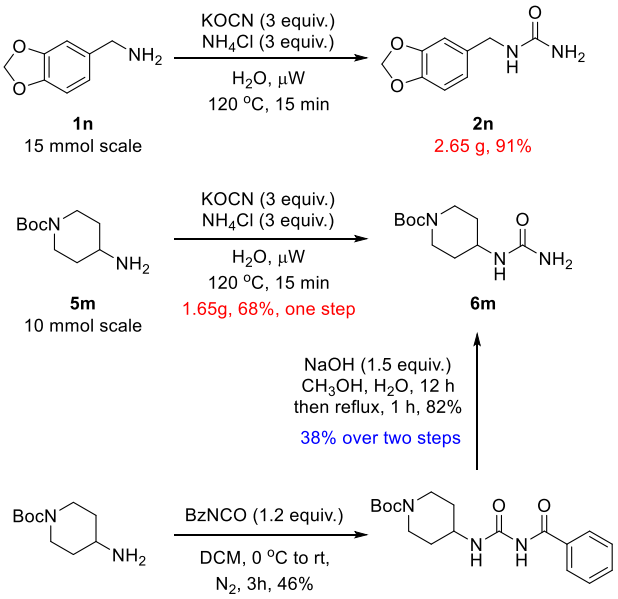
We envisaged the interesting possibility that our method might be a useful stepping-stone to access more elaborate chemical scaffolds (Scheme 6). We were pleased to observe that treating secondary amines (*e.g.* **7a** and **7b**) to our conditions enabled the construction of 1,1-disubstitued ureas **8a** and **8b**. Starting from hydrazine **7c** or hydroxylamine **7d**, our method generated semicarbazide **8c** and hydroxycarbamide **8d** respectively, whereas 5-aminolevulinic acid and 2-aminoacetophenone reacted to produce the corresponding imidazolone derivatives **8e** and **8f**, respectively, in one pot.



Scheme 6. Access to other chemical scaffolds from the same method. All reactions were performed at a 0.5 mmol scale, in a microwave reactor set to high-absorption level. Reaction conditions: [a]120°C, 15 min; [b]130°C, 10 min; [c]120°C, 30 min. *The corresponding amine hydrochloride salt was used as the starting material.

The scalability of our process was examined next. Compound **2n** is reported as a self-tanning agent.[16] A multigram scale reaction was performed with piperonylamine (**1n**) to produce urea **2n** in 91% yield (Scheme 7). The Boc-protected substrate **5m** was also successfully transformed to **6m** in one step at a 10 mmol scale (Scheme 7). In comparison, synthesis of **6m** using previously established methods, *i.e.* using a toxic isocyanate reagent under inert atmosphere and excess base in a two-step process, was found to afford the desired product in an overall yield of only 38%.[17]

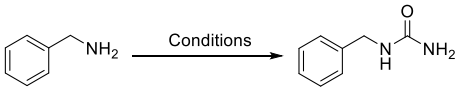
Although the mechanism of the reaction between an amine and cyanate has been elucidated,[18] we were intrigued by the role of ammonium chloride in our methodology. Ammonium ions are known to react with cyanate to generate the molecule of urea (a process known as Wöhler synthesis) which may serve as a possible reaction intermediate.[19] Ammonium salts have also been reported to dramatically accelerate transamidation reactions by cooperatively activating both the carbonyl and the amino groups.[20]



Scheme 7. Synthesis of **2n** and **6m** at a multigram scale using the method reported here, compared to the synthesis of **6m** using existing methods.

To examine the role of ammonium chloride in our new synthetic methodology, we first compared ammonium salts with different degrees of substitution (Table 2, entries 1-5). Using tetramethylammonium chloride as a promoter drastically decreased the yield, which is consistent with the necessity of a proton source. In contrast, replacing ammonium chloride with trimethylamine hydrochloride afforded the desired product, but in lower yield (60%) than with ammonium chloride (92%). This suggests that ammonium chloride may be more than a proton source. The use of dimethylamine hydrochloride or methylamine hydrochloride instead of ammonium chloride lowered the yield to 40-42%. We speculate that the higher nucleophilicity of the corresponding amines might contribute to byproduct formation, resulting in lower yields of the desired ureas. Next, to examine the effect of the promoter anion moiety on the reaction (Table 2, entries 6), 1.5 equivalent of ammonium sulfate was used instead of 3.0 equivalent of ammonium chloride. No significant change on the yield was observed, indicating that the anion is unlikely to play an important mechanistic role in this reaction. Finally, to verify the hypothesis that the molecule of urea might be a possible intermediate (Table 2, entries 7-8), urea was directly reacted with the amine in the presence of KCl (to maintain the same non-participating ions). To our surprise, this afforded the desired product in 80% yield, strengthening the theory that urea might be an intermediate in the reaction. This was further confirmed using isotopically labelled ^{15}N-ammonium chloride (99% labelled). The desired product was obtained in 64% yield (the reduced yield implies a possible kinetic isotope effect), ten percent of which was ^{15}N-labelled as quantified by ^{1}H-NMR (see Supporting Information). This is consistent with urea acting as an intermediate in the reaction, although the low percentage of labelling suggests the availability of an alternative reaction path.

Table 2. Results of the mechanistic investigations

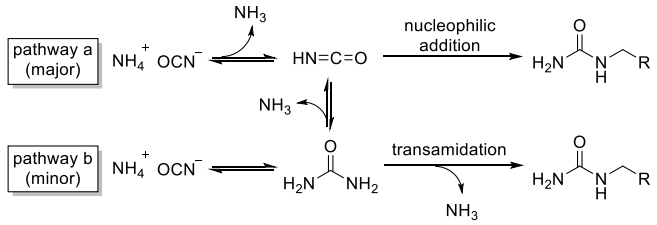


1a **2a**

Entry[a]	Condition[b]	Yield[c]/%
1	KOCN + NH_4Cl	92
2	KOCN + Me_4NCl	20
3	KOCN + $Me_3N{\cdot}HCl$	60
4	KOCN + $Me_2NH{\cdot}HCl$	40
5	KOCN + $MeNH_2{\cdot}HCl$	42
6	KOCN + $(NH_4)_2SO_4$[d]	93
7	Urea + KCl	80
8	KOCN + $^{15}NH_4Cl$	64 (10% ^{15}N labelled)

[a] All reactions were performed at a 0.5 mmol scale, in a microwave reactor set to high-absorption level; [b] Reaction conditions: benzylamine (0.5 mmol), KOCN or urea (3 equiv.), ammonium salts or KCl (3 equiv.), H_2O (0.5 mL), 120°C, 15 min; [c] Isolated yield. [d] 1.5 equiv. of ammonium sulfate was used.

Based on the results presented above, we propose a mechanism involving both a major and a minor pathways (Scheme 8). Considering the very small difference in pK_a between ammonium chloride (pK_a = 9.24) and the starting material amines (*i.e.* benzylamine pK_a = 9.34), it is unlikely that a large portion of starting material is protonated under the reaction conditions. The nucleophilicity of amines dramatically decreases when protonated, which would be detrimental to this reaction. Therefore, we propose that ammonium primarily interacts with cyanate. In the major pathway, ammonium acts as a proton source, releasing ammonia and the reactive species isocyanic acid. Nucleophilic addition of the amine on isocyanic acid affords the desired monosubstituted urea product. In this process, ammonium may also activate isocyanic acid and direct the amine via hydrogen bonding. In the minor pathway, ammonium cyanate first isomerizes to urea, which undergoes either transamidation to give the product, or dearrangement[20b-20c] to generate isocyanic acid which feeds into the major pathway.



Scheme 8. Proposed mechanism for the ammonium chloride-promoted synthesis of monosubstituted ureas.

Conclusion

To our knowledge, no synthetic methodology to access monosubstituted ureas has been reported that tolerates a broad range of functional groups. We show here that ammonium chloride can promote the reaction between amines and potassium cyanate in water to selectively produce monosubstituted ureas under microwave irradiation. This method has several advantages over previous approaches. Remarkably, it shows exceptional functional group tolerance, including compatibility with other nucleophiles, acid-labile groups, and most standard protecting groups. This new methodology is also very rapid (typically 15 min), scalable, and does not require chromatographic separation, while avoiding organic solvents and harsh reagents. Given that ammonium chloride is inexpensive, abundant, and less corrosive than mineral acids, our approach provides a more environmental-friendly alternative for the preparation of monosubstituted ureas and their analogs. We therefore expect it to find broad application.

Experimental Section

General information

Microwave reactions were run in a Biotage® Initiator microwave synthesizer set to high-absorption level. The reaction vessels were Biotage® microwave vials with Teflon caps and aluminum seals. Potassium cyanate was purchased from Alfa Aesar. Ammonium chloride was from ACP chemicals. Unless otherwise noted, all commercial reagents were used without further purification. Water was obtained from a Milli-Q® water purification system with a specific resistance of 18.2 MΩ cm at 25°C. Uncorrected melting points were measured on a Thiele block equipped with a digital thermometer. Infrared spectra were recorded on PerkinElmer Spectrum One FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVIIIHD 500 MHz NMR. Exact mass determinations were obtained by electrospray ionization (ESI) on a Bruker Maxis atmospheric pressure ionization (API) Quadruple Time-of-Flight (QTOF) Mass Spectrometrometer.

HPLC purity analysis

Purity analysis was performed on an Agilent 1100 series HPLC system using a Phenomenex Luna® LC column (C18, 200 × 4.6 mm, 100 Å, 5 µm), with water as mobile phase A, acetonitrile as mobile phase B pumped at a flow rate of 1.0 mL/min. The detector was set to 214 nm. All changes in solvent ratio during elution were linear. Method A (A/B): 90% A to 5% A over 20 min, and then ramped down to 5% A over 5 min; Method B (A/B): keep 90% A for 3 min, then to 70% A over 12 min, then to 50% A over 3 min, keep at 50% A for 5 min, then to 5% A over 2 min, then keep at 5% A for 3 min; Method C (A/B): keep 99% A for 5 min, then to 90% A over 5 min, keep at 90% A for 3 min, then to 75% A over 7 min, keep at 75% A for 3 min, then to 10% A over 10 min, keep at 10% for 2 min; Method D (A/B): keep 99% A for 3 min, then to 80% A over 12 min, keep at 80% A for 3 min, then to 20% A over 10 min, keep at 20% A for 2 min, then to 5% A over 3 min, keep at 5% for 2 min.

General protocol for the preparation monosubstituted ureas

Potassium cyanate (121.7 mg, 1.5 mmol), ammonium chloride (80.2 mg, 1.5 mmol) were added to a Biotage® microwave vial (capacity: 0.5-2 mL) equipped with a magnetic bar. The desired amine (0.5 mmol) and milli-Q water (0.5 mL) were next added before the vial was capped and sealed. The mixture was subject to microwave irradiation in a reactor set to high-absorption level and the reaction proceeded at the indicated temperature and time. The reaction was then cooled to room temperature using a flow of compressed air, and further cooled to 0°C in an ice bath. The resulting precipitate was filtered, washed with ice cold water and diethyl ether, dried under vacuum to give the desired monosubstituted urea product.

1-Benzylurea (**2a**): The general procedure was used with benzylamine (55 µL, 0.5 mmol) at 120°C for 15 minutes to give the desired product **2a** as a white solid (69 mg, 92%). Mp: 144-145°C; IR (neat, cm^{-1}): 3432 (m, br), 3325 (m, br), 3031 (w), 2873 (w), 1649 (s), 1597 (s), 1561 (s), 1466 (m), 1387 (m), 1141 (m), 749 (m), 695 (s); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.42-7.07 (m, 5H), 6.40 (t, J = 6.1 Hz, 1H), 5.52 (bs, 2H), 4.17 (d, J = 6.0 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.65, 140.93, 128.18, 127.00, 126.51, 42.80. HRMS (ESI^{+}) m/z [$C_8H_{10}N_2ONa$]$^{+}$

calcd: 173.0685; found: 173.0684; HPLC: method A t_R = 8.92 min (95%); method B t_R = 14.46 min (96%). A measurement of reaction endpoint *p*H was performed as follows. Upon reaction completion, the mixture was cooled down to rt, then carefully transferred and filtered into a 25 mL volumetric flask. The reaction container was washed several times with milli-Q water, transferred and filtered into the same volumetric flask. The volume of the solution was adjusted to 25 mL. The *p*H measurement of the diluted solution was achieved by *p*H meter and the reading was 9.89.

1-(4-Methoxybenzyl)urea (**2b**): The general procedure was used with 4-methoxybenzyl amine (65 μL, 0.5 mmol) at 130°C for 10 minutes to give the desired product **2b** as a white solid (77 mg, 86%). Mp: 156-157°C; IR (neat, cm^{-1}): 3424 (m, br), 3333 (m, br), 2880 (w), 2837 (w), 1647 (s), 1597 (s), 1557 (s), 1512 (s), 1244 (s), 1032 (m), 810 (w); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.17 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 6.32 (t, J = 6.0 Hz, 1H), 5.49 (bs, 2H), 4.09 (d, J = 6.0 Hz, 2H), 3.72 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.29, 157.71, 132.45, 127.99, 113.26, 54.69, 41.93. HRMS (ESI$^+$) *m/z* $[C_9H_{12}N_2O_2Na]^+$ calcd: 203.0791; found: 203.0791; HPLC: method A t_R = 8.74 min (92%); method B t_R = 14.58 min (94%).

1-(4-Fluorobenzyl)urea (**2c**): The general procedure was used with 4-fluorobenzyl amine (57 μL, 0.5 mmol) at 120°C for 15 minutes to give the desired product **2c** as a white solid (58 mg, 69%). Mp: 169-170°C; IR (neat, cm^{-1}): 3436 (m, br), 3333 (m, br), 1651 (s), 1597 (s), 1559 (s), 1510 (s), 1470 (m), 1222 (s), 828 (s); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.28 (m, 2H), 7.13 (m, 2H), 6.43 (t, J = 6.1 Hz, 1H), 5.54 (bs, 2H), 4.15 (d, J = 6.1 Hz, 2H); ^{19}F NMR (DMSO-d_6, 471 MHz): δ -116.66; ^{13}C NMR (DMSO-d_6, 125 MHz): δ 161.03 (d, J = 240.0 Hz), 158.65, 137.18 (d, J = 2.5 Hz), 128.91 (d, J = 7.5 Hz), 114.87 (d, J = 21.3 Hz), 42.09. HRMS (ESI$^+$) *m/z* $[C_8H_9N_2OFNa]^+$ calcd: 191.0591; found: 191.0590; HPLC: method A t_R = 9.70 min (96%); method B t_R = 16.45 min (96%).

1-(4-Chlorobenzyl)urea (**2d**): The general procedure was used with 4-chlorobenzyl amine (61 μL, 0.5 mmol) at 130°C for 10 minutes to give the desired product **2d** as a white solid (67 mg, 73%). Mp: 187-188°C; IR (neat, cm^{-1}): 3440 (m, br), 3329 (m, br), 2884 (w), 1653 (s), 1597 (s), 1557 (s), 1490 (w), 1472 (w), 1316 (w), 1086 (m), 1014 (w), 844 (w), 816 (m); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.36 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 6.45 (t, J = 6.1 Hz, 1H), 5.56 (bs, 2H), 4.15 (d, J = 6.1 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.64, 140.13, 130.98, 128.82, 128.10, 42.11. HRMS (ESI$^+$) *m/z* $[C_8H_9N_2OClNa]^+$ calcd: 207.0296; found: 207.0286; HPLC: method A t_R = 11.29 min (94%); method B t_R = 20.28 min (93%).

1-(4-Bromobenzyl)urea (**2e**): The general procedure was used with 4-bromobenzyl amine (63 μL, 0.5 mmol) at 130°C for 10 minutes to give the desired product **2e** as a white solid (86 mg, 75%). Mp: 189-191°C; IR (neat, cm^{-1}): 3436 (m, br), 3337 (m, br), 2932 (w), 2880 (w), 1651 (s), 1597 (s), 1553 (s), 1486 (m), 1476 (m), 1403 (w), 1387 (w), 1320 (w), 1137 (w), 1070 (m), 1012 (m), 838 (m), 812 (m); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.50 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 6.45 (t, J = 6.1 Hz, 1H), 5.56 (bs, 2H), 4.13 (d, J = 6.1 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.62, 140.57, 131.01, 129.20, 119.42, 42.16. HRMS (ESI$^+$) *m/z* $[C_8H_9N_2OBrNa]^+$ calcd: 250.9790; found: 250.9782; HPLC: method A t_R = 11.73 min (85%); method B t_R = 20.82 min (90%).

1-(4-(Trifluoromethyl)benzyl)urea (**2f**): The general procedure was used with 4-(trifluoromethyl)benzyl amine (71 μL, 0.5 mmol) at 120°C for 15 minutes to give the desired product **2f** as a white solid (81 mg, 74%). Mp: 147-149°C; IR (neat, cm^{-1}): 3440 (m, br), 3345 (m, br), 1649 (s), 1597 (s), 1553 (s), 1322 (s), 1173 (s), 1117 (s), 1064 (s), 1018 (m), 848 (m), 823 (m); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.66 (d, J = 8.1 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 6.61 (t, J = 6.2 Hz, 1H), 5.64 (bs, 2H), 4.26 (d, J = 6.1 Hz, 2H); ^{19}F NMR (DMSO-d_6, 471 MHz): δ -60.77; ^{13}C NMR (DMSO-d_6, 125 MHz): δ 159.20, 146.57, 127.99, 127.67 (q, J = 31.3 Hz), 125.49 (q, J = 3.8 Hz), 124.88 (q, J = 270.0 Hz), 42.88. HRMS (ESI$^+$) *m/z* $[C_9H_9N_2OF_3Na]^+$ calcd: 241.0559; found: 241.0558; HPLC: method A t_R = 12.33 min (94%); method B t_R = 21.43 min (94%).

1-(4-Cyanobenzyl)urea (**2g**): The general procedure was used with 4-cyanobenzyl amine hydrochloride (84 mg, 0.5 mmol) at 120°C for 15 minutes to give the desired product **2g** as a white solid (79 mg, 90%). Mp: 208-210°C; IR (neat, cm^{-1}): 3448 (m), 3337 (m), 2884 (w), 2230 (m), 1649 (s), 1601 (s), 1561 (s), 1506 (m), 1387 (m), 1314 (m), 1143 (m), 848 (m), 828 (m); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.78 (d, J = 8.3 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 6.57 (t, J = 6.1 Hz, 1H), 5.64 (bs, 2H), 4.25 (d, J = 6.1 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.68, 147.23, 132.16, 127.72, 119.01, 109.19, 42.56. HRMS (ESI$^+$) *m/z* $[C_9H_9N_3ONa]^+$ calcd: 198.0638; found: 198.0640; HPLC: method A t_R = 8.28 min (97%); method B t_R = 13.02 min (97%).

1-(3-Nitrobenzyl)urea (**2h**): The general procedure was used with 3-nitrobenzyl amine hydrochloride (94 mg, 0.5 mmol) at 120°C for 15 minutes to give the desired product **2h** as a beige solid (88 mg, 90%). Mp: 176-177°C; IR (neat, cm^{-1}): 3468 (m, br), 3317 (m, br), 1649 (s), 1583 (s), 1514 (s), 1428 (m), 1343 (s), 1151 (w), 1092 (w), 727 (s), 669 (m); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.12-8.05 (m, 2H), 7.70 (d, J = 7.9 Hz, 1H), 7.60 (t, J = 7.8 Hz, 2H), 6.65 (t, J = 6.2 Hz, 1H), 5.68 (bs, 2H), 4.30 (d, J = 6.2 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.73, 147.80, 143.81, 133.75, 129.69, 121.50, 121.34, 42.14. HRMS (ESI$^+$) *m/z* $[C_8H_9N_3O_3Na]^+$ calcd: 218.0536; found: 218.0526; HPLC: method A t_R = 9.57 min (97%); method B t_R = 16.17 min (98%).

Methyl 4-(ureidomethyl)benzoate (**2i**): The general procedure was used with methyl 4-(aminomethyl)benzoate hydrochloride (101 mg, 0.5 mmol) at 120°C for 15 minutes to give the desired product **2i** as a white solid (93 mg, 89%). Mp: 187-189°C; IR (neat, cm^{-1}): 3420 (m, br), 3321 (m, br), 2960 (w), 2884 (w), 1722 (s), 1645 (s), 1597 (s), 1559 (s), 1431 (m), 1278 (s), 1173 (m), 1101 (s), 1018 (m), 764 (m), 707 (m); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.91 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 6.54 (t, J = 6.2 Hz, 1H), 5.62 (bs, 2H), 3.84 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 166.18, 158.72, 146.90, 129.17, 127.88, 127.07, 52.02, 42.58. HRMS (ESI$^+$) *m/z* $[C_{10}H_{12}N_2O_3Na]^+$ calcd: 231.0740; found: 231.0732; HPLC: method A t_R = 9.37 min (99%); method B t_R = 16.31 min (99%).

4-(Ureidomethyl)benzenesulfonamide (**2j**): The general procedure was used with 4-(aminomethyl)benzenesulfonamide hydrochloride (111 mg, 0.5 mmol) at 120°C for 15 minutes to give the desired product **2j** as a white solid (78 mg, 68%). Mp: 183-185°C; IR (neat, cm^{-1}): 3455 (m), 3404 (m), 3373 (m), 3174 (m ,br), 3059 (m, br), 2896 (w), 1672 (m), 1619 (s), 1551 (s), 1435 (m), 1331 (m), 1310 (s), 1193 (w), 1163 (s), 1096 (s), 917 (m), 810 (m); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.76 (d, J = 8.3 Hz, 2H), 7.41 (d, J = 8.3 Hz, 2H), 7.26 (bs, 2H), 6.58 (t, J = 6.1 Hz, 1H), 5.61 (bs, 2H), 4.23 (d, J = 6.1 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.69, 145.27, 142.35, 127.19, 125.60, 42.44. HRMS (ESI$^+$) *m/z* $[C_8H_{11}N_3O_3SNa]^+$ calcd: 252.0413; found: 252.0405; HPLC: method C t_R = 13.49 min (95%); method B t_R = 12.08 min (97%).

4-(Ureidomethyl)benzoic acid (**2k**): The general procedure was used with 4-(aminomethyl)benzoic acid (76 mg, 0.5 mmol) at 130°C for 10 minutes to give the desired product **2k** as a white solid (65 mg, 67%). The desired product was precipitated out by adding 3 M HCl. Mp: 305°C (decompose); IR (neat, cm^{-1}): 3432 (m, br), 3333 (m, br), 2884 (w), 1684 (s), 1649 (s), 1599 (s), 1555 (s), 1427 (m), 1320 (s), 1290 (s), 1179 (w), 939 (m), 860 (w), 764 (m), 701 (m); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.89 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 6.55 (t, J = 6.2 Hz, 1H), 5.62 (bs, 2H), 4.24 (d, J = 6.1 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 167.33, 158.79, 146.33, 129.35, 129.13, 126.94, 42.63. HRMS (ESI$^+$) *m/z* $[C_9H_{10}N_2O_3Na]^+$ calcd: 217.0584; found: 217.0579; HPLC: method A t_R = 6.45 min (94%); method B t_R = 9.09 min (98%).

1-(4-(Allyloxy)benzyl)urea (**2l**): The general procedure was used with (4-(allyloxy)phenyl)methanamine (82 mg, 0.5 mmol) at 130°C for 10 minutes to give the desired product **2l** as an off-white solid (86 mg, 83%). Mp: 143-145°C; IR (neat, cm^{-1}): 3424 (m, br), 3333 (m, br), 2920 (w), 2876 (w), 1649 (s), 1597 (s), 1553 (s), 1510 (s), 1468 (m), 1431 (m), 1300 (m), 1240 (s), 1030 (s), 939 (s), 822 (s); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.16 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 6.39 (t, J = 6.1 Hz, 1H), 6.02 (ddt, J = 17.3, 10.4, 5.2 Hz, 1H), 5.52 (bs, 2H), 5.37 (dq, J = 17.3, 1.7 Hz, 1H), 5.24 (dq, J = 10.5, 1.6 Hz, 1H), 4.53 (dt, J = 5.2 Hz, 1.6 Hz, 2H), 4.09 (d, J = 6.0 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.76, 156.99, 133.86, 133.00, 128.35, 117.31, 114.44, 68.17, 42.30. HRMS (ESI$^+$) *m/z* $[C_{11}H_{14}N_2O_2Na]^+$ calcd: 229.0947; found: 229.0944. HPLC: method A t_R = 11.55 min (93%); method B t_R = 20.66 min (95%).

1-(4-(Prop-2-yn-1-yloxy)benzyl)urea (**2m**): The general procedure was used with (4-(prop-2-yn-1-yloxy)phenyl)methanamine (81 mg, 0.5 mmol) at 130°C for 10 minutes to give the desired product **2m** as a beige solid (85 mg, 83%). Mp: 131-133°C; IR (neat, cm^{-1}): 3428 (m, br), 3329 (m, br), 3277 (m, br), 2920 (w), 2876 (w), 1647 (s), 1595 (s), 1548 (s), 1508 (s), 1468 (m), 1385 (m), 1300 (m), 1236 (s), 1034 (s), 824 (m); DMSO-d_6, 500 MHz): δ 7.18 (d, J = 8.6 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 6.39 (t, J = 6.0 Hz, 1H), 5.52 (bs, 2H), 4.76 (d, J = 2.4 Hz, 2H), 4.10 (d, J = 5.9 Hz, 2H), 3.53 (t, J = 2.4 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.71, 155.97, 133.66, 128.31, 114.66, 79.39, 78.11, 55.40, 42.28. HRMS (ESI$^+$) *m/z* $[C_{11}H_{12}N_2O_2Na]^+$ calcd: 227.0791; found: 227.0785; HPLC: method A t_R = 10.50 min (91%); method B t_R = 18.97 min (95%).

1-(Benzo[*d*][1,3]dioxol-5-ylmethyl)urea (**2n**): The general procedure was used with piperonylamine (66 μL, 0.5 mmol) at 120°C for 15 minutes to give the desired product **2n** as a white solid (87 mg, 90%). Mp: 169-170°C; IR (neat, cm^{-1}): 3432 (m ,br), 3325 (m, br), 2916 (w), 2884 (w), 1645 (s), 1597 (s), 1563 (s), 1504 (s), 1484 (m), 1466 (m), 1363 (m), 1318 (w), 1250 (s), 1212 (m), 1038 (m), 1028 (m), 919 (s), 862 (m), 806 (m); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.85-6.78 (m, 2H), 6.71 (m, 1H), 6.39 (t, J = 6.1 Hz, 1H), 5.96 (s, 2H), 5.52 (bs, 2H), 4.07 (d, J = 6.1 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.65, 147.18, 145.84, 134.93, 120.08, 107.93, 107.70, 100.73, 42.60. HRMS (ESI$^+$) *m/z* $[C_9H_{10}N_2O_3Na]^+$ calcd: 217.0584; found: 217.0578; HPLC: method A t_R = 8.93 min (97%); method B t_R = 14.87 min (98%).

1-(Furan-2-ylmethyl)urea (**2o**): The general procedure was used with fufurylamine hydrochloride (67 mg, 0.5 mmol) at 120°C for 15 minutes to give the desired product **2o** as a beige solid (38 mg, 55%). Mp: 103-105°C; IR (neat, cm^{-1}): 3452 (m, br), 3301 (m, br), 3190 (m, br), 2950 (w), 1655 (s), 1607 (s), 1542 (s), 1375 (m), 1331 (s), 1205 (m), 1151 (m), 1074 (w), 929 (w), 745 (s), 732 (s); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.55 (dd, J = 1.9, 0.9 Hz, 1H), 6.37-6.36 (m, 2H), 6.18 (dd, J = 3.2, 0.9 Hz, 1H), 5.55 (bs, 2H), 4.15 (d, J = 5.8 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.36, 153.71, 141.82, 110.37, 106.10, 36.24. HRMS (ESI$^+$) *m/z* $[C_6H_8N_2O_2Na]^+$ calcd: 163.0478; found: 163.0473. HPLC: method A t_R = 6.60 min (87%); method B t_R = 8.32 min (87%).

1-(Thiophen-2-ylmethyl)urea (**2p**): The general procedure was used with 2-thiophenemethylamine (51 μL, 0.5 mmol) at 120°C for 15 minutes to give the desired product **2p** as a white solid (70 mg, 90%). Mp: 127-128°C; IR (neat, cm^{-1}): 3428 (m, br), 3325 (m, br), 1649 (s), 1599 (s), 1559 (s), 1462 (w), 1310 (w), 848 (w), 717 (m), 697 (s); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.35 (dd, J = 4.8, 1.5 Hz, 1H), 6.96-6.90 (m, 2H), 6.47 (t, J = 6.1 Hz, 1H), 5.56 (bs, 2H), 4.33 (d, J = 6.1 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.34, 144.36, 126.60, 124.63, 124.61, 37.98. HRMS (ESI$^+$) *m/z* $[C_6H_8N_2OSNa]^+$ calcd: 179.0250; found: 179.0243. HPLC: method A t_R = 8.07 min (93%); method B t_R = 11.96 min (95%).

1-(Pyridin-4-ylmethyl)urea (**2q**): The general procedure was used with 4-picolylamine (51 μL, 0.5 mmol) at 120°C for 15 minutes to give the desired product **2q** as a white solid (72 mg, 95%). Mp: 190-191°C; IR (neat, cm^{-1}): 3384 (m, br), 3305 (m, br), 1649 (s), 1605 (m), 1559 (s), 1417 (s), 1349 (m), 1312 (m), 1145 (w), 996 (w), 798 (m); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.47 (m, 2H), 7.22 (m, 2H), 6.57 (t, J = 6.2 Hz, 1H), 5.66 (bs, 2H), 4.20 (d, J = 6.2 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.79, 150.22, 149.44, 121.95, 41.91. HRMS (ESI$^+$) *m/z* $[C_7H_9N_3ONa]^+$ calcd: 174.0638; found: 174.0636; HPLC: method C t_R = 2.12 min (97%); method D t_R = 2.38 min (97%).

1-((1*H*-Benzo[*d*]imidazol-2-yl)methyl)urea (**2r**): The general procedure was used with 2-(aminomethyl)benzimidazole (74 mg, 0.5 mmol) at 130°C for 10 minutes to give the desired product **2r** as a brick red solid (60 mg, 63%). Mp: 232 °C (decompose); IR (neat, cm^{-1}): 3416 (w, br), 3182 (w, br), 2928 (w, br), 1643 (s), 1546 (s), 1440 (m), 1262 (m), 1016 (w), 747 (s); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 12.21 (bs, 1H), 7.50 (bs, 2H), 7.13 (dd, J = 6.0, 3.1 Hz, 2H), 6.63 (t, J = 5.7 Hz, 1H), 5.79 (s, 2H), 4.43 (d, J = 5.7 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.87, 153.50, 143.11, 121.71, 118.31, 111.34, 38.03. HRMS (ESI$^+$) *m/z* $[C_9H_{10}N_4ONa]^+$ calcd: 213.0747; found: 213.0740; HPLC: method C t_R = 18.94 min (99%); method D t_R = 16.22 min (99%).

(*R*)-1-(1-Phenylethyl)urea (**2s**): The general procedure was used with (*R*)-(+)-α-methylbenzylamine (64 μL, 0.5 mmol) at 120°C for 15 minutes to give the desired product **2s** as a white solid (60 mg, 73%). Mp: 117-118°C; IR (neat, cm^{-1}): 3440 (m, br), 3321 (m, br), 2972 (w), 1653 (s), 1600 (s), 1550 (s), 1448 (w), 1369 (m), 1145 (w), 1022 (w), 747 (w), 693 (m); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.34-7.25 (m, 4H), 7.21 (m, 1H), 6.46 (d, J = 7.2 Hz, 1H), 5.45 (bs, 2H), 4.70 (p, J = 7.0 Hz, 1H), 1.30 (d, J = 7.1 Hz, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 157.97, 145.84, 128.18, 126.40, 125.78, 48.47, 23.36. HRMS (ESI$^+$) *m/z* $[C_9H_{12}N_2ONa]^+$ calcd: 187.0842; found: 187.0836; HPLC: method A t_R = 9.56 min (87%); method B t_R = 16.58 min (92%).

1-Cinnamylurea (**2t**): The general procedure was used with cinnamylamine (67 mg, 0.5 mmol) at 120°C for 15 minutes to give the desired product **2t** as a white solid (62 mg, 70%). Mp: 148-150°C; IR (neat, cm^{-1}): 3728 (m, br), 3333 (m, br), 3027 (w), 2873 (w), 1647 (s), 1597 (s), 1555 (s), 1494 (m), 1339 (m), 1139 (m), 965 (s), 737 (s), 685 (s); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.39 (d, J = 7.2 Hz, 2H), 7.31 (t, J = 7.2 Hz, 2H), 7.22 (t, J = 7.2 Hz, 1H), 6.46 (dt, J = 16.0, 1.7 Hz, 1H), 6.25 (dt, J = 15.9, 5.6 Hz, 1H), 6.18 (t, J = 5.9 Hz, 1H), 5.53 (bs, 2H), 3.77 (td, J = 5.7, 1.7 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.54, 136.73, 129.27, 128.65, 128.62, 127.26, 126.05, 41.15. HRMS (ESI$^+$) *m/z* $[C_{10}H_{12}N_2ONa]^+$ calcd: 199.0842; found: 199.0835; HPLC: method A t_R = 11.21 min (92%); method B t_R = 20.29 min (93%).

1-(2-Fluoro-6-(trifluoromethyl)benzyl)urea (**2u**): The general procedure was used with 2-fluoro-6-(trifluoromethyl)benzyl amine hydrochloride (115 mg, 0.5 mmol) at 120°C for 15 minutes to give the desired product **2u** as a white solid (83 mg, 72%). Mp: 197-198°C; IR (neat, cm^{-1}): 3464 (m, br), 3289 (m, br), 1647 (m), 1553 (m), 1316 (m), 1254 (w), 1117 (s), 800 (m); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.62-7.54 (m, 3H), 6.18 (t, J = 5.3 Hz, 1H), 5.50 (bs, 2H), 4.36 (d, J = 5.4 Hz, 2H); ^{19}F NMR (DMSO-d_6, 471 MHz): δ -57.43, -113.43; ^{13}C NMR (DMSO-d_6, 125 MHz): δ 161.60 (d, J = 246.3 Hz), 157.92, 130.18 (d, J = 8.8 Hz), 129.39 (qd, J = 30.0, 5.0 Hz), 125.07 (d, J = 17.5 Hz), 123.62 (qd, J = 272.5, 3.8 Hz), 121.94 (qd, J = 5.4, 3.1Hz), 120.13 (d, J = 22.5 Hz), 33.75. HRMS (ESI$^+$) *m/z* $[C_9H_8N_2O_1F_4Na]^+$ calcd: 259.0465; found: 259.0459; HPLC: method A t_R = 11.77 min (88%); method B t_R = 20.86 min (88%).

1-((1*S*,2*R*)-2-Hydroxy-2,3-dihydro-1*H*-inden-1-yl)urea (**4a**): The general procedure was used with (1*S*,2*R*)-(-)-*cis*-1-amino-2-indanol (75 mg, 0.5 mmol) at 120°C for 15 minutes to give the desired product 4a as a white solid (86 mg, 90%). Mp: 232°C (decompose); IR (neat, cm^{-1}): 3424 (m, br), 3337 (m, br), 3210 (w, br), 2944 (w), 1647 (s), 1593 (s), 1559 (s), 1375 (m), 1327 (m), 1187 (m), 1169 (m), 1046 (s), 818 (w), 737 (s); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.23-7.14 (m, 4H), 6.15 (d, J = 8.9 Hz, 1H), 5.74 (bs, 2H), 5.09 (d, J = 4.1 Hz, 1H), 4.99 (dd, J = 8.9, 4.9 Hz, 1H), 4.36 (m, 1H), 3.00 (dd, J = 16.2, 4.8 Hz, 1H), 2.76 (d, J = 16.1 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.90, 143.71, 140.39, 126.95, 126.19, 124.85, 123.89, 72.36, 57.43, 39.77. HRMS (ESI$^+$) *m/z* $[C_{10}H_{12}N_2O_2Na]^+$ calcd: 215.0791; found: 215.0782; HPLC: method A t_R = 8.05 min (95%); method B t_R = 13.06 min (97%).

1-(4-Hydroxy-3-methoxybenzyl)urea (**4b**): The general procedure was used with vinallyl amine hydrochloride (95 mg, 0.5 mmol) at 120°C for 15 minutes to give the desired product **4b** as a beige solid (75 mg, 77%). The desired product was precipitated out by adding 3 M HCl, if necessary. Mp: 169-171°C; IR (neat, cm^{-1}): 3440 (m, br), 3337 (m, br), 3202 (m, br), 2955 (w), 2932 (w), 1639 (s), 1559(s), 1528 (s), 1456 (w), 1427 (m), 1377 (m), 1355 (m), 1272 (m), 1248 (s), 1216 (s), 1109 (s), 1030 (s), 808 (s), 731 (m), 689 (m); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.78 (bs, 1H), 6.82 (d, J = 2.0 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 6.64 (dd, J = 8.0, 2.0 Hz, 1H), 6.28 (bs, 1H), 5.46 (bs, 2H), 4.06 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.66, 147.41, 145.27, 131.57, 119.58, 115.20, 111.63, 55.56, 42.78. HRMS (ESI$^+$) *m/z* $[C_9H_{12}N_2O_3Na]^+$ calcd: 219.0740; found: 219.0734; HPLC: method A t_R = 6.20 min (78%); method B t_R = 8.10 min (83%).

1-(2-Aminobenzyl)urea (**4c**): The general procedure was used with 2-aminobenzyl amine (61 mg, 0.5 mmol) at 120°C for 15 minutes to give the desired product **4c** as a beige solid (56 mg, 68%). Mp: 184-186°C; IR (neat, cm^{-1}): 3456 (m, br), 3388 (m, br), 3329 (m, br), 3238 (w, br), 2884 (w), 1633 (s), 1577 (s), 1550 (s), 1500 (s), 1458 (m), 1322 (m), 1139 (m), 1032 (w), 747 (s); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.99-6.90 (m, 2H), 6.59 (dd, J = 7.9, 1.2 Hz, 1H), 6.47 (td, J = 7.3, 1.2 Hz, 1H), 6.28 (t, J = 6.2 Hz, 1H), 5.53 (bs, 2H), 5.14 (bs, 2H), 4.03 (d, J = 6.1 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 159.07, 146.40, 129.10, 127.74, 123.52, 115.56, 114.47, 39.86. HRMS (ESI$^+$) *m/z* $[C_8H_{11}N_3ONa]^+$ calcd: 188.0794; found: 188.0787; HPLC: method C t_R = 9.56 min (89%); method D t_R = 9.30 min (92%).

1-(4-(*tert*-Butoxy)benzyl)urea (**4d**): The general procedure was used with 4-(*tert*-butoxy)benzyl amine (90 mg, 0.5 mmol) at 130°C for 10 minutes to give the desired product **4d** as a beige solid (72 mg, 65%). Mp: 90-92°C; IR (neat, cm^{-1}): 3408 (m, br), 3202 (m, br), 2976 (m), 2932 (w), 1651 (s), 1611 (s), 1534 (s), 1502 (s), 1161 (m), 897 (m), 834 (w); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.15 (d, J = 8.5 Hz, 2H), 6.90 (d, J = 8.5 Hz, 2H), 6.40 (t, J = 6.0 Hz, 1H), 5.52 (bs, 2H), 4.12 (d, J = 6.0 Hz, 2H), 1.27 (s, 9H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.68, 153.61, 135.56, 127.70, 123.58, 77.67, 42.33, 28.55. HRMS (ESI$^+$) *m/z* $[C_{12}H_{18}N_2O_2Na]^+$ calcd: 245.1260; found: 245.1253; HPLC: method A t_R = 12.11 min (84%); method B t_R = 21.23 min (84%).

1-(4-(Methoxymethoxy)benzyl)urea (**4e**): The general procedure was used with 4-(methoxymethoxy)benzyl amine (84 mg, 0.5 mmol) at 130°C for 10 minutes to give the desired product **4e** as a beige solid (70 mg, 67%). Mp: 129-131°C; IR (neat, cm^{-1}): 3428 (m ,br), 3333 (m, br), 2952 (w), 2924 (w), 2880 (w), 1651 (s), 1597 (s), 1557 (s), 1512 (s), 1468 (w), 1230 (m), 1153 (s), 1074 (m), 1008 (s), 921 (m), 824 (w); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.17 (d, J = 8.6 Hz, 2H), 6.96 (d, J = 8.6 Hz, 2H), 6.38 (t, J = 6.0 Hz, 1H), 5.51 (bs, 2H), 5.15 (s, 2H), 4.10 (d, J = 6.0 Hz, 2H), 3.36 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.67, 155.53, 134.13, 128.30, 116.01, 93.90, 55.44, 42.30. HRMS (ESI$^+$) *m/z* $[C_{10}H_{14}N_2O_3Na]^+$ calcd: 233.0897; found: 233.0890; HPLC: method A t_R = 9.46 min (90%); method B t_R = 16.44 min (93%).

1-(4-(1,3-Dioxolan-2-yl)benzyl)urea (**4f**): The general procedure was used with (4-(1,3-dioxolan-2-yl)phenyl)methanamine (90 mg, 0.5 mmol) at 80°C for 60 minutes to give the desired product **4f** as a white solid (63 mg, 58%). Mp: 168-170°C; IR (neat, cm^{-1}): 3432 (m, br), 3301 (m, br), 2884 (m), 1645 (s), 1583 (s), 1551 (s), 1470 (m), 1385 (s), 1322 (m), 1224 (m), 1137 (m), 1080 (s), 941 (s), 840 (m), 788 (s), 703 (s); ^{1}H

NMR (DMSO-d_6, 500 MHz): δ 7.37 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 8.2 Hz, 2H), 6.43 (t, J = 6.1 Hz, 1H), 5.69 (s, 1H), 5.54 (bs, 2H), 4.18 (d, J = 6.1 Hz, 2H), 4.02(m, 2H), 3.93 (m, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.67, 142.00, 136.40, 126.79, 126.51, 102.77, 64.75, 42.59. HRMS (ESI$^+$) m/z $[C_{11}H_{14}N_2O_3Na]^+$ calcd: 245.0897; found: 245.0894; HPLC: method A t_R = 8.32 min (78%); method B t_R = 13.75 min (78%).

1-(4-((2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy)benzyl)urea (**4g**): The general procedure was used with (4-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)phenyl)methanamine (119 mg, 0.5 mmol) at 130^{o}C for 10 minutes to give the desired product **4g** as a yellow solid (110 mg, 78%). Mp: 107-109^{o}C; IR (neat, cm^{-1}): 3428 (m, br), 3337 (m, br), 2996 (w), 2932 (w), 2880 (w), 1653 (s), 1601 (s), 1557 (s), 1512 (s), 1379 (m), 1246 (s), 1052 (s), 836 (s), 822 (m); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.16 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 6.40 (t, J = 6.0 Hz, 1H), 5.53 (bs, 2H), 4.39 (m, 1H), 4.13-4.04 (m, 3H), 3.98 (dd, J = 10.2, 4.6 Hz, 1H), 3.95 (dd, J = 10.1, 6.1 Hz, 1H), 3.74 (dd, J = 8.3, 6.3 Hz, 1H), 1.35 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.70, 157.14, 133.18, 128.32, 114.21, 108.82, 73.74, 68.76, 65.78, 42.24, 26.63, 25.40. HRMS (ESI$^+$) m/z $[C_{14}H_{20}N_2O_4Na]^+$ calcd: 303.1315; found: 303.1318; HPLC: method A t_R = 11.09 min (95%); method B t_R = 20.21 min (95%).

1-Pentylurea (**6a**): The general procedure was used with 1-pentylamine (58 μL, 0.5 mmol) at 130^{o}C for 10 minutes to give the desired product **6a** as a white solid (45 mg, 70%). Mp: 97-99^{o}C; IR (neat, cm^{-1}): 3392 (m, br), 3206 (m, br), 2948 (w), 2932 (w), 2857 (w), 1653 (s), 1601 (s), 1538 (s), 1482 (w), 1341 (w), 1153 (w); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 5.88 (t, J = 5.7 Hz, 1H), 5.34 (bs, 2H), 2.93 (td, J = 7.0, 5.7 Hz, 2H), 1.34 (m, 2H), 1.30-1.16 (m, 4H), 0.86 (t, J = 7.1 Hz, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.72, 29.69, 28.63, 21.92, 13.97. HRMS (ESI$^+$) m/z $[C_6H_{14}N_2ONa]^+$ calcd: 153.0998; found: 153.0993; HPLC: method A t_R = 9.96 min (96%); method B t_R = 17.07 min (96%).

1-(4-Phenylbutyl)urea (**6b**): The general procedure was used with 4-phenylbutylamine (79 μL, 0.5 mmol) at 120^{o}C for 15 minutes to give the desired product **6b** as a white solid (72 mg, 75%). Mp: 123-125^{o}C; IR (neat, cm^{-1}): 3392 (m, br), 3210 (m, br), 2944 (w), 2920 (w), 2853 (w), 1655 (s), 1595 (s), 1530(s), 1476 (m), 1337 (w), 1300 (w), 1147 (w), 753 (m), 699 (s); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.26 (m, 2H), 7.19-7.14 (m, 3H), 5.94 (t, J = 5.8 Hz, 1H), 5.37 (bs, 2H), 2.97 (td, J = 7.0, 5.8 Hz, 2H), 2.56 (t, J = 7.7 Hz, 2H), 1.54 (m, 2H), 1.37 (m, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.74, 142.23, 128.28, 128.22, 125.62, 38.93, 34.90, 29.71, 28.45. HRMS (ESI$^+$) m/z $[C_{11}H_{16}N_2ONa]^+$ calcd: 215.1155; found: 215.1147; HPLC: method A t_R = 12.30 min (94%); method B t_R = 21.46 min (94%).

1-(2-Chlorophenethyl)urea (**6c**): The general procedure was used with 2-(2-chlorophenyl)ethylamine (78 mg, 0.5 mmol) at 120^{o}C for 15 minutes to give the desired product **6c** as a light yellow solid (92 mg, 92%). Mp: 116-118^{o}C; IR (neat, cm^{-1}): 3416 (m, br), 3365 (m, br), 3210 (w, br), 2948 (w), 1647 (s), 1597 (s), 1557 (s), 1450 (m), 1347 (m), 1052 (m), 770 (m), 745 (s), 701 (m); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.40 (dd, J = 7.7, 1.5 Hz, 1H), 7.31 (dd, J = 7.5, 2.0 Hz, 1H), 7.27 (td, J = 7.4, 1.6 Hz, 1H), 7.23 (td, J = 7.5, 2.0 Hz, 1H), 6.09 (t, J = 6.0 Hz, 1H), 5.47 (bs, 2H), 3.21 (dt, J = 7.5, 6.1 Hz, 2H), 2.80 (t, J = 7.4 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.69, 137.09, 133.15, 131.05, 129.19, 128.03, 127.21, 39.02, 33.84. HRMS (ESI$^+$) m/z $[C_9H_{11}N_2OClNa]^+$ calcd: 221.0452; found: 221.0451; HPLC: method A t_R = 11.45 min (88%); method B t_R = 20.58 min (90%).

4-(2-Ureidoethyl)benzenesulfonamide (**6d**): The general procedure was used with 4-(2-aminoethyl)benzenesulfonamide (100 mg, 0.5 mmol) at 130^{o}C for 10 minutes to give the desired product **6d** as a white solid (77 mg, 63%). Mp: 164-166^{o}C; IR (neat, cm^{-1}): 3476 (w, br), 3369 (m, br), 3329 (m, br), 1645 (s), 1567 (s), 1312 (s), 1133 (s), 1094 (s), 915 (m), 683 (m); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.75 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.3 Hz, 2H), 7.31 (bs, 2H), 6.05 (bs, 1H), 5.57 (bs, 2H), 3.23 (t, J = 7.1 Hz, 2H), 2.75 (t, J = 7.1 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.75, 144.05, 141.98, 129.18, 125.71, 40.48, 35.83. HRMS (ESI$^+$) m/z $[C_9H_{13}N_3O_3SNa]^+$ calcd: 266.0570; found: 266.0568; HPLC: method A t_R = 6.33 min (92%); method B t_R = 8.58 min (95%).

1-(2-(Thiophen-2-yl)ethyl)urea (**6e**): The general procedure was used with 2-thiopheneethylamine (59 μL, 0.5 mmol) at 120^{o}C for 15 minutes to give the desired product **6e** as a beige solid (50 mg, 59%). Mp: 86-87^{o}C; IR (neat, cm^{-1}): 3388 (m, br), 3202 (m, br), 2940 (w), 1649 (s), 1603 (s), 1538 (s), 1433 (w), 1345 (m), 1153 (w), 850 (w), 818 (w), 685 (s); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.32 (dd, J = 5.1, 1.2 Hz, 1H), 6.95 (dd, J = 5.1, 3.4 Hz, 1H), 6.87 (dd, J = 3.4, 1.1 Hz, 1H), 6.08 (t, J = 5.9 Hz, 1H), 5.52 (bs, 2H), 3.22 (td, J = 7.1, 5.8 Hz, 2H), 2.88 (t, J = 7.0, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.66, 141.96, 126.95, 125.02, 123.85, 41.02, 30.39. HRMS (ESI$^+$) m/z $[C_7H_{10}N_2OSNa]^+$ calcd: 193.0406; found: 193.0400; HPLC: method A t_R = 9.06 min (93%); method B t_R = 15.19 min (96%).

6-Ureidohexanoic acid (**6f**): The general procedure was used with aminocaproic acid (66 mg, 0.5 mmol) at 130^{o}C for 10 minutes to give the desired product **6f** as a white solid (51 mg, 59%). The desired product was precipitated out by adding 3 M HCl, and washed with 1 M HCl. Mp: 167-168^{o}C; IR (neat, cm^{-1}): 3404 (m, br), 3349 (m, br), 3326 (m, br), 2948 (w), 2869 (w), 1706 (s), 1659 (m), 1557 (s), 1375 (m), 1296 (m), 1197 (m), 985 (w); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 12.01 (bs, 1H), 5.94 (bs, 1H), 5.34 (bs, 2H), 2.92 (t, J = 6.9 Hz, 2H), 2.18 (t, J = 7.4 Hz, 2H), 1.48 (p, J = 7.4 Hz, 2H), 1.34 (p, J = 7.4 Hz, 2H), 1.24 (m, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 174.53, 158.84, 33.71, 29.77, 26.01, 24.34. HRMS (ESI$^+$) m/z $[C_7H_{14}N_2O_3Na]^+$ calcd: 197.0897; found: 197.0896; HPLC: method A t_R = 7.99 min (71%); method B t_R = 13.15 min (82%).

Benzyl (2-ureidoethyl)carbamate (**6g**): The general procedure was used with *N*-Z-ethylenediamine hydrochloride (115 mg, 0.5 mmol) at 120^{o}C for 15 minutes to give the desired product **6g** as a white solid (92 mg, 77%). Mp: 125-127^{o}C; IR (neat, cm^{-1}): 3396 (m, br), 3277 (m, br), 3218 (m, br), 2928 (w), 1706 (s), 1670 (s), 1625 (s), 1550 (s), 1427 (m), 1272 (s), 1141 (m), 1026 (m), 731 (s); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.44-7.28 (m, 5H), 7.26 (t, J = 5.4 Hz, 1H), 6.06 (bs, 1H), 5.50 (bs, 2H), 5.01 (s, 2H), 3.05-2.99 (m, 4H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.91, 156.23, 137.21, 128.40, 127.81, 127.79, 65.26, 41.20, 39.07. HRMS (ESI$^+$) m/z $[C_{11}H_{15}N_3O_3Na]^+$ calcd: 260.1006; found: 260.0995; HPLC: method A t_R = 9.75 min (96%); method B t_R = 17.70 min (98%).

Benzyl (2-(3-ureidopropanamido)ethyl)carbamate (**6h**): The general procedure was used with benzyl (2-(3-aminopropanamido)ethyl) carbamate hydrochloride (151 mg, 0.5 mmol) at 130°C for 10 minutes to give the desired product **6h** as a white solid (81 mg, 53%). Mp: 163-164°C; IR (neat, cm^{-1}): 3444 (w, br), 3305 (bs), 3087 (w, br), 2940 (w), 1688 (s), 1639 (s), 1546 (s), 1276 (s), 1238 (m), 1145 (m), 994 (m); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.99 (t, J = 5.5 Hz, 1H), 7.41-7.29 (m, 6H), 6.00-5.50 (m, 3H), 5.01 (s, 2H), 3.18 (t, J = 6.6 Hz, 2H), 3.10 (q, J = 5.9 Hz, 2H), 3.05 (q, J = 5.8 Hz, 2H), 2.21 (t, J = 6.6 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 170.96, 158.93, 156.23, 137.17, 128.39, 127.82, 127.80, 65.32, 40.05, 38.62, 36.09, 35.93. HRMS (ESI$^+$) m/z $[C_{14}H_{20}N_4O_4Na]^+$ calcd: 331.1377; found: 331.1388; HPLC: method A t_R = 9.60 min (94%); method B t_R = 17.55 min (94%).

1-(2-(1*H*-Indol-3-yl)ethyl)urea (**6i**): The general procedure was used with tryptamine (80 mg, 0.5 mmol) at 120°C for 15 minutes to give the desired product **6i** as a beige solid (85 mg, 84%). Mp: 137-138°C; IR (neat, cm^{-1}): 3412 (m), 3376 (w, br), 3345 (w, br), 3154 (w, br), 2944 (w), 2892 (w), 1635 (m), 1555 (s), 1454 (m), 1331 (m), 1141 (w), 1088 (w), 737 (s); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 10.82 (s, 1H), 7.53 (d, J = 7.9 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.14 (d, J = 2.3 Hz, 1H), 7.07 (m, 1H), 6.98 (m, 1H), 6.00 (t, J = 5.8 Hz, 1H), 5.46 (bs, 2H), 3.27 (td, J = 7.3, 5.7 Hz, 2H), 2.78 (t, J = 7.3 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.83, 136.31, 127.31, 122.67, 120.93, 118.39, 118.23, 112.05, 111.39, 40.02, 26.14. HRMS (ESI$^+$) m/z $[C_{11}H_{13}N_3ONa]^+$ calcd: 226.0951; found: 226.0951; HPLC: method A t_R = 10.39 min (98%); method B t_R = 19.00 min (98%).

1-(2-(5-Methoxy-1*H*-indol-3-yl)ethyl)urea (**6j**): The general procedure was used with mexamine (95 mg, 0.5 mmol) at 120°C for 15 minutes to give the desired product **6j** as a brown solid (80 mg, 69%). The desired product was precipitated out by adding 1 M HCl, and washed with 1 M HCl. Mp: 133-134°C; IR (neat, cm^{-1}): 3408 (m), 3349 (m, br), 3182 (m, br), 2940 (w), 2888 (w), 1651 (m), 1619 (s), 1542 (s), 1486 (s), 1435 (m), 1218 (s), 1173 (m), 1030 (m), 808 (m); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 10.68 (bs 1H), 7.23 (d, J = 8.7 Hz, 1H), 7.10 (m, 1H), 7.04 (d, J = 2.4 Hz, 1H), 6.72 (dd, J = 8.7, 2.4 Hz, 1H), 6.08 (bs, 1H), 5.01 (bs, 2H), 3.76 (s, 3H), 3.27 (t, J = 7.2 Hz, 2H), 2.76 (t, J = 7.2 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.91, 152.98, 131.44, 127.64, 123.35, 112.00, 111.83, 111.06, 100.27, 55.37, 40.02, 26.10. HRMS (ESI$^+$) m/z $[C_{12}H_{15}N_3O_2Na]^+$ calcd: 256.1056; found: 256.1051; HPLC: method A t_R = 9.99 min (87%); method B t_R = 18.10 min (93%).

1-(3,4-Dimethoxyphenethyl)urea (**6k**): The general procedure was used with homoveratrylamine (91 mg, 0.5 mmol) at 120°C for 15 minutes to give the desired product **6k** as a yellow solid (75 mg, 67%). Mp: 147-148°C; IR (neat, cm^{-1}): 3448 (m, br), 3337 (m, br), 3007 (w), 2928 (w), 1647 (s), 1589 (s), 1565 (s), 1516 (s), 1262 (s), 1232 (s), 1137 (s), 1024 (s), 842 (m), 806 (m), 766 (m); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.85 (d, J = 8.2 Hz, 1H), 6.79 (d, J = 2.0 Hz, 1H), 6.70 (dd, J = 8.1, 2.0 Hz, 1H), 5.90 (t, J = 5.8 Hz, 1H), 5.46 (bs, 2H), 3.74 (s, 3H), 3.71 (s, 3H), 3.18 (m, 2H), 2.60 (t, J = 7.2 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.70, 148.63, 147.17, 132.23, 120.46, 112.57, 111.91, 55.54, 55.38, 40.97, 35.72. HRMS (ESI$^+$) m/z $[C_{11}H_{16}N_2O_3Na]^+$ calcd: 247.1053; found: 247.1063; HPLC: method A t_R = 8.63 min (93%); method B t_R = 14.96 min (94%).

(*E*)-1-(3-(((1-Phenylethylidene)amino)oxy)propyl)urea (**6l**): The general procedure was used with (*E*)-1-phenylethan-1-one *O*-(3-aminopropyl) oxime (96 mg, 0.5 mmol) at 120°C for 15 minutes to give the desired product **6l** as a beige solid (91 mg, 77%). Mp: 105-107°C; IR (neat, cm^{-1}): 3388 (m, br), 3206 (m, br), 2964 (w), 2880 (w), 1651 (s), 1601 (s), 1540 (s), 1387 (m), 1155 (w), 1052 (s), 1028 (s), 909 (s), 759 (s), 691 (s); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.65 (m, 2H), 7.43-7.35 (m, 3H), 6.06 (t, J = 5.8 Hz, 1H), 5.43 (bs, 2H), 4.14 (t, J = 6.4 Hz, 2H), 3.07 (m, 2H), 2.18 (s, 3H), 1.76 (p, J = 6.6 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.84, 153.95, 136.11, 129.15, 128.46, 125.87, 71.33, 36.23, 29.88, 12.39. HRMS (ESI$^+$) m/z $[C_{12}H_{17}N_3O_2Na]^+$ calcd: 258.1213; found: 258.1206; HPLC: method A t_R = 12.83 min (78%); method B t_R = 21.93 min (80%).

tert-Butyl 4-ureidopiperidine-1-carboxylate (**6m**): The general procedure was used with 4-amino-1-Boc-piperidine (100 mg, 0.5 mmol) at 120°C for 15 minutes to give the desired product **6m** as a white solid (85 mg, 70%). Mp: 208°C (decompose); IR (neat, cm^{-1}): 3404 (w, br), 3325 (w, br), 3198 (w, br) 2972 (w), 2928 (w), 2857 (w), 1690 (s), 1651 (s), 1593 (m), 1551 (m), 1417 (m), 1359 (m), 1149 (s), 1028 (m), 764 (m); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 5.99 (d, J = 7.8 Hz, 1H), 5.37 (bs, 2H), 3.77 (m, 2H), 3.48 (m, 1H), 2.83 (m, 2H), 1.70 (m, 2H), 1.38 (s, 9H), 1.15 (m, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.04, 153.95, 78.62, 46.07, 32.22, 28.12. HRMS (ESI$^+$) m/z $[C_{11}H_{21}N_3O_3Na]^+$ calcd: 266.1475; found: 266.1472; HPLC: method A t_R = 10.63 min (98%); method B t_R = 19.70 min (97%).

1-(4-((Tetrahydro-2*H*-pyran-2-yl)oxy)phenethyl)urea (**6n**): The general procedure was used with 2-(4-((tetrahydro-2*H*-pyran-2-yl)oxy)phenyl) ethan-1-amine (111 mg, 0.5 mmol) at 130°C for 10 minutes to give the desired product **6n** as an off-white solid (83 mg, 63%). Mp: 102-104°C; IR (neat, cm^{-1}): 3416 (w, br), 3369 (w, br), 3210 (w, br), 2940 (w), 2869 (w), 1651 (s), 1599 (s), 1540 (s), 1510 (s), 1353 (m), 1232 (s), 1072 (m), 1032 (s), 965 (m), 820 (m); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.10 (d, J = 8.5 Hz, 2H), 6.94 (d, J = 8.5 Hz, 2H), 5.95 (t, J = 5.8 Hz, 1H), 5.45 (bs, 2H), 5.39 (t, J = 3.5 Hz, 1H), 3.76 (ddd, J = 12.1, 8.9, 3.6 Hz, 1H), 3.53 (m, 1H), 3.18-3.14 (m, 2H), 2.60 (t, J = 7.3 Hz, 2H), 1.88-1.75 (m, 2H), 1.70 (m, 1H), 1.66-1.45 (m, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.69, 154.92, 132.72, 129.49, 116.36, 95.90, 61.55, 41.00, 35.34, 29.97, 24.75, 18.73. HRMS (ESI$^+$) m/z $[C_{14}H_{20}N_2O_3Na]^+$ calcd: 287.1366; found: 287.1364; HPLC: method A t_R = 12.79 min (72%); method B t_R = 21.90 min (80%).

1-(3-((4-Methoxybenzyl)oxy)propyl)urea (**6o**): The general procedure was used with 3-((4-methoxybenzyl)oxy)propan-1-amine (98 mg, 0.5 mmol) at 120°C for 15 minutes to give the desired product **6o** as an off-white solid (93 mg, 78%). Mp: 101-103°C; IR (neat, cm^{-1}): 3432 (m, br), 3333 (m, br), 3210 (m, br), 2940 (w), 2861 (w), 1649 (s), 1595 (s), 1559 (s), 1512 (s), 1353 (m), 1248 (s), 1096 (s), 1028 (s), 814 (m); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.24 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 6.01 (t, J = 5.8 Hz, 1H), 5.44 (bs, 2H), 4.35 (s, 2H), 3.73 (s, 3H), 3.39 (t, J = 6.4 Hz, 2H), 3.02 (m, 2H), 1.61 (p, J = 6.5 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.88, 158.67, 130.58, 129.12, 113.64, 71.60, 67.23, 55.05, 36.54, 30.27. HRMS (ESI$^+$) m/z $[C_{12}H_{18}N_2O_3Na]^+$ calcd: 261.1210; found: 261.1208; HPLC: method A t_R = 10.46 min (97%); method B t_R = 19.40 min (96%).

1-(2-Phenyl-1,3-dioxan-5-yl)urea (**6p**): The general procedure was used with 2-phenyl-1,3-dioxan-5-amine (90 mg, 0.5 mmol) at 120ºC for 15 minutes to give the desired product **6p** as a white solid (55 mg, 50%). The product exists as a mixture of confermers. Mp: 186-188ºC; IR (neat, cm^{-1}): 3444 (w, br), 3341 (w, br), 3301 (w, br), 2980 (w), 2865 (w), 1653 (s), 1561 (s), 1379 (m), 1155 (m), 1096 (s), 983 (s), 743 (m), 697 (s); ^{1}H NMR (DMSO-d_6, 500 MHz): (*cis*) δ 7.49 (m, 2H), 7.38-7.36 (m, 3H), 6.52 (d, J = 8.5 Hz, 1H), 5.69 (bs, 2H), 5.58 (s, 1H), 4.12 (m, 2H), 3.90 (dd, J = 11.7, 1.4 Hz, 2H), 3.58 (m, 1H); (*trans*) δ 7.42 (m, 2H), 7.38-7.36 (m, 3H), 6.01 (d, J = 8.3 Hz, 1H), 5.58 (bs, 2H), 5.45 (s, 1H), 4.15 (m, 2H), 3.81 (m, 1H), 3.53 (t, J = 11.0 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): (*cis*) δ 158.18, 138.61, 128.73, 128.03, 126.21, 100.65, 70.52, 43.69; (*trans*) δ 158.03, 138.20, 128.70, 127.94, 126.16, 100.24, 69.90, 42.44. HRMS (ESI$^+$) m/z $[C_{11}H_{14}N_2O_3Na]^+$ calcd: 245.0897; found: 245.0902; HPLC: method A t_R = 10.21 min (49%); t_R = 10.34 min (43%); method B t_R = 18.18 min (46%); t_R = 18.63 min (47%).

1-Benzyl-1-methylurea (**8a**): The general procedure was used with *N*-benzylmethylamine (65 μL, 0.5 mmol) at 120ºC for 15 minutes to give the desired product **8a** as a white solid (44 mg, 54%). Mp: 131-133ºC; IR (neat, cm^{-1}): 3392 (m, br), 3190 (m, br), 3023 (w), 2932 (w), 1653 (s), 1607 (s), 1593 (s), 1505 (s), 1448 (w), 1413 (m), 1355 (w), 1100 (m), 963 (w), 731 (m), 701 (m); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.33 (m, 2H), 7.27-7.17 (m, 3H), 5.94 (bs, 2H), 4.39 (s, 2H), 2.73 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.87, 138.89, 128.35, 127.18, 126.78, 50.99, 34.01. HRMS (ESI$^+$) m/z $[C_9H_{12}N_2ONa]^+$ calcd: 187.0842; found: 187.0835; HPLC: method A t_R = 13.49 min (98%); method B t_R = 18.00 min (98%).

3,4-Dihydroisoquinoline-2(1*H*)-carboxamide (**8b**): The general procedure was used with tetrahydroisoquinoline (63 μL, 0.5 mmol) at 120ºC for 15 minutes to give the desired product **8b** as an off-white solid (53 mg, 60%). Mp: 166-168ºC; IR (neat, cm^{-1}): 3384 (m, br), 3214 (m, br), 2896 (w), 2861 (w), 1647 (s), 1600 (s), 1486 (s), 1448 (s), 1302 (m), 1096 (w), 931 (w), 739 (s); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.20-7.07 (m, 4H), 6.04 (bs, 2H), 4.47 (s, 2H), 3.52 (t, J = 5.9 Hz, 2H), 2.75 (t, J = 5.9 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.09, 134.79, 134.29, 128.56, 126.14, 126.13, 125.93, 45.28, 41.02, 28.24. HRMS (ESI$^+$) m/z $[C_{10}H_{12}N_2ONa]^+$ calcd: 199.0842; found: 199.0849; HPLC: method A t_R = 10.70 min (97%); method B t_R = 19.51 min (98%).

2-Phenylhydrazine-1-carboxamide (**8c**): The general procedure was used with phenylhydrazine (50 μL, 0.5 mmol) at 120ºC for 30 minutes to give the desired product **8b** as a light yellow solid (55 mg, 73%). Mp: 170-171ºC; IR (neat, cm^{-1}): 3384 (w, br), 3365 (m, br), 3246 (m, br), 1623 (s), 1474 (m), 1397 (w), 1082 (w), 747 (m), 691 (m); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.71 (bs, 1H), 7.56 (bs, 1H), 7.14 (m, 2H), 6.72-6.69 (m, 3H), 5.92 (bs, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 160.18, 149.58, 128.69, 118.56, 112.15. HRMS (ESI$^+$) m/z $[C_7H_9N_3ONa]^+$ calcd: 174.0638; found: 174.0631; HPLC: method A t_R = 8.28 min (95%); method B t_R = 12.75 min (96%).

1-(Benzyloxy)urea (**8d**): The general procedure was used with *O*-benzylhydroxylamine hydrochloride (80 mg, 0.5 mmol) at 130ºC for 10 minutes to give the desired product **8d** as a white solid (50 mg, 60%). Mp: 137-139 ºC; IR (neat, cm^{-1}): 3392 (m, br), 3222 (m, br), 3031 (w), 2924 (w), 1678 (w), 1619 (s), 1452 (m), 1357 (m), 1211 (w), 1107 (m), 996 (w), 933 (m), 794 (m); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 9.02 (bs, 1H), 7.56-7.14 (m, 5H), 6.34 (bs, 2H), 4.72 (s, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 160.82, 136.60, 128.70, 128.20, 127.97, 77.25. HRMS (ESI$^+$) m/z $[C_8H_{10}N_2O_2Na]^+$ calcd: 189.0634; found: 189.0627; HPLC: method A t_R = 9.82 min (96%); method B t_R = 16.76 min (97%).

3-(2-Oxo-2,3-dihydro-1*H*-imidazol-4-yl)propanoic acid (**8e**): The general procedure was used with 5-aminolevulinic acid hydrochloride (84 mg, 0.5 mmol) at 120ºC for 15 minutes to give the desired product **8e** as an off-white solid (66 mg, 85%). Mp: 239ºC (decompose); IR (neat, cm^{-1}): 3345 (w, br), 3261 (w, br), 3190 (w, br), 1680 (bs), 1302 (m), 1240 (m), 1016 (w), 921 (w), 774 (m); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 9.82 (s, 1H), 9.53 (s, 1H), 5.95 (s, 1H), 2.47-2.42 (m, 4H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 173.63, 154.84, 120.96, 103.96, 32.22, 20.85. HRMS (ESI$^+$) m/z $[C_6H_8N_2O_3Na]^+$ calcd: 179.0427; found: 179.0426; HPLC: method C t_R = 12.25 min (98%); method D t_R = 10.68 min (98%).

4-Phenyl-1,3-dihydro-2*H*-imidazol-2-one (**8f**): The general procedure was used with 2-aminoacetonphenone hydrochloride (86 mg, 0.5 mmol) at 120ºC for 15 minutes to give the desired product **8f** as a yellow solid (55 mg, 69%). Mp: 315ºC (decompose); IR (neat, cm^{-1}): 3142 (m, br), 3027 (m, br), 2797 (m, br), 1690 (m), 1645 (m), 1615 (s), 1129 (m), 762(m), 727 (s), 661 (m), 685 (m); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 10.56 (bs, 1H), 10.08 (bs, 1H), 7.79-7.01 (m, 5H), 6.88 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 155.06, 129.98, 128.63, 126.15, 122.77, 121.94, 105.75. HRMS (ESI$^+$) m/z $[C_9H_8N_2ONa]^+$ calcd: 193.0406; found: 193.0400; HPLC: method A t_R = 9.88 min (99%); method B t_R = 17.86 min (98%).

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