A modular flow reactor for performing Curtius rearrangements as a continuous flow process†

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The use of a mesofluidic flow reactor is described for performing Curtius rearrangement reactions of carboxylic acids in the presence of diphenylphosphoryl azide and trapping of the intermediate isocyanates with various nucleophiles.

Introduction

The Curtius rearrangement is synthetically a very powerful transformation for converting carboxylic acid moieties into their chemically diametric amino functionalities.[1] As a direct chemical interconversion this process has tremendous value, but it also has an important strategic impact because of the prevalence of the amide linkage in many pharmaceutical compounds. The transposition of the coupling partners in an amide bond is a classical medicinal chemistry tactic to facilitate exploration of SAR and also when faced with issues of metabolic stability or poor physiological properties. The Curtius rearrangement simplifies the synthesis route by avoiding the requirement of generating paired coupling materials, enabling the direct derivatization of the complimentary carboxylic acids. Despite the many advantages offered by this reaction, its use especially at scale has been avoided because of significant safety concerns regarding the generation and use of potentially explosive and highly toxic azide promoters and the associated acyl azide intermediates.

Flow based chemical processing offers tremendous benefits in terms of containment and improved safety profiles due to the small quantities of active ingredients being manipulated at any single point.[2] We have previously exploited these advantages to gain access to a variety of pharmaceutically important heterocyclic building blocks such as oxazoles,[3] triazoles,[4] pyrazoles,[5] guanidines,[6] imidazoles and thiazoles[7] as well as using flow techniques in the construction of more architecturally complex natural products *via* multi-step sequences.[8] Many of the transformations required the handling of potentially hazardous, highly sensitive or reactive intermediates under controlled and highly reproducible conditions. Consequently, the improved safety features derived from working in a flow mode coupled with the ability to continuously process material enabling a time-dependent scale-up is ideally suited to many of the previously 'forbidden' chemistries such as the Curtius rearrangement. For this reason we have developed a fully automated flow process for performing Curtius rearrangements with *in situ* trapping of the resultant isocyanate rearrangement product as the corresponding carbamate or urea derivate. Furthermore, the use of polymer-supported scavengers as in-line purification aids has facilitated the isolation of the desired products without the need for laborious purification.[9]

Results and discussion

To conduct the Curtius rearrangements in a convenient fashion we used the commercially available flow synthesis platform from VapourTec (R2+ and R4 combination, Fig. 1).[10]

Fig. 1 VapourTec R2 + and R4 combination flow reactor.

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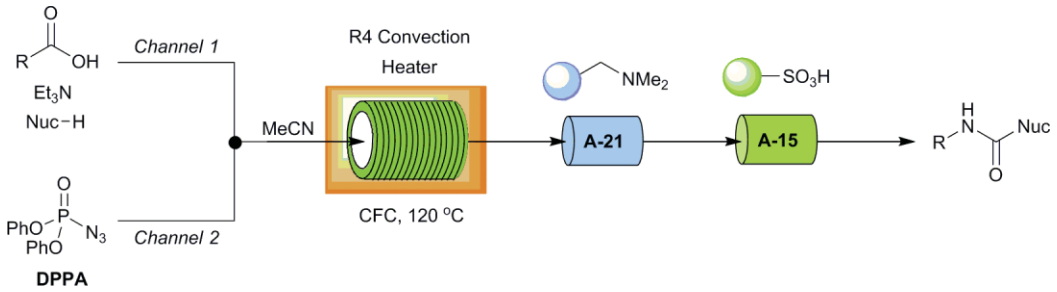
† We dedicate this publication to Professor Andrew B. Holmes, friend and colleague, on the occasion of his 65th birthday.



Scheme 1 General scheme for the Curtius rearrangement of carboxylic acids under continuous flow conditions.

This system as shown integrates a pumping and reagent selection module (R2+; top stage) with a four-channel air-circulated heating component (R4; lower stage). In its current configuration, the unit consists of a low pressure input selection valve for routing either solvents or bulk stock solutions directly to the two incorporated HPLC pumps. Two additional Rheodyne 6-port-2-position switching valves are located on the top right of the R2+ module and can each facilitate reagent or substrate introduction to the flow lines through the control of individual reagent loops. The independently governed flow streams are each driven by a compact self-regulating Knauer K120 HPLC-pump (operating under a constant 100 psi back-pressure imposed by a static in-line regulator). Mixing of the streams occurs in a simple T-piece and the combined flow path is directed into a convection flow coil (CFC; made from various materials, poly(fluoroacetate) (PFA) in this system), allowing precisely regulated heating profiles up to 150 °C. A second exchangeable 100 psi back-pressure regulator was coupled in-line subsequent to the CFC reactor to allow superheating of the reaction mixture prior to it entering a glass column[11] packed with immobilised scavengers. The direct collection of the purified product was then easily accomplished by simply collecting the eluting reaction stream and evaporation of the solvent. The collection process can be readily automated using an attached UV-triggered liquid-handler unit.[8b,10] Furthermore, the entire flow process including all the reaction variables such as flow rate (residence time), pressure and temperature are all easily modified 'on-the-fly'. These parameters can be adjusted *via* the user interface or through software sequencing enabling rapid reaction exploration, profiling and final optimisation. All critical parameters are supervised by scrutiny algorithms enabling constant safety monitoring by firmware or a linked PC. More complex sequences of events such as array synthesis can be achieved through multiple sequential injections of substrates. Furthermore, the creation and timing of additional auxiliary operations such as generating solvent washing cycles between reactions is also readily automated, giving a seamless synthetic routine.

Our initial investigations showed that diphenylphosphoryl azide (DPPA) in combination with 2 equiv. of triethylamine gave the best results for the direct conversion of carboxylic acids. At elevated temperatures the Curtius rearrangement product could be formed and trapped with an *in situ* nucleophile, avoiding the need for isolation of the reactive intermediates. The increased solubility of many of the initially formed salts dictated the need for a polar solvent; acetonitrile was found to be optimum but other solvents such as chloroform, DMF and toluene were also found to be suitable for certain substrates. Furthermore, the use of DPPA as the azide source allowed the convenient use of Amberlyst 21 (A-21), an immobilised trimethylamine equivalent, as a scavenger for the diphenylphosphonic acid formed in the activation step as well as any unreacted carboxylic acid. Using the solid-supported scavenger, A-21, in combination with Amberlyst 15 (sulfonic acid resin; A-15) as a mixed bed scavenger also made it possible to remove the triethylamine base from the reaction in a complementary manner. These two scavengers could be placed either as a 1:1 mixture in a single pre-packed column, or alternatively, in two separate sequential columns (Scheme 1).

In a general procedure a mixture of triethylamine (2 equiv.), the appropriate nucleophile (1–3 equiv.) and the carboxylic acid (1.1 equiv.) were loaded into channel 1 and DPPA (1 equiv.) into channel 2 (both samples being prepared as solutions in acetonitrile at 50–66.7 mM concentrations). The two reactant streams were united using a simple T-mixing piece and the combined fluidic output directed into a CFC reactor (10 mL volume). A total flow rate of 0.2–0.5 mL min^{-1}, equating to a reactor residence time of 20–50 min at a temperature of 120 °C, was used to ensure complete conversion. The resulting flow stream was then purified by passage through a glass column packed with a mixture of A-21 and A-15 (1:1; 3.5 equiv. each) at ambient temperature. Removal of the solvent using a Biotage V10 solvent evaporator[12] enabled direct isolation of a wide range of products in both high yield (>75%) and excellent purity (>90% as determined by LC-MS and ^{1}H-NMR; Fig. 2).

IR sampling studies demonstrated the rapid generation of the acyl azide[13] intermediate even at ambient temperature. However, in order to effect the subsequent rearrangement step, elevated temperatures were required. Under superheating conditions at 120 °C a variety of benzoic acid derivatives were readily transformed to their corresponding isocyanate products within a 20 min residence time. Upon formation, these isocyanates were immediately trapped by a variety of nucleophiles including alcohols, amines, oximes, hydrazines and acyl hydrazides.

As indicated, a range of different nucleophiles were successfully carried through the initial Curtius rearrangement before reacting with the isocyanate, thereby giving direct access to a small collection of readily deprotected amine motifs. Consequently, we were pleased to observe the formation of Cbz- and Alloc-protected anilines using the described flow procedure (Fig. 2 and 4). However, the synthesis of the Boc-protected aniline **7** (Fig. 2) by the same approach was found to be more difficult, a fact we ascribe to the decreased nucleophilicity of *tert*-butanol. To overcome this issue, we made use of the previously described R2+ and

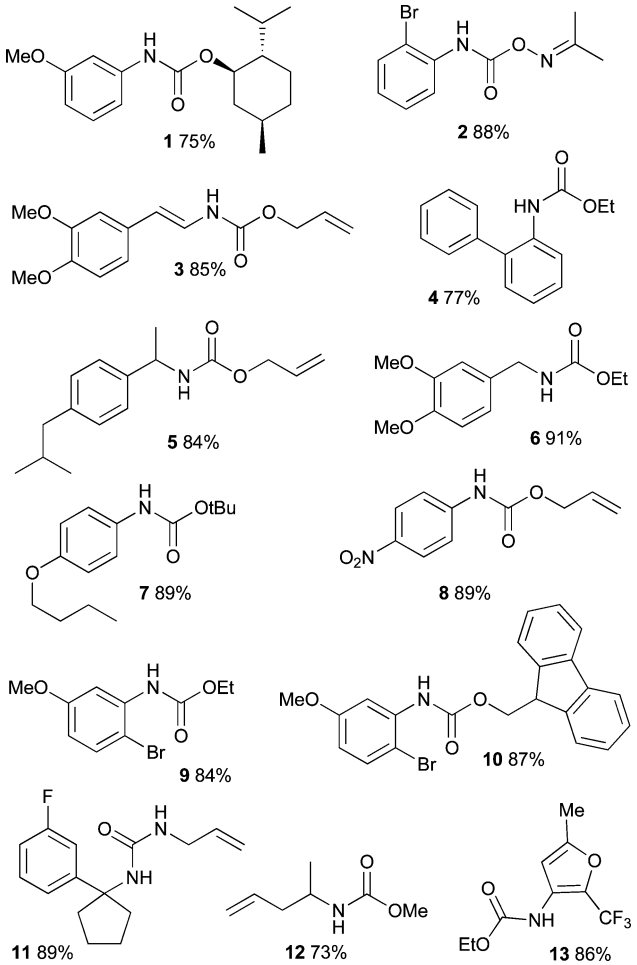


Fig. 2 Curtius rearrangement products.

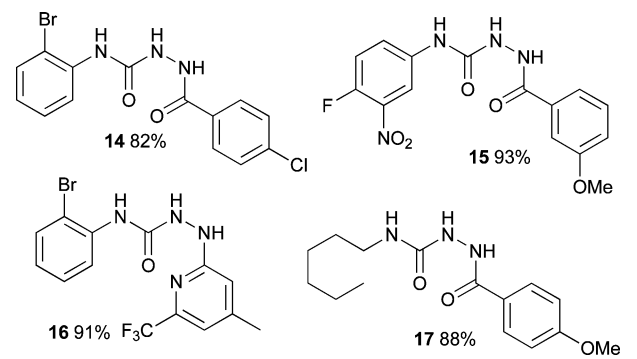


Fig. 3 Mixed urea products.

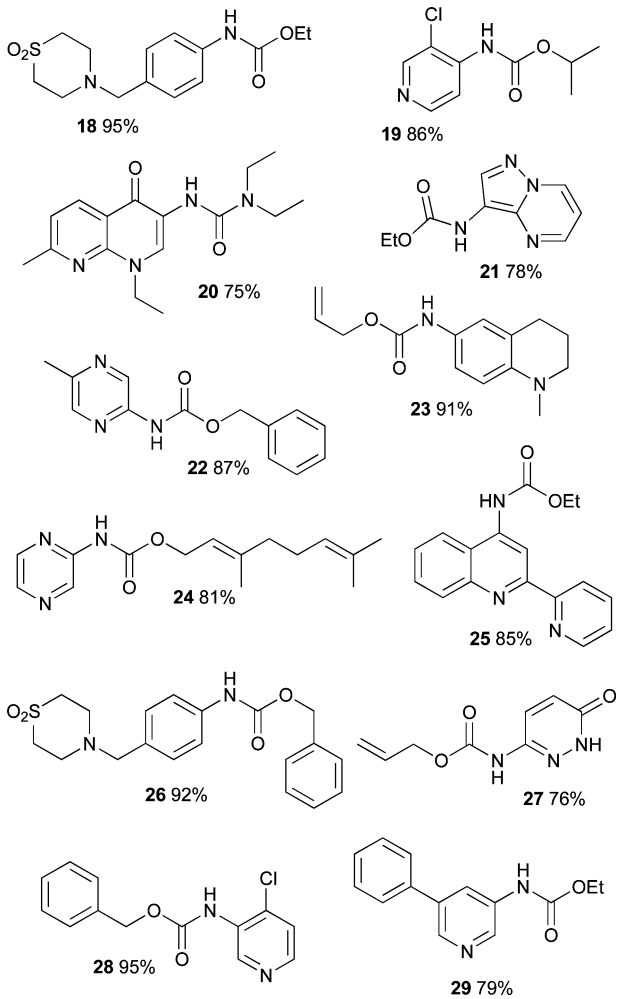
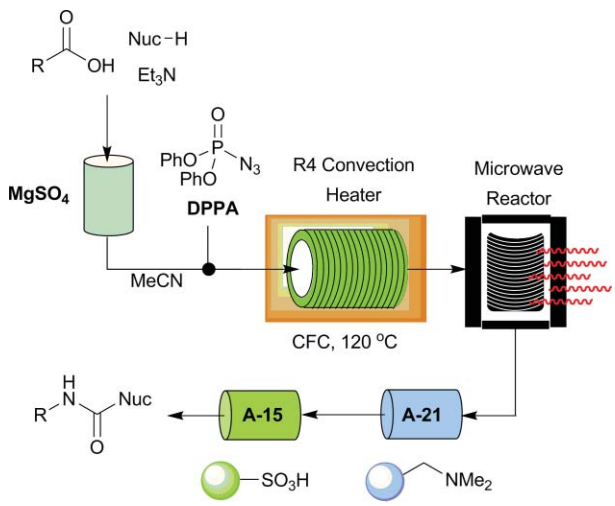


Fig. 4 Curtius rearrangement products derived from heterocyclic carboxylic acids.



Scheme 2 Microwave and R2+ and R4 reactor set-up.

R4 system and a PTFE-tubing reactor located within the cavity of an Emrys-Optimiser microwave (Scheme 2).[14] This microwave device comprised of a simple multi-layered coil of perfluorinated polymer tubing wound around a central Teflon core then housed in the field of the microwave cavity.[5,15] Connections to additional components including the R2+ and R4 unit were easily achieved through standard HPLC fittings. Microwave heating of this flow coil at 120 °C gave the desired Boc-protected amine **7** within a 2 min residence time in excellent conversion. An in-line column of A-21 was subsequently used to remove the phosphonic acid residues and excess acid starting material. In this experiment, the residual triethylamine was then removed along with the solvent under reduced pressure to furnish the product in 89% yield. The generation of the Fmoc-protected system **10** also required a modification to the general procedure due to degradation of

the Fmoc adduct in the presence of the triethylamine and A-21 bases. This problem was easily overcome by the direct substitution of 2,6-lutidine for triethylamine and PS-2,6-di-*tert*-butylpyridine for A-21;[16] all other parameters were maintained as previously described.

Interestingly, in the case of *tert*-butanol and other hindered nucleophiles small quantities of the dimerized urea adduct were observed (3–8%). Presumably, this occurs due to competitive attack of the isocyanate by residual water followed by decarboxylation and reaction with a second isocyanate. Indeed, attempts to prepare the free amine products through the use of water as the nucleophilic component led almost exclusively to the isolation of the corresponding urea adducts. However, it was found that the introduction of a short plug of anhydrous magnesium or sodium sulfate in-line prior to the CFC reactor was sufficient to remove traces of water in our standard reactions and eliminate these minor urea side-products.

This observation inspired us to evaluate the potential for the generation of mixed semicarbazide adducts using hydrazine-derived nucleophiles. Such materials, although synthetically extremely useful, are notoriously difficult to handle because of their limited solubilities in solvents such as MeCN.[17] Our approach was to therefore prepare these products making use of their insolubility to aid in their isolation. In these examples, the hydrazido nucleophile was placed in a collection flask at the output of the reactor. The standard procedure was then followed to generate the isocyanate rearranged product, which was subjected to the same in-line purification using a mixture of A-21 and A-15. The reaction stream was constantly fed into the collection flask containing the awaiting nucleophile, which underwent rapid reaction to furnish the semicarbazide. This product on forming immediately precipitated, permitting facile isolation and purification by direct filtration and drying of the solid product (Fig. 3).

To extend the originally described protocol further and enable the use of additional heterocyclic carboxylic acid building blocks, it was necessary to adapt the purification procedure. Certain products (Fig. 4) could be selectively sequestered from the reaction mixture directly onto the A-15 resin (5 equiv.) as they exited the CFC reactor *via* a 'catch and release' protocol.[18] A rapid washing sequence ensured that only the ionically bound product remained within the column. A relay selection valve then enabled a secondary stream containing a solution of excess ammonia in methanol to be eluted through the A-15 trapping column, liberating the desired product. In certain cases a small plug of silica gel was also used to remove a dark-coloured unknown impurity from the reaction mixture, leading to significantly improved purities (10–15% increase). Evaporation of the solvent along with carried-through triethylamine then enabled isolation of the product, again in high yields and excellent purities (Fig. 4).

Although in most cases we only carried out this chemistry on a 1–5 mmol scale, we were able to very simply configure the equipment to enable more continuous production of the desired product, synthesising gram quantities of functionalised material. We had previously demonstrated a small-scale preparation of ethyl 2-(pyridin-2-yl)quinolin-4-ylcarbamate **25** (Fig. 4; 85%) starting from the corresponding carboxylic acid; however, we required larger amounts for use in a ligand encapsulation study. This also posed an interesting challenge, as in the scaled synthesis of the carboxylic acid precursor we experienced significant difficulties in its isolation. Alternatively, the corresponding sodium salt could be readily attained and so was evaluated as a substitute starting material for the Curtius rearrangement process. A small solvent screen indicated that the salt was only suitably soluble in DMF and short-chain alcohols. Neat ethanol was therefore chosen as the solvent for channel one (52.5 mM solution of the salt). This was possible as we had already determined empirically that the Curtius rearrangement occurred faster than ethanol addition to the intermediate acyl azide species. However, ethanol is known to react slowly with DPPA, hence the DPPA reagent delivered from the second channel was dissolved in MeCN (68 mM, 1.3 equiv.). Since the starting material possesses two pyridine-like moieties and was already the sodium salt, no triethylamine was required to promote the reaction. The two channels were combined using a standard T-mixing piece leading to four connected CFC reactors (40 mL total reactor volume) heated at 120 °C with a total flow rate of 2 mL min^{-1}, equating to a 20 min residence time. The isolation of the product was achieved using A-15 (45 g, 3 equiv.) placed within a Kontes Chromaflex chromatography column.[19] Following a washing sequence (1:1 MeCN–ethanol at 2 mL min^{-1} for 1 h) the desired product was released by flushing with 20% triethylamine in methanol (400 mL at 5 mL min^{-1}). In total, seven 5 g batches were prepared and run sequentially, affording over 25 g of product with an average yield of 75%.

Conclusions

In conclusion, we have demonstrated the clean and safe handling of hazardous compounds such as azides and acyl azides in the Curtius rearrangement using a commercially available flow reactor system from VapourTec. Using DPPA, we were able to generate a small collection of carbamates, ureas, semicarbazides and related compounds in high yields (75–95%) and excellent purities (>90%). Purification was achieved by in-line scavenging of excess starting materials and spent reagents using a combination of the readily available low-cost scavenger resins A-15 and A-21. Furthermore, we have successfully applied this methodology to the synthesis of carbamate products on larger scales up to 25 g.

Experimental

Unless otherwise stated, reaction solutions were prepared in MeCN in 20 mL glass vials. ^{1}H-NMR spectra were recorded on a Bruker Avance DPX-400, DRX-500 or DPX-600 spectrometer with residual $CHCl_3$, DMSO, MeCN or DCM as the internal reference ($CHCl_3$ $\delta_H = 7.26$ ppm; DMSO $\delta_H = 2.50$ ppm, MeCN $\delta_H = 1.94$ ppm; DCM $\delta_H = 5.32$ ppm). ^{13}C-NMR spectra were also recorded in either $CDCl_3$, DMSO, MeCN or DCM on the same spectrometers with the central peak of the residual solvent as the internal reference ($\delta_C = 77.0$ ppm; DMSO $\delta_C = 39.5$ ppm; MeCN $\delta_C = 118.3$; DCM $\delta_C = 53.8$ ppm). COSY, DEPT 135, HMQC, HMBC and NOESY spectroscopic techniques were used to aid the assignment of signals in the ^{13}C-NMR spectra. Infrared spectra were recorded neat on a Perkin-Elmer Spectrum One FT-IR spectrometer. Letters in the parentheses refer to relative absorbency of the peak: w, weak, <40% of the main peak; m, medium, 41–74% of the main peak; s, strong, >74% of the main peak. LC-MS analysis was performed on an Agilent HP 1100 chromatograph (Luna Max RP column) attached to an

Table 1 LC-MS conditions

Time/min	MeCN (%)	Flow rate/mL min^{-1}
0.00	5	1
3.00	95	1
5.00	95	1
5.50	5	1
8.00	5	1

HPLC/MSD mass spectrometer. Elution was carried out using a reversed-phase gradient of MeCN–water with both solvents containing 0.1% formic acid. The gradient is described in Table 1. For HRMS a LCT Premier Micromass spectrometer was used.

General procedures

One-pot procedure. A solution of 2-bromo-5-methoxybenzoic acid (230 mg; 1 mmol), triethylamine (280 μL; 2 mmol), DPPA (215 μL; 1 mmol) and ethanol (100 μL; 2.8 mmol) was prepared in MeCN (15 mL). The reaction mixture was pumped using the described R2+ and R4 flow system at a flow rate of 0.5 mL min^{-1} through a 10 mL PFA CFC heated at 120 °C. After exiting the CFC this flow stream was passed through a single Omnifit glass column (10 mm i.d. by 150 mm length) filled with A-15 (3 g) and A-21 (3 g) as scavengers at ambient temperature. Evaporation of the solvent furnished the desired product ethyl-2-bromo-5-methoxyphenylcarbamate as a white crystalline solid (229 mg, 0.84 mmol, 84%).

Two-pot procedure. A solution of 2-(4-isobutylphenyl)propanoic acid (227 mg; 1.1 mmol), triethylamine (280 μL; 2 mmol) and allyl alcohol (150 μL; 3.0 mmol) was prepared in MeCN (10 mL). The solution (channel 1) was mixed *via* the R2+ and R4 flow system with a second stream (channel 2) containing DPPA (215 μL; 1 mmol) in MeCN (10 mL) using a T-mixing piece before the combined streams (individual flow rates 0.25 mL min^{-1} each) were directed into a 10 mL CFC heated at 120 °C. The solution was then passed through a single Omnifit glass column (10 mm i.d. by 150 mm length) filled with A-15 (3 g) and A-21 (3 g) as scavengers at ambient temperature. The desired product (allyl-1-(4-isobutylphenyl)ethylcarbamate) was obtained as a colourless oil (219 mg, 0.84 mmol, 84%) after evaporation of the solvent.

Catch and release procedure. A solution of 3-chloroisonicotinic acid (173 mg; 1.1 mmol), triethylamine (280 μL; 6 mmol) and isopropanol (200 μL; 4.2 mmol) was prepared in MeCN (15 mL) (channel 1). A second solution containing DPPA (215 μL; 1 mmol) in MeCN (15 mL) (channel 2) was combined with the first (individual flow rates 0.25 mL min^{-1} each) using the R2+ and R4 flow system. The united flow stream was directed into a 10 mL CFC heated at 120 °C. After exiting the CFC reactor the reaction mixture passed firstly through an Omnifit glass column (10 mm i.d. by 150 mm length) filled with A-21 scavenger (3 g) to remove excess starting material as well as the diphenylphosphonic acid by-product. The solution then entered a second similar Omnifit glass column filled with A-15 (3 g) in order to catch the pyridyl-derived product at ambient temperature. This second Omnifit glass column was then washed with MeCN (10 mL) to remove any unbound material then eluted with a solution of ammonia in methanol (1.5 mL, 2 M solution) dissolved in MeCN (8.5 mL) to release the sequestered pyridyl-based carbamate. Following evaporation of solvents the desired product isopropyl-3-chloropyridin-4-ylcarbamate was obtained as white solid (184 mg, 0.86 mmol; 86%).

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl-3-methoxyphenyl carbamate (1). Flow rate: 0.2 mL min^{-1}, yield: 75%, purity: 97%, Rt = 5.38 min, M + H m/z = 306.4. ^{1}H-NMR (500 MHz, $CDCl_3$): δ/ppm 7.14–7.20 (2H, m), 6.83 (1H, d, J = 8.0 Hz), 6.60 (1H, d, J = 8.0 Hz), 6.54 (1H, s), 4.64 (1H, td, J = 18.9 Hz, 4.4 Hz), 3.79 (3H, s), 2.08–2.16 (1H, m), 1.96 (1H, m), 1.62–1.72 (2H, m), 1.45–1.55 (1H, m), 1.36 (1H, tt, J = 11.6, 3.0 Hz), 0.95–1.13 (2H, m), 0.82–0.92 (7H, m), 0.80 (3H, d, J = 7.0 Hz), ^{13}C-NMR (125 MHz, $CDCl_3$): δ/ppm 160.3 (C), 153.2 (C), 139.4 (C), 129.7 (CH), 110.5 (CH), 109.1 (CH), 103.9 (CH), 75.1 (CH), 55.2 (CH_3), 47.3 (CH), 41.3 (CH_2), 34.2 (CH_2), 31.4 (CH), 26.2 (CH), 23.5 (CH_2), 22.0 (CH_3), 20.8 (CH_3), 16.4 (CH_3). IR: ν 3320.3 (w), 2953.5 (m), 2926.2 (m), 2868.9 (m), 1695.1 (s), 1599.3 (s), 1539.7 (s), 1496.4 (s), 1455.6 (s), 1428.4 (s), 1283.9 (s), 1264.3 (s), 1222.7 (s), 1179.0 (m), 1161.0 (m), 1041.0 (s), 852.3 (m), 767.2 (s), 688.1 (m) cm^{-1}. HRMS calculated for $C_{18}H_{28}NO_3$ 306.2069, found 306.2078.

Propan-2-one-*O*-2-bromophenyl carbamoyl oxime (2). Flow rate: 0.4 mL min^{-1}, yield: 88%, purity: 98%, Rt = 4.42 min, M + Na m/z = 293.2. ^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm 8.95 (1H, s), 8.26 (1H, d, J = 8.0 Hz), 7.54 (1H, d, J = 8.0 Hz), 7.34 (1H, t, J = 8.0 Hz), 6.96 (1H, t, J = 8.0 Hz), 2.11 (3H, s), 2.08 (3H, s), ^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm 162.1 (C), 152.5 (C), 135.8 (C), 132.7 (CH), 128.8 (CH), 125.2 (CH), 120.7 (CH), 113.9 (C), 22.4 (CH_3), 17.4 (CH_3). IR: ν 3291.6 (m), 3078.2 (w), 2994.3 (w), 1736.6 (s), 1590.1 (s), 1575.4 (m), 1520.7 (s), 1427.2 (s), 1373.6 (s), 1305.2 (m), 1279.1 (m), 1234.1 (m), 1047.0 (m), 1025.9 (s), 1005.8 (s), 898.6 (s), 837.7 (m), 766.2 (s), 745.1 (s), 655.7 (s) cm^{-1}. HRMS calculated for $C_{10}H_{11}N_2O_2NaBr$ 292.9902, found: 292.9903.

(*E*)-Allyl-3,4-dimethoxystyryl carbamate (3). Flow rate: 0.2 mL min^{-1}, yield: 85%, purity: 94%, Rt = 4.29 min, M + H m/z = 263.3. ^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm 7.10 (1H, m), 6.75–6.83 (3H, m), 6.70 (1H, s), 5.87–6.00 (2H, m), 5.34 (1H, d, J = 16.8 Hz), 5.25 (1H, d, J = 10.0 Hz), 4.65 (2H, d, J = 4.4 Hz), 3.87 (3H, s), 3.85 (3H, s), ^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm 153.4 (C), 149.2 (C), 148.0 (C), 129.2 (C), 122.5 (CH), 121.4 (CH), 118.3 (CH_2+CH), 111.5 (CH), 110.9 (CH), 107.9 (CH), 66.2 (CH_2), 55.9 (CH_3), 55.8 (CH_3). IR: ν 3316.8 (w), 2935.5 (w), 2835.3 (w), 1706.7 (s), 1661.2 (s), 1585.4 (m), 1508.4 (s), 1464.1 (m), 1259.6 (s), 1224.3 (s), 1139.8 (m), 1054.3 (m), 1027.1 (m), 945.8 (m), 856.7 (m), 802.1 (m), 764.8 (m) cm^{-1}. HRMS calculated for $C_{14}H_{18}NO_4$ 264.1236, found 264.1235.

Ethyl-2-biphenyl carbamate (4)[20]. Flow rate: 0.4 mL min^{-1}, yield: 77%, purity: 93%, Rt = 4.65 min, M + H m/z = 242.3. ^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm 8.16 (1H, d, J = 8.0 Hz), 7.33–7.53 (6H, m), 7.22 (1H, d, J = 8.0 Hz), 7.13 (1H, t, J = 8.0 Hz), 6.63 (1H, s), 4.18 (2H, q, J = 7.6 Hz), 1.26 (3H, t, J = 7.6 Hz), ^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm 154.0 (C), 138.6 (C), 135.4 (C), 130.5 (CH), 130.2 (C), 129.7 (2CH), 129.5 (2CH), 128.9 (CH), 128.3 (CH), 123.7 (CH), 120.1 (CH), 61.6 (CH_2), 14.9 (CH_3). IR: ν 3424.7 (w), 3059.3 (w), 2981.7 (w), 1731.6 (s), 1585.2 (m), 1516.1 (s), 1493.8 (s), 1447.3 (s), 1302.9 (m), 1203.6 (s), 1063.1 (s),

1046.7 (s), 952.0 (m), 745.1 (s), 701.9 (s). HRMS calculated for $C_{15}H_{15}NO_2Na$ 264.1000, found 264.1000.

Allyl-1-(4-isobutylphenyl)ethyl carbamate (5). Flow rate: 0.5 mL min^{-1}, yield: 84%, purity: 93%, Rt = 4.99 min, M + H $m/z = 262.4$. ^{1}H-NMR (400 MHz, d_6-DMSO): δ/ppm 7.67 (1H, d, $J = 7.6$ Hz), 7.19 (2H, d, $J = 8.4$ Hz), 7.07 (2H, d, $J = 8.4$ Hz), 5.80–5.95 (1H, m), 5.25 (1H, d, $J = 17.2$ Hz), 5.14 (1H, d, $J = 10.8$ Hz), 4.62 (1H, quin., $J = 3.6$ Hz), 4.37–4.50 (2H, m), 2.39 (2H, d, $J = 6.8$ Hz), 1.80 (1H, sept., $J = 6.8$ Hz), 1.34 (3H, m), 0.84 (6H, d, $J = 8.0$ Hz), ^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm 155.4 (C), 141.0 (C), 132.9 (CH), 129.8 (CH), 129.3 (2CH), 125.7 (2CH), 120.1 (CH), 117.6 (C), 65.5 (CH_2), 50.3 (CH), 45.0 (CH_2), 30.2 (CH_3), 22.3 ($2CH_3$). IR: ν 3310.1 (m), 2954.2 (m), 2927.5 (m), 2868.8 (m), 1699.8 (s), 1513.7 (s), 1452.5 (m), 1243.3 (s), 1058.0 (s), 929.4 (m), 846.6 (m), 800.2 (m), 777.7 (m) cm^{-1}. HRMS calculated for $C_{16}H_{24}NO_2$ 262.1807, found: 262.1799.

Ethyl-3,4-dimethoxybenzyl carbamate (6)[21]. Flow rate: 0.4 mL min^{-1}, yield: 91%, purity: 98%, Rt = 3.88 min, M + H $m/z = 239.3$. ^{1}H-NMR (400 MHz, d_3-MeCN): δ/ppm 6.79–6.88 (3H, m), 5.92 (1H, s), 4.19 (2H, d, $J = 6.0$ Hz), 4.06 (2H, q, $J = 6.8$ Hz), 3.78 (3H, s), 3.77 (3H, s), 1.20 (3H, t, $J = 6.8$ Hz), ^{13}C-NMR (100 MHz, d_3-MeCN): δ/ppm 156.4 (C), 148.9 (C), 148.1 (C), 132.1 (C), 119.1 (CH), 111.4 (CH), 110.9 (CH), 60.0 (CH_2), 55.1 (CH_3), 55.0 (CH_3), 43.7 (CH_2), 13.8 (CH_3). IR: ν 3346.4 (m), 2970.9 (w), 2934.8 (w), 2839.8 (w), 1686.1 (s), 1593.0 (m), 1534.0 (m), 1516.6 (s), 1481.0 (m), 1469.1 (m), 1448.6 (m), 1431.8 (m), 1418.9 (m), 1370.9 (m), 1337.0 (m), 1292.6 (m), 1231.1 (s), 1189.7 (m), 1132.4 (s), 1043.7 (m), 1021.2 (s), 925.8 (m), 806.7 (s), 767.3 (m), 737.1 (m), 717.9 (m) cm^{-1}. HRMS calculated for $C_{12}H_{18}NO_4$ 240.1236, found: 240.1232.

***tert*-Butyl-4-butoxyphenyl carbamate (7).** Flow rate: 0.3 mL min^{-1}, yield: 89%, purity: 96%, Rt = 5.1 min, M $m/z = 210.3$ (carbamic acid). ^{1}H-NMR (400 MHz, CD_2Cl_2): δ/ppm 7.25 (2H, d, $J = 8.8$ Hz), 6.83 (2H, d, $J = 8.8$ Hz), 6.44 (1H, s), 3.93 (2H, t, $J = 6.8$ Hz), 1.76 (2H, quin., $J = 6.8$ Hz), 1.45–1.55 (11H, m), 0.98 (3H, t, 6.8 Hz), ^{13}C-NMR (125 MHz, CD_2Cl_2): δ/ppm 155.5 (C), 153.3 (C), 131.7 (C), 120.6 (2CH), 114.9 (2CH), 80.2 (C), 68.2 (CH_2), 31.6 (CH_2), 28.3 ($3CH_3$), 19.5 (CH_2), 13.9 (CH_3). IR: ν 3361.6 (m), 2934.7 (m), 2871.1 (w), 1698.6 (s), 1598.0 (w), 1527.0 (s), 1413.7 (m), 1316.2 (w), 1250.4 (s), 1172.7 (s), 1056.2 (m), 1011.5 (m), 829.7 (m), 739.6 (w) cm^{-1}. HRMS calculated for $C_{15}H_{23}NO_3Na$ 288.1576, found 288.1589.

Allyl-4-nitrophenyl carbamate (8). Flow rate: 0.5 mL min^{-1}, yield: 89%, purity: 91%, Rt = 4.38 min, M − H $m/z = 221.2$. ^{1}H-NMR (400 MHz, d_3-MeCN): δ/ppm 8.28 (1H, s), 8.15 (2H, d, $J = 9.2$ Hz), 7.63 (2H, d, $J = 9.2$ Hz), 5.97 (1H, ddt, $J = 17.3$, 10.2, 5.8 Hz), 5.39 (1H, ddt, $J = 17.2$, 1.6, 1.6 Hz), 5.30 (1H, ddt, $J = 10.8$, 1.6, 1.6 Hz), 4.66 (2H, d, $J = 5.6$ Hz), ^{13}C-NMR (100 MHz, d_3-MeCN): δ/ppm 152.7 (C), 144.9 (C), 132.4 (CH), 130.3 (C), 124.6 (2CH), 117.4 (2CH), 117.0 (CH_2), 65.4 (CH_2). IR: ν 3376.9 (s), 3113.1 (w), 3090.0 (w), 2949.9 (w), 1732.9 (s), 1685.9 (m), 1613.3 (m), 1596.7 (m), 1546.6 (s), 1508.2 (s), 1493.7 (s), 1412.1 (m), 1321.6 (s), 1305.3 (s), 1245.2 (m), 1206.2 (s), 1110.8 (s), 1056.9 (s), 1001.5 (m), 937.5 (s), 852.2 (s), 765.0 (s), 748.2 (s), 711.4 (m), 691.4 (m), 673.7 (m) cm^{-1}. HRMS calculated for $C_{10}H_9N_2O_4$ 221.0567, found: 221.0562.

Ethyl-2-bromo-5-methoxyphenyl carbamate (9)[22]. Flow rate: 0.5 mL min^{-1}, yield: 84%, purity: 99%, Rt = 4.54 min, M + H $m/z = 273.3$. ^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm 7.82 (1H, s), 7.31 (1H, d, $J = 8.8$ Hz), 7.09 (1H, s), 6.47 (1H, d, $J = 8.8$ Hz), 4.21 (2H, q, $J = 7.2$ Hz), 3.76 (3H, s), 1.31 (3H, t, $J = 7.2$ Hz), ^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm 160.1 (C), 153.3 (C), 137.0 (C), 132.7 (CH), 111.1 (CH), 105.7 (CH), 103.1 (C), 61.9 (CH_2), 55.8 (CH_3), 14.8 (CH_3). IR: ν 3389.0 (m), 3108.3 (w), 2984.7 (w), 2915.7 (w), 2839.6 (w), 1732.5 (s), 1584.6 (s), 1523.6 (s), 1455.1 (m), 1426.7 (m), 1307.6 (m), 1284.7 (m), 1238.9 (s), 1204.9 (s), 1177.7 (s), 1112.7 (m), 1070.1 (m), 1042.3 (s), 1015.9 (m), 866.7 (s), 788.5 (s), 760.1 (s) cm^{-1}. HRMS calculated for $C_{10}H_{13}NO_3Br$ 274.0079, found: 274.0066. X-Ray Data: File reference CCDC 675720, Formula: $C_{10}H_{12}Br_1N_1O_3$; Unit cell parameters: a 4.45490(10), b 11.1152(2), c 21.9618(4), α 90.00, β 90.00, γ 90.00; space group $P2_12_12_1$.

(9*H*-Fluoren-9-yl)methyl 2-bromo-5-(methoxyphenyl)carbamate (10). Flow rate: 0.3 mL min^{-1}, yield: 87%, purity: 97%, Rt = 5.68 min, M + Na m/z 446.2. ^{1}H-NMR (600 MHz, d_2-DCM): δ/ppm 7.83 (2H, d, $J = 7.8$ Hz), 7.68 (2H, d, $J = 7.8$ Hz), 7.42–7.46 (3H, m), 7.37 (2H, t, $J = 7.8$ Hz), 7.30 (1H, d, $J = 9.0$ Hz), 7.22 (1H, s), 6.57 (1H, dd, $J = 9.0$, 3.0 Hz), 4.51 (2H, d, $J = 7.8$ Hz), 4.35 (1H, t, $J = 7.8$ Hz), 3.81 (3H, s), ^{13}C-NMR (150 MHz, d_2-DCM): δ/ppm 159.8 (C), 152.9 (C), 143.7 (2C), 141.3 (2C), 136.5 (C), 132.4 (CH), 130.0 (C), 127.8 (2CH), 127.1 (2CH), 125.0 (2CH), 120.2 (CH), 120.0 (2CH), 110.6 (CH), 67.4 (CH_2), 55.5 (CH_3), 47.0 (CH). IR: ν 3404.2 (w), 2952.2 (w), 2169.0 (m), 1736.6 (s), 1587.4 (s), 1520.9 (s), 1488.2 (m), 1452.1 (s), 1429.4 (m), 1304.1 (m), 1284.0 (m), 1244.6 (m), 1206.0 (s), 1182.2 (s), 1076.3 (m), 1045.3 (s), 1018.1 (m), 962.8 (s), 852.5 (m), 786.6 (m), 757.9 (s), 739.9 (s), 688.6 (m) cm^{-1}. HRMS calculated for $C_{22}H_{19}NO_3Br$ 424.0548, found: 424.0549.

1-Allyl-3(1-(3-fluorophenyl)cyclopentyl)urea (11). Flow rate: 0.4 mL min^{-1}, yield: 89%, Rt = 5.87 min, purity: 97%, M + H $m/z = 263.4$. ^{1}H-NMR (600 MHz, $CDCl_3$): δ/ppm 7.22 (1H, m), 7.13 (1H, d, $J = 8.0$ Hz), 7.07 (1H, d, $J = 8.0$ Hz), 6.85 (1H, t, $J = 8.0$ Hz), 5.83 (1H, br. s), 5.64–5-73 (1H, ddt, $J = 17.2$, 10.0, 5.2 Hz), 5.15 (1H, br. s), 4.99 (1H, ddt, $J = 17.2$, 1.6, 1.6 Hz), 4.96 (1H, m), 3.59 (2H, t, $J = 5.4$ Hz), 2.05–2.12 (2H, m), 1.87–1.97 (2H, m), 1.70–1.80 (4H, m), ^{13}C-NMR (150 MHz, $CDCl_3$): δ/ppm 162.9 (C, $J_{C\text{-}F} = 243$ Hz), 157.9 (C), 149.4 (C), 135.5 (CH), 129.5 (CH), 121.1 (CH), 114.7 (CH_2), 113.2 (CH, $J = 22$ Hz), 112.8 (CH, $J = 22$ Hz), 65.4 (C), 42.3 (CH_2), 40.3 ($2CH_2$), 23.4 ($2CH_2$). IR: ν 3317.4 (m), 2957.1 (w), 1682.4 (w), 1630.3 (s), 1614.4 (s), 1588.0 (s), 1558.8 (s), 1489.2 (s), 1438.0 (s), 1257.1 (s), 989.4 (m), 912.9 (m), 868.9 (m), 775.1 (s), 689.9 (s) cm^{-1}. HRMS calculated for $C_{15}H_{20}N_2OF$ 263.1560, found 263.1573.

Methylpent-4-en-2-yl carbamate (12)[23]. Flow rate: 0.2 mL min^{-1}, yield: 73%, purity: 96%, Rt = 4.42 min. ^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm 5.70–5.80 (1H, m), 5.04–5.09 (2H, m), 4.63 (1H, s), 3.77 (1H, m), 3.63 (3H, s), 2.17–2.22 (2H, m), 1.12–1.15 (3H, m), ^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm 156.3 (C), 134.2 (CH), 117.9 (CH_2), 51.8 (CH), 46.4 (CH_3), 41.1 (CH_2), 20.5 (CH_3). IR: ν 3319.0 (m), 3076.0 (w), 2971.8 (m), 1698.5 (s), 1598.1 (w), 1533.6 (s), 1454.5 (m), 1336.4 (m), 1257.7 (s), 1226.2 (m), 1192.1 (m), 1104.3 (m), 1070.1 (m), 963.1 (m),

916.5 (m), 779.2 (m) cm^{-1}. HRMS calculated for $C_7H_{13}NO_2Na$ 166.0839, found: 166.0838.

Ethyl-5-methyl-2-(trifluoromethyl)furan-3-yl carbamate (13). Flow rate: 0.4 mL min^{-1}, yield: 86%, purity: 98%, Rt = 4.46 min, M m/z = 166.2 (amine). ^{1}H-NMR (400 MHz, d_3-MeCN): δ/ppm 7.26 (1H, s), 6.63 (1H, s), 4.16 (2H, q, J = 7.2 Hz), 2.28 (3H, s), 1.26 (3H, t, J = 7.2 Hz), ^{13}C-NMR (125 MHz, $CDCl_3$): δ/ppm 154.3 (C), 153.0 (C), 127.7 (C), 120.4 (CF_3, q, J = 264.0 Hz), 120.0 (C, q, J = 5.0 Hz), 103.2 (CH), 61.8 (CH_2), 14.3 (CH_3), 13.6 (CH_3). IR: ν 3288.7 (m), 2997.5 (w), 1696.9 (s), 1654.4 (s), 1579.1 (m), 1519.2 (m), 1479.1 (m), 1458.9 (m), 1431.0 (m), 1310.0 (s), 1255.9 (s), 1176.1 (s), 1149.9 (s), 1101.1 (s), 1009.9 (s), 958.8 (s), 906.9 (w), 800.9 (s), 774.9 (s), 729.4 (s), 688.1 (m) cm^{-1}. HRMS calculated for $C_9H_{10}NO_3NaF_3$ 260.0508, found 260.0505.

4-(2-Bromophenyl)-1-(4-chlorbenzoyl)semicarbazide (14). Flow rate: 0.4 mL min^{-1}, yield: 82%, purity: 98%, Rt = 4.28 min, M + H m/z = 370.2. ^{1}H-NMR (400 MHz, d_6-DMSO): δ/ppm 10.52 (1H, s), 9.07 (1H, s), 8.23 (1H, s), 8.00 (1H, d, J = 7.6 Hz), 7.93 (2H, d, J = 8.0 Hz), 7.50–7.60 (3H, m), 7.30 (1H, t, J = 7.6 Hz), 6.95 (1H, t, J = 7.6 Hz), ^{13}C-NMR (100 MHz, d_6-DMSO): δ/ppm 165.8 (C), 155.5 (C), 137.3 (C), 137.1 (C), 132.8 (CH), 131.5 (C), 129.8 (2CH), 129.0 (2CH), 128.5 (CH), 124.6 (CH), 122.4 (CH), 113.6 (C). IR: ν 3262.3 (m), 3213.0 (m), 3022.4 (m), 1666.1 (s), 1649.0 (s), 1584.4 (s), 1566.8 (s), 1544.6 (s), 1524.4 (s), 1438.2 (s), 1335.7 (s), 1290.7 (m), 1248.1 (m), 1231.1 (m), 1178.3 (m), 1091.9 (s), 1043.6 (m), 1025.8 (m), 1009.8 (m), 911.9 (s), 842.2 (s), 742.0 (s), 734.7 (s), 667.6 (s) cm^{-1}. HRMS calculated for $C_{14}H_{12}N_3O_2ClBr$ 367.9801, found: 367.9797.

4-(3-Nitro-4-fluorophenyl)-1-(3-methoxybenzoyl)semicarbazide (15). Flow rate: 0.4 mL min^{-1}, yield: 93%, purity: 98%, Rt = 2.73 min, M + H m/z 315.1;^{1}H-NMR (400 MHz, d_6-DMSO): δ/ppm 10.29 (1 H, br. s, NH), 9.34 (1 H, br. s, NH), 8.50 (1 H, br. s, NH), 8.40 (1 H, dd, J = 6.8, 2.7 Hz), 7.84 (1 H, m), 7.51–7.47 (3 H, m), 7.45 (1 H, t, J = 7.9 Hz), 7.14 (1 H, m), 3.81 (3 H, s, OMe); ^{13}C-NMR (100 MHz; d_6-DMSO) δ/ppm 166.6 (C), 159.55 (C), 148.7 (C), 137.15 (C), 137.1 (C), 136.7 (C), 134.3 (C), 129.9 (CH), 120.2 (CH), 119.0 (CH), 118.8 (CH), 118.1 (CH), 115.2 (CH), 113.1 (CH), 55.7 (CH_3). IR: ν 3272.2 (m), 3215.1 (m), 3032.3 (m), 1684.2 (s), 1670.1 (s), 1555.5 (s), 1519.7 (s), 1503.4 (s), 1454.9 (s), 1436.8 (s), 1288.0 (m), 1260.1 (m), 1240.7 (m), 1188.2 (m), 1101.4 (s), 1077.4 (m), 951.4 (s), 863.1 (s), 782.3 (s), 772.9 (s) cm^{-1}. HRMS calculated for $C_{15}H_{13}FN_4O_5$ 348.0870, found 348.0877.

4-(2-Bromophenyl)-1-(6-methyl-4-(trifluoromethyl)picolinoyl)-semicarbazide (16). Flow rate: 0.5 mL min^{-1}, yield: 91%, purity: 99%, Rt = 4.47 min, M + H m/z = 391.2. ^{1}H-NMR (400 MHz, d_6-DMSO): δ/ppm 8.89 (1H, s), 8.84 (1H, s), 8.26 (1H, s), 7.97 (1H, d, J = 7.6 Hz), 7.57 (1H, d, J = 7.6 Hz), 7.31 (1H, t, J = 7.6 Hz), 6.96 (1H, t, J = 7.6 Hz), 6.91 (1H, s), 6.70 (1H, s), 2.40 (s, 3H), ^{13}C-NMR (125 MHz, d_6-DMSO): δ/ppm 160.6 (C), 158.9 (C), 155.7 (C), 138.6 (C, q, J = 32 Hz), 136.9 (C), 132.5 (CH), 128.2 (CH), 124.5 (CH), 123.3 (C, q, J = 272 Hz), 122.4 (CH), 114.0 (C), 109.1 (CH), 98.8 (CH), 23.9 (CH_3). IR: ν 3315.1 (w), 3226.6 (w), 3038.3 (w), 2983.6 (w), 1653.7 (s), 1586.3 (s), 1553.6 (s), 1513.2 (m), 1455.5 (s), 1438.4 (s), 1404.9 (s), 1386.9 (m), 1363.0 (m), 1281.3 (s), 1242.5 (m), 1169.5 (s), 1127.7 (s), 1119.8 (s), 1101.5 (m), 1026.3 (m), 861.1 (m), 842.6 (m), 743.4 (s) cm^{-1}. HRMS calculated for $C_{14}H_{13}BrF_3N_4O$ 389.0225, found: 389.0229.

4-(4-Methoxyphenyl)-1-hexyl semicarbazide (17). Flow rate: 0.4 mL min^{-1}, yield: 88%, purity: 97%, Rt = 3.70 min, M + H m/z 308.2; ^{1}H-NMR (600 MHz, d_6-DMSO) δ/ppm 9.53 (1 H, br. s, NH), 8.46 (1 H, br. s, NH), 7.87 (1 H, br. s, NH), 7.32 (2 H, d, J = 8.3 Hz), 6.82 (2 H, d, J = 8.3 Hz), 3.68 (3 H, s, OMe), 2.11 (2 H, t, J = 7.4 Hz), 1.52 (2 H, m), 1.13 (8 H, m), 0.84 (3 H, t, J = 7.2 Hz),^{13}C-NMR (150 MHz; d_6-DMSO) δ/ppm 172.58 (C), 156.0 (C), 154.8 (C), 133.1 (C), 120.6 (CH), 114.2 (CH), 55.5 (CH_3), 33.57(CH_2), 31.54(CH_2), 28.95(CH_2), 28.83(CH_2), 25.3 (CH_2), 22.4 (CH_2), 14.3 (CH_3). IR: ν 3344.4 (m), 3221.0 (m), 3040.5 (m), 1654.7 (s), 1584.8 (s), 1561.5 (s), 1510.7 (s), 1458.1 (s), 1395.2 (s), 1307.9 (m), 1108.3 (m), 1073.6 (s), 1065.6 (m), 1039.5 (m), 900.1 (s), 873.6 (s), 697.6 (s) cm^{-1}. HRMS calculated for $C_{15}H_{23}N_3O_3$ 293.1739, found 293.1741.

Ethyl-{4[(1,1-dioxido-4-thiomorpholinyl)methyl]phenyl}carbamate (18). Flow rate: 0.3 mL min^{-1}, yield: 95%, purity: 94%, Rt = 3.21 min, M + Na m/z = 335.3. ^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm 7.34 (2H, d, J = 8.0 Hz), 7.18 (2H, d, J = 8.0 Hz), 7.12 (1H, s), 4.18 (2H, q, J = 7.2 Hz), 3.55 (2H, s), 3.00 (4H, t, J = 4.8 Hz), 2.91 (4H, t, J = 4.8 Hz), 1.26 (3H, t, J = 7.2 Hz), ^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm 154.0 (C), 138.0 (C), 132.5 (C), 129.9 (2CH), 119.2 (2CH), 61.7 (CH_2), 61.4 (CH_2), 51.9 ($2CH_2$), 50.9 ($2CH_2$), 14.9 (CH_3). IR: ν 3342.3 (m), 2984.3 (w), 2821.8 (w), 1719.1 (s), 1599.1 (s), 1538.8 (s), 1316.4 (m), 1287.9 (s), 1266.9 (s), 1223.3 (s), 1115.1 (s), 1070.2 (s), 947.8 (m), 835.5 (m), 768.8 (m), 672.4 (m) cm^{-1}. HRMS calculated for $C_{14}H_{21}N_2O_4S$ 313.1222, found 313.1223.

Isopropyl-3-chloropyridin-4-yl carbamate (19). Flow rate: 0.4 mL min^{-1}, yield: 86%, purity: 97%, Rt = 3.0 min, M + H m/z = 215.2. ^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm 8.45 (1H, s), 8.35 (1H, d, J = 6.4 Hz), 8.14 (1H, d, J = 6.4 Hz), 7.27 (1H, s), 5.05 (1H, sept., J = 6.0 Hz), 1.31 (6H, d, J = 8.0 Hz), ^{13}C-NMR (125 MHz, $CDCl_3$): δ/ppm 152.0 (C), 148.9 (2CH), 141.9 (C), 118.8 (C), 112.7 (CH), 70.1 (CH), 21.9 ($2CH_3$). IR: ν 3176.9 (w), 3128.8 (w), 3015.3 (w), 2925.7 (w), 1736.2 (w), 1695.5 (s), 1576.7 (s), 1507.7 (s), 1398.2 (s), 1306.0 (s), 1272.8 (m), 1250.2 (s), 1214.4 (m), 1183.3 (m), 1136.7 (m), 1103.0 (s), 1087.5 (m), 1041.1 (s), 827.9 (m), 715.5 (s), 669.8 (m) cm^{-1}. HRMS calculated for $C_9H_{12}N_2O_2Cl$ 215.0587, found: 215.0582. X-Ray Data: File reference: CCDC 675721; Formula: $C_9H_{11}Cl_1N_2O_2$; Unit cell parameters: a 5.8684(2), b 13.1218(5), c 12.8548(5), α 90.00, β 97.008(2), γ 90.00; space group $P2_1/c$.

1,1-Diethyl-3-(1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridin-3-yl)urea (20). Flow rate: 0.3 mL min^{-1}, yield: 75%, purity: 99%, Rt = 4.16 min, M + Na m/z = 325.36. ^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm 9.01 (1H, s), 8.53 (1H, d, J = 8.0 Hz), 7.70 (1H, s), 7.10 (1H, d, J = 8.0 Hz), 4.47 (2H, q, J = 7.2 Hz), 3.39 (4H, q, J = 7.2 Hz), 2.61 (3H, s), 1.41 (3H, t, J = 7.2 Hz), 1.23 (6H, t, J = 7.2 Hz), ^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm 170.7 (C), 162.4 (C), 155.0 (C), 146.6 (C), 135.9 (CH), 129.1 (CH), 125.2 (C), 119.5 (CH), 116.0 (C), 46.4 (CH_2), 42.1 ($2CH_2$), 25.7 (CH_3), 15.5 (CH_3), 14.2 ($2CH_3$). IR: ν 3362.5 (w), 3097.9 (w), 2982.6 (w), 2931.4 (w), 1651.7 (m), 1625.8 (m), 1581.3 (s), 1531.5 (m), 1488.3 (s), 1434.7 (s), 1360.1 (m), 1296.4 (m),

1243.0 (s), 1161.9 (m), 1127.4 (m), 1083.1 (m), 1053.5 (m), 928.0 (m), 893.1 (m), 781.6 (s), 753.4 (m), 682.1 (m) cm^{-1}. HRMS calculated for $C_{16}H_{23}N_4O_2$ 303.1821, found: 303.1821.

Ethylpyrazolo[1,5-*a*]pyrimidin-3-yl carbamate (21). Flow rate: 0.4 mL min^{-1}, yield: 78%, purity: 94%, Rt = 2.60 min, M + H m/z = 207.2. ^{1}H-NMR (500 MHz, $CDCl_3$): δ/ppm 8.54 (1H, dd, J = 7.1, 1.7 Hz), 8.51 (1H, br s), 8.33 (1H, br d, J = 2.5 Hz), 7.02 (1H, br s), 6.74 (1H, dd, J = 7.1, 4.0 Hz), 4.26 (2H, q, J = 7.0 Hz), 1.31 (3H, t, J = 7.0 Hz), ^{13}C-NMR (125 MHz, $CDCl_3$): δ/ppm 154.3 (C), 147.3 (CH), 138.4 (C), 136.9 (CH), 134.8 (CH), 110.8 (C), 107.7 (CH), 61.6 (CH_2), 14.5 (CH_3). IR: ν 3238.9 (m), 3212.8 (m), 3066.6 (w), 2980.9 (w), 1710.4 (s), 1635.1 (m), 1592.4 (m), 1535.4 (s), 1484.8 (s), 1405.6 (m), 1380.0 (m), 1342.1 (m), 1309.3 (m), 1250.1 (s), 1210.3 (s), 1164.5 (s), 1110.1 (m), 1096.9 (m), 1048.5 (s), 983.4 (m), 880.0 (m), 772.5 (s), 741.7 (s), 671.0 (m) cm^{-1}. HRMS calculated for $C_9H_{11}N_4O_2$ 207.0882, found 207.0889.

Benzyl-5-methylpyrazin-2-yl carbamate (22). Flow rate: 0.4 mL min^{-1}, yield: 87%, purity: 94%, Rt = 4.16 min, M + H m/z = 244.3. ^{1}H-NMR (500 MHz, d_6-DMSO): δ/ppm 10.46 (1H, s), 8.96 (1H, s), 8.22 (1H, s), 7.32–7.45 (5H, m), 5.19 (2H, s), 2.42 (3H, s), ^{13}C-NMR (125 MHz, d_6-DMSO): δ/ppm 153.4 (C), 147.4 (C), 146.6 (C), 141.5 (CH), 136.4 (C), 134.2 (CH), 128.6 (2CH), 128.2 (CH), 128.1 (2CH), 66.3 (CH_2), 20.3 (CH_3). IR: ν 2979.0 (w), 1719.3 (s), 1567.3 (m), 1510.3 (m), 1438.6 (m), 1453.5 (m), 1353.8 (m), 1227.4 (s), 1054.7 (s), 1030.9 (m), 968.4 (m), 926.3 (m), 894.1 (m), 873.3 (m), 846.2 (m), 797.5 (w), 758.6 (m), 744.5 (s), 706.0 (s) cm^{-1}. HRMS calculated for $C_{13}H_{14}N_3O_2$ 244.1086, found 244.1081.

Allyl-1-methyl-1,2,3,4-tetrahydroquinolin-6-yl carbamate (23). Flow rate: 0.3 mL min^{-1}, yield 91%, purity: 96%, Rt = 3.51 min, M + H m/z = 247.34. ^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm 6.95–7.05 (2H, m), 6.54 (1H, d, J = 8.8 Hz), 6.43 (1H, s), 5.90–6.00 (1H, m), 5.35 (1H, d, J = 17.2 Hz), 5.24 (1H, d, J = 10.2 Hz), 4.64 (2H, d, J = 5.2 Hz), 3.17 (2H, t, J = 6.0 Hz), 2.85 (3H, s), 2.74 (2H, t, J = 6.0 Hz), 1.97 (2H, quin., J = 6.0 Hz), ^{13}C-NMR (125 MHz, $CDCl_3$): δ/ppm 153.8 (C), 143.8 (C), 132.8 (CH), 126.9 (C), 123.6 (C), 121.0 (CH), 118.9 (CH), 117.9 (CH_2), 111.4 (CH), 65.6 (CH_2), 51.3 (CH_2), 39.4 (CH_3), 27.8 (CH_2), 22.4 (CH_2). IR: ν 3310.4 (m), 2933.8 (m), 2815.4 (m), 1699.1 (s), 1593.1 (m), 1514.4 (s), 1463.9 (m), 1431.9 (m), 1304.8 (m), 1226.1 (s), 1208.1 (s), 1095.6 (m), 1065.5 (m), 1048.1 (m), 997.1 (m), 930.4 (m), 805.9 (m), 767.0 (m) cm^{-1}. HRMS calculated for $C_{14}H_{19}N_2O_2$ 247.1442, found 247.1441.

(*E*)-3,7-Dimethylocta-2,6-dienylpyrazin-2-yl carbamate (24). Flow rate: 0.4 mL min^{-1}, yield: 81%, purity: 98%, Rt = 4.80 min, M + H m/z = 276.35. ^{1}H-NMR (500 MHz, CD_2Cl_2): δ/ppm 9.35 (1H, s), 9.21 (1H, s), 8.25–8.29 (2H, m), 5.45 (1H, t, J = 6.0 Hz), 5.12 (1H, t, J = 6.0 Hz), 4.75 (2H, d, J = 7.5 Hz), 2.07–2.15 (4H, m), 1.77 (3H, s), 1.67 (3H, s), 1.61 (3H, s), ^{13}C-NMR (125 MHz, CD_2Cl_2): δ/ppm 153.3 (C), 149.1 (C), 143.6 (C), 141.8 (CH), 139.3 (CH), 136.1 (CH), 132.1 (C), 123.9 (CH), 118.3 (CH), 62.8 (CH_2), 39.8 (CH_2), 26.6 (CH_2), 25.6 (CH_3), 17.6 (CH_3), 16.5 (CH_3). IR: ν 3172.0 (w), 2968.0 (m), 2913.0 (m), 2852.8 (m), 1718.0 (s), 1563.4 (s), 1419.1 (s), 1374.7 (m), 1305.2 (m), 1238.4 (s), 1184.8 (m), 1079.5 (s), 1040.7 (s), 1007.2 (m), 932.6 (m), 884.3 (m), 859.8 (m), 828.8 (m), 810.1 (m), 767.7 (m), 734.3 (m), 671.5 (m) cm^{-1}. HRMS calculated for $C_{15}H_{22}N_3O_2$ 276.1712, found: 276.1716. File reference: CCDC 675583; Formula: $C_{15}H_{21}N_3O_2$; Unit cell parameters: a 6.1269(1), b 38.152(1), c 6.9750(3), α 90.00, β 114.441(3), γ 90.00; space group $P2_1/n$.

Ethyl-2-(pyridin-2-yl)quinolin-4-yl carbamate (25). Flow rate: 0.4 mL min^{-1}, yield: 85%, purity: 98%, Rt = 3.65 min, M + H m/z = 294.3. ^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm 9.19 (1H, s), 8.75 (1H, d, J = 4.0 Hz), 8.57 (1H, d, J = 7.6 Hz), 8.18 (1H, d, J = 7.6 Hz), 7.80–7.90 (2H, m), 7.71 (1H, t, J = 7.6 Hz), 7.53 (1H, t, J = 7.6 Hz), 7.45 (1H, s), 7.30–7.35 (1H, m), 4.34 (2H, q, J = 6.8 Hz), 1.37 (3H, t, J = 6.8 Hz), ^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm 157.2 (C), 156.4 (C), 153.1 (C), 149.3 (CH), 148.6 (C), 141.6 (C), 136.7 (CH), 130.9 (CH), 129.4 (CH), 126.4 (CH), 123.9 (CH), 121.7 (CH), 119.7 (C), 119.1 (CH), 107.3 (CH), 62.0 (CH_2), 14.5 (CH_3). IR: ν 3309.1 (w), 3060.8 (w), 2981.3 (w), 1716.9 (m), 1619.7 (m), 1598.7 (m), 1555.7 (s), 1529.4 (s), 1495.5 (m), 1474.3 (m), 1450.0 (m), 1378.2 (m), 1271.7 (s), 1209.6 (s), 1037.8 (m), 1023.1 (m), 884.1 (m), 797.1 (m), 761.6 (m), 745.8 (m), 681.5 (m) cm^{-1}. HRMS calculated for $C_{17}H_{16}N_3O_2$ 294.1243, found 294.1237.

Benzyl-{4[(1,1-dioxido-4-thiomorpholinyl)methyl]phenyl}carbamate (26). Flow rate: 0.4 mL min^{-1}, yield: 92%, purity: 92%, Rt = 4.69 min, M + H m/z = 375.4. ^{1}H-NMR (400 MHz, d_6-DMSO): δ/ppm 9.82 (1H, br. s, NH), 7.48–7.26 (7H, m), 7.18 (2H, d, J = 8.0 Hz), 5.13 (2H, s), 3.58 (2H, s), 3.09 (4H, br. s), 2.79 (4H, br. s); ^{13}C-NMR (100 MHz, d_6-DMSO): δ/ppm 153.7 (C), 138.6 (C), 137.0 (C), 129.7 (CH), 128.8 (2 × CH), 128.5 (2 × CH), 118.4 (CH), 114.2 (CH), 55.1 (CH_2), 59.5 (CH_2), 50.6 (CH_2), 50.3 (CH_2); IR: ν 3338.0 (m), 2823.4 (w), 1714.0 (s), 1614.9 (m), 1600.5 (m), 1540.0 (s), 1464.1 (m), 1415.0 (m), 1315.1 (s), 1290.9 (s), 1264.4 (s), 1224.8 (s), 1182.6 (s), 1123.7 (s), 1096.8 (s), 1048.1 (s), 1029.0 (s), 946.1 (m), 839.6 (m), 766.9 (s), 740.8 (s), 697.8 (s), 663.0 (s) cm^{-1}; HRMS calculated for $C_{19}H_{22}N_2O_4S$ 375.1379, found 375.1397.

Allyl-6-oxo-1,6-dihydropyridazin-3-yl carbamate (27). Flow rate: 0.4 mL min^{-1}, yield: 76%, purity: 95%, Rt = 1.58 min, M + H m/z = 196.2. ^{1}H-NMR (400 MHz, d_6-DMSO): δ/ppm 12.58 (1H, s), 10.15 (1H, s), 7.76 (1H, d, J = 10.0 Hz), 6.89 (1H, d, J = 10.0 Hz), 5.94 (1H, ddt, J = 17.2, 10.8, 5.2 Hz), 5.32 (1H, ddt, J = 17.2, 1.6, 1.6 Hz), 5.10 (1H, ddt, J = 10.8, 1.6, 1.6 Hz), 4.58 (2H, dt, J = 5.6 Hz, 1.6 Hz), ^{13}C-NMR (100 MHz, d_6-DMSO): δ/ppm 160.0 (C), 153.9 (C), 141.6 (C), 133.3 (CH), 131.5 (CH), 129.4 (CH), 118.2 (CH_2), 65.6 (CH_2). IR: ν 3077.2 (w), 2952.4 (w), 1720.5 (m), 1657.1 (s), 1592.5 (s), 1518.5 (s), 1456.6 (m), 1391.5 (m), 1313.6 (m), 1216.1 (s), 1130.3 (m), 1062.2 (m), 1003.7 (m), 932.6 (m), 844.5 (m), 824.2 (m), 765.1 (m) cm^{-1}. HRMS calculated for $C_8H_{10}N_3O_3$ 196.0722, found 196.0724.

Benzyl-4-chloropyridin-3-yl carbamate (28). Flow rate: 0.4 mL min^{-1}, yield: 95%, purity: 98%, Rt = 4.09 min, M + H m/z = 263.25. ^{1}H-NMR (400 MHz, $CDCl_3$): δ/ppm 9.39 (1H, s), 8.23 (1H, d, J = 5.2 Hz), 7.35–7.45 (5H, m), 7.29 (1H, d, J = 5.2 Hz), 7.11 (1H, s), 5.25 (2H, s), ^{13}C-NMR (100 MHz, $CDCl_3$): δ/ppm 153.1 (C), 145.0 (CH), 142.7 (CH), 135.8 (C), 132.5 (C), 131.9 (C), 129.1 (2CH), 129.0 (CH), 128.9 (2CH), 124.1 (CH), 68.3 (CH_2). IR: ν 3180.5 (w), 3137.2 (w), 3031.1 (w), 2895.3 (w), 1708.3 (s), 1578.7 (m), 1537.4 (m), 1456.3 (m),

1456.3 (m), 1416.1 (m), 1397.6 (m), 1311.4 (s), 1242.0 (s), 1219.0 (s), 1088.9 (w), 1065.8 (m), 1039.8 (s), 914.2 (m), 862.3 (m), 815.0 (m), 751.3 (s), 738.5 (s), 694.4 (s), 663.7 (s) cm^{-1}. HRMS calculated for $C_{13}H_{12}ClN_2O_3$ 263.0587, found: 263.0585.

Ethyl-5-phenylpyridin-3-yl carbamate (29). Flow rate: 0.4 mL min^{-1}, yield: 79%, Rt = 3.86 min, purity: 92%, M + H m/z = 243.3. ^{1}H-NMR (400 MHz, d_6-DMSO): δ/ppm 9.99 (1H, s), 8.63 (1H, s), 8.50 (1H, s), 8.15 (1H, s), 7.63 (2H, d, J = 7.2 Hz), 7.50 (2H, t, J = 7.2 Hz), 7.41 (1H, t, J = 7.2 Hz), 4.15 (2H, q, J = 7.2 Hz), 1.24 (3H, t, J = 7.2 Hz), ^{13}C-NMR (100 MHz, d_6-DMSO): δ/ppm 154.1 (C), 141.8 (CH), 139.3 (CH), 137.4 (C), 136.5 (C), 135.9 (C), 129.5 (2CH), 128.6 (CH), 127.2 (2CH), 123.2 (CH), 61.0 (CH_2), 14.8 (CH_3). IR: ν 3434.8 (w), 3057.7 (w), 2978.2 (w), 2925.8 (w), 1726.4 (s), 1608.4 (m), 1593.1 (m), 1554.9 (m), 1460.8 (m), 1435.2 (m), 1417.8 (m), 1365.8 (m), 1324.0 (m), 1255.5 (s), 1219.8 (s), 1157.1 (m), 1087.9 (m), 1077.2 (m), 1052.4 (s), 1024.8 (s), 999.6 (s), 913.6 (m), 870.2 (m), 823.0 (m), 757.7 (s), 697.6 (s) cm^{-1}. HRMS calculated for $C_{14}H_{15}N_2O_2$ 243.1134, found 243.1140. X-Ray data: File reference: CCDC 675582; Formula: $C_{14}H_{14}N_2O_2$; Unit cell parameters: a 7.2306(5), b 6.1299(5), c 27.069(2), α 90.00, β 90.00(3), γ 90.00; space group $Pna2_1$.

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