Supporting Information

Acoustic Droplet Ejection Enabled Automated Reaction Scouting

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1. General information
   1.1. Materials and methods

All reagents and solvents were purchased from commercial suppliers and used without any purification unless otherwise noted. All isocyanides were prepared in house by either performing the Ugi,\textsuperscript{1-4} Hoffman\textsuperscript{5,6} or our recently described Leukart-Wallach reductive amination procedure\textsuperscript{7} (Scheme S1).

![Ugi Method](image)

\textbf{Ugi Method}

\[
\begin{align*}
R^-\text{NH}_2 & \xrightarrow{<\text{HCOOH}>} R^-\text{NHCHO} & -\text{H}_2\text{O} & \rightarrow R^-\text{NC}
\end{align*}
\]

![Hoffmann Method](image)

\textbf{Hoffmann Method}

\[
\begin{align*}
R^-\text{NH}_2 & \xrightarrow{<\text{CCI}_2>} R^-\text{NC}
\end{align*}
\]

![Leukart Wallach Reductive Amination Method](image)

\textbf{Leukart Wallach Reductive Amination Method}

\[
\begin{align*}
R_1\text{O} & \xrightarrow{<\text{HCOOH}>} R_1\text{NHCHO} & -\text{H}_2\text{O} & \rightarrow R_1\text{NC}
\end{align*}
\]

\textit{Scheme S1. Isocyanide Syntheses.}

Other reagents were purchased from Sigma Aldrich, ACR, Acros and AK Scientific and were used without further purification. Nuclear magnetic resonance spectra (NMR) were recorded on a Bruker Avance 500 spectrometer (\textsuperscript{1}H NMR (500 MHz), \textsuperscript{13}C NMR (126 MHz)). Chemical shifts for \textsuperscript{1}H NMR were reported as $\delta$ values and coupling constants were in hertz (Hz). The following abbreviations were used for spin multiplicity: $s$ = singlet, $bs$ = broad singlet, $d$ = doublet, $t$ = triplet, $q$ = quartet, $m$ = multiplet. Chemical shifts for \textsuperscript{13}C NMR reported in ppm relative to the solvent peak. Flash chromatography was performed using RediSep R\textsubscript{t} Normal-phase Silica Flash Columns (Silica Gel 60 Å, 230-400 mesh). Electrospray ionization mass spectra (ESI-MS) were recorded on a Waters Investigator Semi-prep 15 SFC-MS instrument. High resolution mass spectra were recorded using an LTQ-Orbitrap-XL (Thermo Fisher Scientific; ESI\textsuperscript{+} mode) at a resolution of 60000@m/z400.

Analytical chemicals and reagents: MeOH (technical grade), CH\textsubscript{3}CN (HPLC gradient grade), dioxane (99+% extra pure, stabilized), ethylene glycol (99+% extra pure) and fuming HCl (37%, for analysis). Formic acid (≥98.0%), acetic acid (≥99.8%), trifluoroacetic acid (≥99.0%), methanesulfonic acid (≥99.0%), benzoic acid (≥99.5%), 2,2-dimethoxyacetalddehyde (60 wt. % in H\textsubscript{2}O), 3,4,5-trimethoxybenzylamine (98%), 3,4-dimethoxybenzylamine (97%), piperonylamine (97%), 2,3-dimethoxybenzylamine (99%), 2,5-dimethoxybenzylamine (97%).
2. Optimization of the novel isoquinoline reaction
In a model reaction, (3,5-dimethoxyphenyl)methane amine (1 mmol), 2,2-dimethoxy acetaldehyde (1 mmol), benzoic acid (1 mmol) and phenylethyl isocyanide (1 mmol) were stirred at room temperature in MeOH (1 M) for 15 h. Upon completion (TLC control), solvent was removed under vacuum. The Ugi adduct 1a was directly used without any purification in the acid-catalyzed cyclisation/oxidation reaction.
In order to optimize the cyclisation/oxidation reaction, various acidic conditions (1 mL) were screened (Table S1). The desired product 3a was formed in 68% yield in the presence of 37\% HCl\(_{\text{aq}}\) solution in dioxane (1 mL, 1:1, v/v) as solvent at room temperature (Table S1, entry 10).

![Chemical structures](image)

**Table S1.** Optimization of reaction conditions for Ugi/Schlittler-Müller reaction.

| Entry | Solvent                          | Isolated yield (%) |
|-------|----------------------------------|--------------------|
| 1     | HCOOH                            | 0                  |
| 2     | CH\(_3\)COOH                     | 0                  |
| 3     | CF\(_3\)COOH                     | 0                  |
| 4     | CH\(_3\)SO\(_3\)H (10 eq)/ CH\(_3\)CN | 0                  |
| 5     | CH\(_3\)SO\(_3\)H                | 0                  |
| 6     | CH\(_3\)COOH/conc. H\(_2\)SO\(_4\) (2:1, v/v) | 33                 |
| 7     | CH\(_3\)COOH/ conc. H\(_2\)SO\(_4\) (1:1, v/v) | 26                 |
| 8     | HCl\(_{\text{aq}}\)/ dioxane (1:4, v/v) | 34                 |
| 9     | HCl\(_{\text{aq}}\)/ dioxane (1:2, v/v) | 43                 |
| 10    | HCl\(_{\text{aq}}\)/ dioxane (1:1, v/v) | **68**             |
| 11    | HCl\(_{\text{aq}}\)              | 52                 |

3. General workflow for nanoscale synthesis
The general method typically follows the steps summarized in Table S2, with the implicit details for each step provided in the following text.

**Table S2.** General workflow.

| No. | Step                | Short Description                                                                 |
|-----|---------------------|-----------------------------------------------------------------------------------|
| 1   | Stock solution      | Stock solutions were prepared at 0.5 M in ethylene glycol or 2-methoxy ethanol and sealed and kept at -20 °C. |
| 2   | preparation         | The stock solutions were pipetted into the 384 well source plates.                |
| 3   | Source plate        | Sequence tables and methods were loaded into Echo 555 software and automatic transfer of the reagents started. |
| 4   | Nanoscale synthesis | 384 Well synthesis plate was diluted with methanol and SFC-MS analytic performed with autosampler. |
| 5   | QC by SFC           |                                                                    |
384 Well synthesis plate was diluted with methanol and spotted onto silica TLC plates and eluted. The UV active spots were eluted and transferred into the Advion desktop MS.

4. Nanomole-scale chemical reactions

4.1. General materials
Stock solutions were prepared in glass flat bottom vials (Screening devices, Catalog#: 9920-812FBT, 2.0 mL (Topas) Plate) and they were kept at -20 °C.

Nanomole-scale chemistry was performed using Echo qualified 384-well polypropylene microplate (Labcyte, Catalog#: PP-0200, clear, flat bottom) according to the producers’ manual.

384-Well source and destination plates were sealed by a sealing tape (Thermo Scientific, Catalog#: 232701, polyolefin acrylate) and were kept at -20 °C.

4.2. Instrumentation
The Echo 555 liquid handler (Labcyte) was used in order to transfer nL droplets of starting materials from the 384-well source plate to the 384-well destination plate.

4.3. Nanomole-scale automated chemistry
Stock solutions of aldehyde, acid, amines (A1-A7) and isocyanides (I1-I3, I6-I8, I10-16, I18, I19, I21, I28, I29, I31, I34, I35, I42-I44, I48, I50-I62) were prepared as 0.5 M ethylene glycole. Due to the insolubility of some isocyanides (I4, I5, I9, I11, I20, I22-I27, I30, I32, I33, I36-I41, I45-I47, I49) in ethylene glycole, their stock solutions were instead prepared as 0.5 M in 2-methoxyethanol.

The stock solutions were dispensed to a 384-well source plate using Eppendorf multi-channel pipettes. The Echo 555 was used to transfer 750 nL (375 nmol) of each starting material into the corresponding well in the destination plate. Labcyte Echo plate reformat software using custom mapping mode with the run protocol as defined by a pick list was used (Fig. S1B).

In order to generate a random library of products (N=384), a modified version of our previously reported program RandReactor was used. The smiles files of the starting materials with the corresponding location in the source plate and mrv file of reaction were the input of the RandReactor program. The smiles file of the randomly generated products with their corresponding locations in the source and destination plate were the output of the RandReactor program. The smiles file was converted to a csv file which was the required format for Labcyte Echo plate reformat software (Fig. S1A).

Once the starting materials transfer was completed (~150 min), the destination plate was covered with the sealing film and was then placed for 15 h at 23 °C on an orbital shacker. Then, 10 µL of 37% HCl(aq)/dioxane solution (1:1, v/v) was added to each well using a multichannel
pipettor and the plate was sealed and kept at 23 °C for another 12 h. Then the plate was dried from the solvent by applying a mild stream of nitrogen. The plates were sealed and stored at -20 °C for further processing. The structures of the products are shown in Fig. S2.

**Fig. S1.** A: Pick list in csv format required for Labcyte Echo plate reformat software; B: Labcyte Echo plate reformat software, showing on top the source plate and below the destination plate.
|   | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| A | ![Chemical Structure](image) | ![Chemical Structure](image) | ![Chemical Structure](image) | ![Chemical Structure](image) |
| B | ![Chemical Structure](image) | ![Chemical Structure](image) | ![Chemical Structure](image) | ![Chemical Structure](image) |
| C | ![Chemical Structure](image) | ![Chemical Structure](image) | ![Chemical Structure](image) | ![Chemical Structure](image) |
| D | ![Chemical Structure](image) | ![Chemical Structure](image) | ![Chemical Structure](image) | ![Chemical Structure](image) |
| E | ![Chemical Structure](image) | ![Chemical Structure](image) | ![Chemical Structure](image) | ![Chemical Structure](image) |
| F | ![Chemical Structure](image) | ![Chemical Structure](image) | ![Chemical Structure](image) | ![Chemical Structure](image) |
| G | ![Chemical Structure](image) | ![Chemical Structure](image) | ![Chemical Structure](image) | ![Chemical Structure](image) |
| H | ![Chemical Structure](image) | ![Chemical Structure](image) | ![Chemical Structure](image) | ![Chemical Structure](image) |
| I | ![Chemical Structure](image) | ![Chemical Structure](image) | ![Chemical Structure](image) | ![Chemical Structure](image) |
| J | ![Chemical Structure](image) | ![Chemical Structure](image) | ![Chemical Structure](image) | ![Chemical Structure](image) |
| K | ![Chemical Structure](image) | ![Chemical Structure](image) | ![Chemical Structure](image) | ![Chemical Structure](image) |
| L | ![Chemical Structure](image) | ![Chemical Structure](image) | ![Chemical Structure](image) | ![Chemical Structure](image) |
| M | ![Chemical Structure](image) | ![Chemical Structure](image) | ![Chemical Structure](image) | ![Chemical Structure](image) |
| N | ![Chemical Structure](image) | ![Chemical Structure](image) | ![Chemical Structure](image) | ![Chemical Structure](image) |
| O | ![Chemical Structure](image) | ![Chemical Structure](image) | ![Chemical Structure](image) | ![Chemical Structure](image) |
| P | ![Chemical Structure](image) | ![Chemical Structure](image) | ![Chemical Structure](image) | ![Chemical Structure](image) |
|   | 5 | 6 | 7 | 8 |
|---|---|---|---|---|
| A | ![image](image1.png) | ![image](image2.png) | ![image](image3.png) | ![image](image4.png) |
| B | ![image](image5.png) | ![image](image6.png) | ![image](image7.png) | ![image](image8.png) |
| C | ![image](image9.png) | ![image](image10.png) | ![image](image11.png) | ![image](image12.png) |
| D | ![image](image13.png) | ![image](image14.png) | ![image](image15.png) | ![image](image16.png) |
| E | ![image](image17.png) | ![image](image18.png) | ![image](image19.png) | ![image](image20.png) |
| F | ![image](image21.png) | ![image](image22.png) | ![image](image23.png) | ![image](image24.png) |
| G | ![image](image25.png) | ![image](image26.png) | ![image](image27.png) | ![image](image28.png) |
| H | ![image](image29.png) | ![image](image30.png) | ![image](image31.png) | ![image](image32.png) |
| I | ![image](image33.png) | ![image](image34.png) | ![image](image35.png) | ![image](image36.png) |
| J | ![image](image37.png) | ![image](image38.png) | ![image](image39.png) | ![image](image40.png) |
| K | ![image](image41.png) | ![image](image42.png) | ![image](image43.png) | ![image](image44.png) |
| L | ![image](image45.png) | ![image](image46.png) | ![image](image47.png) | ![image](image48.png) |
| M | ![image](image49.png) | ![image](image50.png) | ![image](image51.png) | ![image](image52.png) |
| N | ![image](image53.png) | ![image](image54.png) | ![image](image55.png) | ![image](image56.png) |
| O | ![image](image57.png) | ![image](image58.png) | ![image](image59.png) | ![image](image60.png) |
| P | ![image](image61.png) | ![image](image62.png) | ![image](image63.png) | ![image](image64.png) |
|   | 9 | 10 | 11 | 12 |
|---|---|----|----|----|
| A | ![Chemical Structure](image1) | ![Chemical Structure](image2) | ![Chemical Structure](image3) | ![Chemical Structure](image4) |
| B | ![Chemical Structure](image5) | ![Chemical Structure](image6) | ![Chemical Structure](image7) | ![Chemical Structure](image8) |
| C | ![Chemical Structure](image9) | ![Chemical Structure](image10) | ![Chemical Structure](image11) | ![Chemical Structure](image12) |
| D | ![Chemical Structure](image13) | ![Chemical Structure](image14) | ![Chemical Structure](image15) | ![Chemical Structure](image16) |
| E | ![Chemical Structure](image17) | ![Chemical Structure](image18) | ![Chemical Structure](image19) | ![Chemical Structure](image20) |
| F | ![Chemical Structure](image21) | ![Chemical Structure](image22) | ![Chemical Structure](image23) | ![Chemical Structure](image24) |
| G | ![Chemical Structure](image25) | ![Chemical Structure](image26) | ![Chemical Structure](image27) | ![Chemical Structure](image28) |
| H | ![Chemical Structure](image29) | ![Chemical Structure](image30) | ![Chemical Structure](image31) | ![Chemical Structure](image32) |
| I | ![Chemical Structure](image33) | ![Chemical Structure](image34) | ![Chemical Structure](image35) | ![Chemical Structure](image36) |
| J | ![Chemical Structure](image37) | ![Chemical Structure](image38) | ![Chemical Structure](image39) | ![Chemical Structure](image40) |
| K | ![Chemical Structure](image41) | ![Chemical Structure](image42) | ![Chemical Structure](image43) | ![Chemical Structure](image44) |
| L | ![Chemical Structure](image45) | ![Chemical Structure](image46) | ![Chemical Structure](image47) | ![Chemical Structure](image48) |
| M | ![Chemical Structure](image49) | ![Chemical Structure](image50) | ![Chemical Structure](image51) | ![Chemical Structure](image52) |
| N | ![Chemical Structure](image53) | ![Chemical Structure](image54) | ![Chemical Structure](image55) | ![Chemical Structure](image56) |
| O | ![Chemical Structure](image57) | ![Chemical Structure](image58) | ![Chemical Structure](image59) | ![Chemical Structure](image60) |
| P | ![Chemical Structure](image61) | ![Chemical Structure](image62) | ![Chemical Structure](image63) | ![Chemical Structure](image64) |
|   | 17  | 18  | 19  | 20  |
|---|-----|-----|-----|-----|
| A | ![Chemical Structure](image1) | ![Chemical Structure](image2) | ![Chemical Structure](image3) | ![Chemical Structure](image4) |
| B | ![Chemical Structure](image5) | ![Chemical Structure](image6) | ![Chemical Structure](image7) | ![Chemical Structure](image8) |
| C | ![Chemical Structure](image9) | ![Chemical Structure](image10) | ![Chemical Structure](image11) | ![Chemical Structure](image12) |
| D | ![Chemical Structure](image13) | ![Chemical Structure](image14) | ![Chemical Structure](image15) | ![Chemical Structure](image16) |
| E | ![Chemical Structure](image17) | ![Chemical Structure](image18) | ![Chemical Structure](image19) | ![Chemical Structure](image20) |
| F | ![Chemical Structure](image21) | ![Chemical Structure](image22) | ![Chemical Structure](image23) | ![Chemical Structure](image24) |
| G | ![Chemical Structure](image25) | ![Chemical Structure](image26) | ![Chemical Structure](image27) | ![Chemical Structure](image28) |
| H | ![Chemical Structure](image29) | ![Chemical Structure](image30) | ![Chemical Structure](image31) | ![Chemical Structure](image32) |
| I | ![Chemical Structure](image33) | ![Chemical Structure](image34) | ![Chemical Structure](image35) | ![Chemical Structure](image36) |
| J | ![Chemical Structure](image37) | ![Chemical Structure](image38) | ![Chemical Structure](image39) | ![Chemical Structure](image40) |
| K | ![Chemical Structure](image41) | ![Chemical Structure](image42) | ![Chemical Structure](image43) | ![Chemical Structure](image44) |
| L | ![Chemical Structure](image45) | ![Chemical Structure](image46) | ![Chemical Structure](image47) | ![Chemical Structure](image48) |
| M | ![Chemical Structure](image49) | ![Chemical Structure](image50) | ![Chemical Structure](image51) | ![Chemical Structure](image52) |
| N | ![Chemical Structure](image53) | ![Chemical Structure](image54) | ![Chemical Structure](image55) | ![Chemical Structure](image56) |
| O | ![Chemical Structure](image57) | ![Chemical Structure](image58) | ![Chemical Structure](image59) | ![Chemical Structure](image60) |
| P | ![Chemical Structure](image61) | ![Chemical Structure](image62) | ![Chemical Structure](image63) | ![Chemical Structure](image64) |
|     | 21 | 22 | 23 | 24 |
|-----|----|----|----|----|
| **A** | ![Structure A](image) | ![Structure A](image) | ![Structure A](image) | ![Structure A](image) |
| **B** | ![Structure B](image) | ![Structure B](image) | ![Structure B](image) | ![Structure B](image) |
| **C** | ![Structure C](image) | ![Structure C](image) | ![Structure C](image) | ![Structure C](image) |
| **D** | ![Structure D](image) | ![Structure D](image) | ![Structure D](image) | ![Structure D](image) |
| **E** | ![Structure E](image) | ![Structure E](image) | ![Structure E](image) | ![Structure E](image) |
| **F** | ![Structure F](image) | ![Structure F](image) | ![Structure F](image) | ![Structure F](image) |
| **G** | ![Structure G](image) | ![Structure G](image) | ![Structure G](image) | ![Structure G](image) |
| **H** | ![Structure H](image) | ![Structure H](image) | ![Structure H](image) | ![Structure H](image) |
| **I** | ![Structure I](image) | ![Structure I](image) | ![Structure I](image) | ![Structure I](image) |
| **J** | ![Structure J](image) | ![Structure J](image) | ![Structure J](image) | ![Structure J](image) |
| **K** | ![Structure K](image) | ![Structure K](image) | ![Structure K](image) | ![Structure K](image) |
| **L** | ![Structure L](image) | ![Structure L](image) | ![Structure L](image) | ![Structure L](image) |
| **M** | ![Structure M](image) | ![Structure M](image) | ![Structure M](image) | ![Structure M](image) |
| **N** | ![Structure N](image) | ![Structure N](image) | ![Structure N](image) | ![Structure N](image) |
| **O** | ![Structure O](image) | ![Structure O](image) | ![Structure O](image) | ![Structure O](image) |
| **P** | ![Structure P](image) | ![Structure P](image) | ![Structure P](image) | ![Structure P](image) |

*Fig. S2.* Heat maps with product structures.
4.4. Quality control (QC)
The analytics of all wells was performed by two complementary methods, SFC-UV-MS and TLC-UV-MS.

4.4.1. SFC-UV-MS analysis

Mass spectra were measured on a Waters Investigator Supercritical Fluid Chromatograph with a 3100 MS Detector (ESI+) on a Kromasil SFC-2.5-2EP (3.0 × 50 mm) column and MassLynx software.

Conditions: mobile phase: CO$_2$ with 35% MeOH (isocratic), run time: 1 min, flow rate: 4 mL/min, temperature: 40 °C, pressure: 120 bar.

Each well of the destination plate was diluted with 100 µL MeOH and then the chromatographic analysis was done by SFC-UV-MS using an autosampler. A right-click and drag operation of the total ion current (TIC) spectrum generated a mass chromatogram for the selected range. If the peak corresponding to M+1 was the major peak, the well got a green designation and otherwise yellow. If the peak of M+1 was absent, the well got a red designation.

The SFC analytic of one well took ~1 min, resulting in an overall measuring time for the 384 well plate of less than one night.
Examples of SFC-UV-MS analytics of the row P1-P24
Exact Mass: 332.10
Molecular Weight: 332.42

3_P2

3_P2 52 (0.445) Cm (41.69)
Exact Mass: 412.18
Molecular Weight: 412.49
Exact Mass: 384.15
Molecular Weight: 384.41
Exact Mass: 302.03
Molecular Weight: 302.78
Exact Mass: 274.02
Molecular Weight: 274.36
Exact Mass: 382.17
Molecular Weight: 382.44
Exact Mass: 282.08
Molecular Weight: 282.36
Exact Mass: 414.16
Molecular Weight: 414.46
Exact Mass: 312,11
Molecular Weight: 312,33
Exact Mass: 366.16
Molecular Weight: 366.42
4.4.2. TLC-UV-MS analysis

Thin layer chromatography was performed on silica gel plates (0.20 mm thick, particle size 25 μm, Merck). Mass analysis of TLC plates was performed on an Advion Plate Express connected to an Advion compact mass spectrometer (CMS) fitted with an electrospray ionization (ESI⁺) and using Mass Express software.

The isocratic elution was performed with MeOH, 5% H₂O, 0.1% formic acid, at a flow rate of 0.2 mL/min. Full scan mass spectra were recorded in the positive ionization mode (ESI⁺) using a capillary temperature of 250 °C, voltage of 150 V, source voltage offset of 20 V, source voltage span of 30, source gas temperature of 200 °C, and an ESI voltage of 3.5 kV.

Each well of the 384 well destination plate was diluted with 20 μL MeOH. In order to analyze the 384 well destination plate, 24 TLC plates with each 16 spots (one row of the 384 well plate) were developed with petroleum ether - ethyl acetate (1:1, v/v). The developed TLC plates were placed into the plate express. Major spots of interest detected by UV were marked with a soft pencil on the plate and then directly transferred to the CMS. Advion Mass Express and Data Express software was used for mass measurements and data processing.
Examples of TLC-UV-MS analytics

Exact Mass: 312.13
Molecular Weight: 312.43

Exact Mass: 390.12
Molecular Weight: 390.36

Exact Mass: 328.09
Molecular Weight: 328.39

Exact Mass: 314.16
Molecular Weight: 314.39
Exact Mass: 418.11
Molecular Weight: 418.85

Exact Mass: 323.13
Molecular Weight: 323.35

Exact Mass: 392.07
Molecular Weight: 392.79

Exact Mass: 352.12
Molecular Weight: 352.37
Exact Mass: 400.04
Molecular Weight: 401.26

Exact Mass: 322.15
Molecular Weight: 322.36

Exact Mass: 316.14
Molecular Weight: 318.36

Exact Mass: 442.19
Molecular Weight: 442.52
5. Statistical reaction analysis

Scheme S2. Frequency of the isocyanides in the plate along with the QC results.
Scheme S3. Frequency of the benzyl amines in the plate along with the QC results.

Scheme S4. QC results for the 384-destination plate.
6. Mg scale reactions

6.1. General procedure
To a stirred solution of 2,2-dimethoxyacetalddehyde (1 mmol) in MeOH (1M) at room temperature, amine (1 mmol), benzoic acid (1 mmol) and isocyanide (1 mmol) were added. The resulting mixture was stirred at room temperature for 15 h. Upon completion, the solvent was evaporated under vacuum. Then, the crude Ugi-adduct was dissolved in 37% HCl(aq) solution in dioxane (1 mL, 1:1, v/v) and was stirred at room temperature for 12 h. The reaction was diluted with dichloromethane (20 mL) and washed with saturated sodium bicarbonate solution (3 x 10 mL). Finally, the solvent was evaporated under vacuum and the crude product was purified by flash column chromatography using petroleum ether/ethyl acetate (Fig. S3).

![Fig. S3. Structures of the randomly resynthesized isoquinolines on mg scale and selected X-ray structures.](image)
6.2. Characterization of the products

**N-((1S,3s)-adamantan-1-yl)thieno[3,2-c]pyridine-6-carboxamide (A3)**

![Chemical structure of A3]

White solid (149 mg, 48% yield), M.P. = 221 – 223 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.97 (d, \(J = 0.9\) Hz, 1H), 8.68 (d, \(J = 1.0\) Hz, 1H), 8.03 (s, 1H), 7.62 (d, \(J = 5.5\) Hz, 1H), 7.50 – 7.47 (m, 1H), 2.19 (d, \(J = 2.8\) Hz, 6H), 2.16 – 2.11 (m, 3H), 1.79 – 1.67 (m, 6H); \(^1^3\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 163.4, 148.2, 144.5, 143.5, 137.2, 130.1, 122.4, 116.1, 51.7, 41.6, 36.4, 29.5; HRMS (ESI) m/z calculated for C\(_{18}\)H\(_{21}\)N\(_2\)O\(_3\) [M+H]\(^+\): 313.1369; found [M+H]\(^+\): 313.1367.

**N-cyclohexylthieno[3,2-c]pyridine-6-carboxamide (A13)**

![Chemical structure of A13]

White solid (119 mg, 46% yield), M.P. = 109 – 111 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 9.0 (d, \(J = 0.9\) Hz, 1H), 8.7 (s, 1H), 8.1 (d, \(J = 8.6\) Hz, 1H), 7.6 (d, \(J = 5.5\) Hz, 1H), 7.5 – 7.5 (m, 1H), 4.1 – 3.9 (m, 1H), 2.1 – 2.0 (m, 2H), 1.9 – 1.7 (m, 2H), 1.7 (m, 1H), 1.5 – 1.4 (m, 2H), 1.4 – 1.3 (m, 2H), 1.3 – 1.2 (m, 1H); \(^1^3\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 163.7, 148.2, 143.9, 137.5, 130.4, 130.2, 122.4, 116.7, 48.4, 33.3, 25.7, 25.7; HRMS (ESI) m/z calculated for C\(_{14}\)H\(_{17}\)N\(_2\)O\(_3\) [M+H]\(^+\): 261.1056; found [M+H]\(^+\): 261.1058.

**5,6,7-Trimethoxy-N-phenethylisoquinoline-3-carboxamide (A22)**

![Chemical structure of A22]

White solid (267 mg, 73% yield), M.P. = 121 – 123 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.90 (s, 1H), 8.76 (s, 1H), 8.28 (t, \(J = 6.2\) Hz, 1H), 7.33 – 7.20 (m, 5H), 7.05 (s, 1H), 4.06 (s, 3H), 4.01 (s, 3H), 4.00 (s, 3H), 3.81 – 3.74 (m, 2H), 2.97 (t, \(J = 7.3\) Hz, 2H); \(^1^3\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 165.2, 155.3, 148.8, 141.8, 144.6, 142.2, 139.2, 128.9, 128.6, 127.9, 127.1, 126.5, 114.7, 101.6, 61.8, 61.3, 56.2, 40.9, 36.1; HRMS (ESI) m/z calculated for C\(_{21}\)H\(_{23}\)N\(_2\)O\(_4\) [M+H]\(^+\): 367.1652; found [M+H]\(^+\): 367.1652.

**5,7-Dimethoxy-N-phenethylisoquinoline-3-carboxamide (B5)**

![Chemical structure of B5]

Grey solid (229 mg, 68% yield), M.P. = 159 – 161 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.90 (s, 1H), 8.83 (s, 1H), 8.24 (t, \(J = 6.2\) Hz, 1H), 7.35 – 7.20 (m, 5H), 6.79 (d, \(J = 2.2\) Hz, 1H), 6.65 (d, \(J = 2.1\) Hz, 1H), 3.97 (s, 3H), 3.93 (s, 3H), 3.81 – 3.74 (m, 2H), 2.98 (t, \(J = 7.3\) Hz, 2H); \(^1^3\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 165.2, 157.0, 148.9, 141.8, 139.3, 131.6, 128.9, 128.7, 126.5, 125.0, 115.3, 101.9, 96.8, 55.9, 55.7, 40.9, 36.2; HRMS (ESI) m/z calculated for C\(_{20}\)H\(_{21}\)N\(_2\)O\(_3\) [M+H]\(^+\): 337.1547; found [M+H]\(^+\): 337.1545.

**5,8-Dimethoxy-N-phenethylisoquinoline-3-carboxamide (B16)**
Yellow solid (121 mg, 36% yield), M.P. = 120 – 122 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 9.41 (s, 1H), 8.89 (s, 1H), 8.36 (t, \(J = 6.2\) Hz, 1H), 7.34 – 7.20 (m, 5H), 6.91 (d, \(J = 8.5\) Hz, 1H), 6.83 (d, \(J = 8.5\) Hz, 1H), 3.97 (s, 3H), 3.95 (s, 3H), 3.83 – 3.75 (m, 2H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 165.0, 150.1, 149.5, 146.0, 144.0, 139.3, 129.5, 129.0, 128.7, 126.5, 122.0, 114.8, 108.5, 106.5, 56.0, 55.9, 41.0, 36.2; HRMS (ESI) m/z calculated for C\(_{20}\)H\(_{21}\)N\(_2\)O\(_3\) [M+H]\(^+\): 337.1547; found [M+H]\(^+\): 337.1546.

N-(4-(benzylloxy)benzyl)-5,6,7-trimethoxyisoquinoline-3-carboxamide (B24)

Grey solid (293 mg, 64% yield), M.P. = 110 – 112 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.91 (s, 1H), 8.80 (s, 1H), 8.45 (t, \(J = 5.9\) Hz, 1H), 7.45 – 7.29 (m, 7H), 7.06 (s, 1H), 6.95 (d, \(J = 8.2\) Hz, 2H), 5.05 (s, 2H), 4.65 (d, \(J = 5.9\) Hz, 2H), 4.07 (s, 3H), 4.02 (s, 3H), 4.01 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 165.0, 158.2, 155.4, 148.8, 148.1, 144.7, 142.2, 137.1, 131.1, 129.4, 128.7, 128.0, 128.0, 127.5, 127.2, 115.1, 115.0, 101.6, 70.1, 61.9, 61.4, 56.3, 43.1; HRMS (ESI) m/z calculated for C\(_{27}\)H\(_{27}\)N\(_2\)O\(_5\) [M+H]\(^+\): 459.1915; found [M+H]\(^+\): 459.1914.

6,7-Dimethoxy-N-phenethylisoquinoline-3-carboxamide (C2)

White solid (220 mg, 66% yield), M.P. = 158 – 160 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.9 (s, 1H), 8.8 (s, 1H), 8.2 (t, \(J = 6.2\) Hz, 1H), 7.3 – 7.2 (m, 5H), 6.8 (s, 1H), 6.6 (s, 1H), 4.0 (s, 3H), 3.9 (s, 3H), 3.8 – 3.7 (m, 2H), 3.0 (t, \(J = 7.3\) Hz, 2H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 165.3, 153.5, 151.7, 148.5, 142.9, 139.3, 132.9, 129.0, 128.7, 126.5, 126.1, 119.1, 106.1, 105.4, 56.4, 56.3, 40.9, 36.2; HRMS (ESI) m/z calculated for C\(_{20}\)H\(_{21}\)N\(_2\)O\(_3\) [M+H]\(^+\): 337.1547; found [M+H]\(^+\): 337.1545.

7,8-Dimethoxy-N-phenethylisoquinoline-3-carboxamide (C10)

Color-less semi-solid (138 mg, 41% yield); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 9.40 (s, 1H), 8.52 (s, 1H), 8.33 (t, \(J = 6.3\) Hz, 1H), 7.73 (d, \(J = 8.9\) Hz, 1H), 7.54 (d, \(J = 8.9\) Hz, 1H), 7.36 – 7.22 (m, 5H), 4.07 (s, 3H), 4.03 (s, 3H), 3.79 (q, \(J = 7.0\) Hz, 2H), 2.98 (t, \(J = 7.3\) Hz, 2H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 165.2, 150.4, 146.1, 144.0, 142.2, 139.2, 131.5, 129.0, 128.7, 126.6, 125.2, 124.6, 120.1, 119.9, 61.8, 56.9, 40.9, 36.2; HRMS (ESI) m/z calculated for C\(_{20}\)H\(_{21}\)N\(_2\)O\(_3\) [M+H]\(^+\): 337.1547; found [M+H]\(^+\): 337.1546.

N-phenethyl-[1,3]dioxolo[4,5-f]isoquinoline-8-carboxamide (D19)
White solid (198 mg, 62% yield), M.P. = 138 – 140 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.80 (s, 1H), 8.40 (s, 1H), 8.27 (t, \(J = 6.3\) Hz, 1H), 7.33 – 7.21 (m, 5H), 7.17 (d, \(J = 8.3\) Hz, 2H), 6.10 (s, 2H), 3.82 – 3.70 (m, 2H); \(^1^3\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 165.1, 151.5, 149.7, 148.7, 143.1, 139.2, 134.5, 128.7, 127.4, 126.5, 119.6, 103.9, 103.3, 102.1, 40.9, 36.1; HRMS (ESI) m/z calculated for C\(_{19}\)H\(_{17}\)N\(_2\)O\(_3\) [M+H\(^+\)]\(^+\): 321.1234; found [M+H\(^+\)]\(^+\): 321.1234.

N-(2-isopropylphenyl)-6,7-dimethoxyisoquinoline-3-carboxamide (E7)

White solid (115 mg, 33% yield), M.P. = 180 – 182 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 10.36 (s, 1H), 8.99 (s, 1H), 8.56 (s, 1H), 8.27 – 8.22 (m, 1H), 7.35 – 7.31 (m, 1H), 7.30 – 7.26 (m, 2H), 7.22 (s, 1H), 7.20 – 7.15 (m, 1H), 4.05 (s, 3H), 4.05 (s, 3H), 3.32 – 3.24 (m, 1H), 1.36 (s, 3H), 1.34 (s, 3H); \(^1^3\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 163.2, 153.7, 151.9, 148.6, 143.1, 139.1, 134.9, 133.0, 126.7, 126.3, 125.7, 125.2, 122.8, 119.5, 106.2, 105.6, 56.5, 56.4, 28.4, 23.1; HRMS (ESI) m/z calculated for C\(_{21}\)H\(_{23}\)N\(_2\)O\(_3\) [M+H\(^+\)]\(^+\): 351.1703; found [M+H\(^+\)]\(^+\): 351.1701.

N-benzyl-5,7-dimethoxyisoquinoline-3-carboxamide (E12)

White solid (215 mg, 67% yield), M.P. = 146 – 148 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 9.64 (s, 1H), 9.01 (s, 1H), 8.57 (s, 1H), 7.29 (s, 1H), 7.22 (s, 1H), 7.21 – 7.17 (m, 1H), 7.17 – 7.13 (m, 2H), 4.07 (s, 3H), 4.04 (s, 3H), 2.69 (q, \(J = 6.0\) Hz, 2H), 2.32 (s, 3H), 1.21 (t, \(J = 7.6\) Hz, 3H); \(^1^3\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 163.8, 153.6, 151.8, 148.6, 141.6, 138.7, 131.6, 128.7, 128.0, 127.4, 124.9, 115.5, 101.9, 96.8, 55.9, 55.7, 43.6; HRMS (ESI) m/z calculated for C\(_{21}\)H\(_{23}\)N\(_2\)O\(_3\) [M+H\(^+\)]\(^+\): 351.1703; found [M+H\(^+\)]\(^+\): 351.1701.

N-(2-ethyl-6-methylphenyl)-6,7-dimethoxyisoquinoline-3-carboxamide (E17)

White solid (109 mg, 31% yield), M.P. = 225 – 227 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.29 (s, 1H), 7.22 (s, 1H), 7.21 – 7.17 (m, 1H), 7.17 – 7.13 (m, 2H), 4.07 (s, 3H), 4.04 (s, 3H), 2.69 (q, \(J = 7.6\) Hz, 2H), 2.32 (s, 3H), 1.21 (t, \(J = 7.6\) Hz, 3H); \(^1^3\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 163.8, 153.6, 151.8, 148.6, 142.7, 141.3, 136.1, 133.7, 132.9, 128.3, 127.5, 126.4, 126.3, 119.5, 106.1, 105.5, 56.4, 56.3, 25.2, 18.8, 14.6; HRMS (ESI) m/z calculated for C\(_{21}\)H\(_{23}\)N\(_2\)O\(_3\) [M+H\(^+\)]\(^+\): 351.1703; found [M+H\(^+\)]\(^+\): 351.1702.

N-(2,2-diphenylethyl)-5,6,7-trimethoxyisoquinoline-3-carboxamide (F8)

White solid (274 mg, 62% yield), M.P. = 171 – 172 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.84 (s, 1H), 8.75 (s, 1H), 8.21 (t, \(J = 6.1\) Hz, 1H), 7.35 – 7.30 (m, 8H), 7.25 – 7.20 (m, 2H), 7.03 (s, 1H), 4.38 (t, \(J = 7.8\) Hz, 1H), 4.19 – 4.14 (m, 2H), 4.06 (s, 3H), 4.01 (s, 3H), 4.01 (s, 3H); \(^1^3\)C NMR
(126 MHz, CDCl$_3$) 165.3, 155.4, 148.8, 148.1, 144.7, 142.4, 142.2, 128.8, 128.3, 128.0, 127.2, 126.8, 114.8, 101.6, 61.9, 61.4, 56.3, 51.0, 44.1; HRMS (ESI) m/z calculated for C$_{27}$H$_{27}$N$_2$O$_4$ [M+H]$^+$: 443.1965; found [M+H]$^+$: 443.1957.

$N$-((1S,3S)-adamantan-1-yl)-5,6,7-trimethoxyisoquinoline-3-carboxamide (F13)

White solid (229 mg, 58% yield), M.P.= 167 – 169 °C; $^1$H NMR (500 MHz, CDCl$_3$) δ 8.92 (s, 1H), 8.73 (s, 1H), 8.01 (s, 1H), 7.07 (s, 1H), 4.04 (s, 3H), 4.02 (s, 6H), 2.21 (d, $J$ = 2.8 Hz, 6H), 2.17 – 2.12 (m, 3H), 1.84 – 1.66 (m, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 164.1, 155.2, 148.5, 148.1, 144.8, 143.3, 128.2, 127.0, 114.3, 101.6, 61.9, 61.4, 56.3, 51.7, 41.8, 36.6, 29.7; HRMS (ESI) m/z calculated for C$_{23}$H$_{29}$N$_2$O$_4$ [M+H]$^+$: 397.2122; found [M+H]$^+$: 397.2117.

$N$-(4-chlorobenzyl)-5,7-dimethoxyisoquinoline-3-carboxamide (F15)

Color-less semi-solid (213 mg, 60% yield); $^1$H NMR (500 MHz, CDCl$_3$) δ 8.91 (s, 1H), 8.86 (s, 1H), 8.49 (t, $J$ = 6.2 Hz, 1H), 7.34 – 7.27 (m, 4H), 6.81 (d, $J$ = 2.1 Hz, 1H), 6.66 (d, $J$ = 2.1 Hz, 1H), 4.67 (d, $J$ = 6.2 Hz, 2H), 3.97 (s, 3H), 3.93 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 165.2, 160.9, 157.1, 149.0, 141.5, 137.3, 133.2, 131.7, 129.3, 128.8, 125.0, 115.7, 102.1, 102.0, 96.9, 96.8, 55.9, 55.8. 42.9; HRMS (ESI) m/z calculated for C$_{19}$H$_{18}$ClN$_2$O$_3$ [M+H]$^+$: 357.1001; found [M+H]$^+$: 357.1001.

$N$-cyclohexyl-6,7-dimethoxyisoquinoline-3-carboxamide (H13)

White solid (198 mg, 63% yield), M.P.= 179 – 180 °C; $^1$H NMR (500 MHz, CDCl$_3$) δ 8.89 (s, 1H), 8.43 (s, 1H), 8.08 (d, $J$ = 8.6 Hz, 1H), 7.21 (s, 1H), 7.16 (s, 1H), 4.01 (s, 3H), 4.01 (s, 3H), 4.00 – 3.96 (m, 1H), 2.07 – 1.97 (m, 2H), 1.80 – 1.73 (m, 2H), 1.67 – 1.60 (m, 1H), 1.47 – 1.37 (m, 2H), 1.37 – 1.28 (m, 2H), 1.26 – 1.18 (m, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 164.2, 153.4, 151.5, 148.3, 143.1, 132.8, 126.0, 119.0, 106.0, 105.4, 57.3, 56.2, 48.2, 33.3, 25.7, 25.0; HRMS (ESI) m/z calculated for C$_{18}$H$_{23}$N$_2$O$_3$ [M+H]$^+$: 315.1702; found [M+H]$^+$: 315.1702.

$N$-(benzo[d][1,3]dioxol-5-ylmethyl)-5,6,7-trimethoxyisoquinoline-3-carboxamide (I6)

Light yellow solid (221 mg, 56% yield), M.P.= 123 – 125 °C; $^1$H NMR (500 MHz, CDCl$_3$) δ 8.92 (s, 1H), 8.79 (s, 1H), 8.44 (t, $J$ = 6.2 Hz, 1H), 7.07 (s, 1H), 6.90 (d, $J$ = 1.7 Hz, 1H), 6.87 – 6.84 (m, 1H), 6.77 (d, $J$ = 7.9 Hz, 1H), 5.93 (s, 2H), 4.62 (d, $J$ = 6.0 Hz, 2H), 4.07 (s, 3H), 4.02 (d, $J$ = 2.1 Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 165.1, 155.5, 148.8, 148.1, 148.0, 147.0, 144.8, 142.1, 132.6, 128.0, 127.2, 121.3, 115.1, 108.7, 108.4, 101.6, 101.1, 61.9, 61.4, 56.3, 43.5; HRMS (ESI) m/z calculated for C$_{21}$H$_{21}$N$_2$O$_6$ [M+H]$^+$: 397.1394; found [M+H]$^+$: 397.1390.

5,6,7-Trimethoxy-N-(thiophen-2-ylmethyl)isoquinoline-3-carboxamide (I17)
White solid (175 mg, 49% yield), M.P. = 115 – 117 °C; \( ^1 \)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 8.92 (d, \( J = 0.9 \) Hz, 1H), 8.80 (s, 1H), 8.51 (t, \( J = 6.1 \) Hz, 1H), 7.24 – 7.22 (m, 1H), 7.08 – 7.05 (m, 2H), 6.98 – 6.95 (m, 1H), 4.90 – 4.86 (m, 2H), 4.07 (s, 3H), 4.02 (d, \( J = 1.7 \) Hz, 6H); \( ^13 \)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 165.0, 155.5, 148.9, 148.1, 144.7, 142.0, 141.3, 128.0, 127.3, 127.0, 126.2, 125.2, 115.2, 101.6, 61.9, 61.4, 56.3, 38.4; HRMS (ESI) m/z calculated for C\(_{18}\)H\(_{19}\)N\(_2\)O\(_4\)S [M+H]\(^+\): 359.1060; found [M+H]\(^+\): 359.1057.

5,6,7-Trimethoxy-N-(2,4,4-trimethylpentan-2-yl)isoquinoline-3-carboxamide (J3)

Color-less semi-solid (127 mg, 34% yield); \( ^1 \)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 8.91 (s, 1H), 8.74 (s, 1H), 8.22 (s, 1H), 7.05 (s, 1H), 4.03 (s, 3H), 4.01 (d, \( J = 1.2 \) Hz, 6H), 1.91 (s, 2H), 1.58 (s, 6H), 1.03 (s, 9H); \( ^13 \)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 164.08, 155.20, 148.58, 148.10, 144.70, 143.33, 128.18, 126.97, 114.16, 101.57, 77.36, 61.85, 61.36, 56.27, 54.79, 51.98, 31.85, 31.62, 29.42; HRMS (ESI) m/z calculated for C\(_{21}\)H\(_{31}\)N\(_2\)O\(_4\) [M+H]\(^+\): 375.2278; found [M+H]\(^+\): 375.2279.

N-(tert-butyl)-6,7-dimethoxyisoquinoline-3-carboxamide (J9)

White solid (78 mg, 27% yield), M.P. = 188 – 190 °C; \( ^1 \)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 8.89 (s, 1H), 8.41 (s, 1H), 8.14 (s, 1H), 7.22 (s, 1H), 7.16 (s, 1H), 4.03 (s, 6H), 1.52 (s, 9H); \( ^13 \)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 164.4, 153.4, 151.5, 148.1, 143.7, 132.9, 125.9, 118.4, 106.0, 105.4, 56.3, 56.2, 50.9, 29.0; HRMS (ESI) m/z calculated for C\(_{16}\)H\(_{21}\)N\(_2\)O\(_3\) [M+H]\(^+\): 289.1547; found [M+H]\(^+\): 289.1547.

Methyl (5,6,7-trimethoxyisoquinoline-3-carbonyl)leucinate (J18)

Color-less semi-solid (129 mg, 33% yield); \( ^1 \)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 8.97 (s, 1H), 8.75 (s, 1H), 8.48 (d, \( J = 8.7 \) Hz, 1H), 7.08 (s, 1H), 4.96 – 4.84 (m, 1H), 4.04 (s, 3H), 4.02 (s, 3H), 3.76 (s, 3H), 1.87 – 1.69 (m, 3H), 1.00 (d, \( J = 6.0 \) Hz, 3H), 0.98 (d, \( J = 6.0 \) Hz, 3H); \( ^13 \)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 173.5, 164.9, 155.4, 148.0, 144.6, 141.6, 127.8, 127.2, 115.1, 101.6, 61.8, 61.3, 56.2, 52.3, 50.8, 41.8, 25.0, 23.0, 21.9; HRMS (ESI) m/z calculated for C\(_{20}\)H\(_{27}\)N\(_2\)O\(_6\) [M+H]\(^+\): 391.1864; found [M+H]\(^+\): 391.1867.

Methyl (6,7-dimethoxyisoquinoline-3-carbonyl) glycinate (K5)

Yellow solid (106 mg, 35% yield), M.P. = 197 – 198 °C; \( ^1 \)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 8.95 (s, 1H), 8.61 (t, \( J = 5.7 \) Hz, 1H), 8.44 (s, 1H), 7.25 (s, 1H), 7.19 (s, 1H), 4.32 (d, \( J = 5.7 \) Hz, 2H), 4.05 (s, 3H), 4.04 (s, 3H), 3.80 (s, 3H); \( ^13 \)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 170.5, 165.6, 153.6, 151.8, 148.7, 142.2, 132.7, 126.3, 119.3, 106.1, 105.5, 56.4, 56.3, 52.5, 41.5; HRMS (ESI) m/z calculated for C\(_{15}\)H\(_{17}\)N\(_2\)O\(_3\) [M+H]\(^+\): 305.1132; found [M+H]\(^+\): 305.1132.
5,7-Dimethoxy-\(N\)-((tetrahydrofuran-2-yl)methyl)isoquinoline-3-carboxamide (K8)

White solid (123 mg, 39% yield), M.P. = 119 – 121 °C; \(^1^H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.94 (s, 1H), 8.81 (s, 1H), 8.44 (t, \(J = 6.1\) Hz, 1H), 6.81 (d, \(J = 2.4\) Hz, 1H), 6.64 (d, \(J = 2.1\) Hz, 1H), 4.17 – 4.05 (m, 1H), 3.96 (s, 3H), 3.93 (s, 3H), 3.84 – 3.71 (m, 2H), 3.51 – 3.40 (m, 1H), 2.11 – 1.98 (m, 1H), 1.98 – 1.85 (m, 2H), 1.75 – 1.58 (m, 1H); \(^1^C\) NMR (126 MHz, CDCl\(_3\)) \(\delta\) 165.4, 160.7, 157.0, 149.0, 141.8, 131.6, 125.0, 115.4, 102.0, 96.9, 78.0, 68.3, 55.9, 55.7, 43.3, 28.9, 26.0; HRMS (ESI) m/z calculated for C\(_{17}\)H\(_{21}\)N\(_2\)O\(_4\) [M+H]\(^+\): 317.1496; found [M+H]\(^+\): 317.1497.

\(N\)-(2,2-diphenylethyl)thieno[3,2-c]pyridine-6-carboxamide (K21)

Yellow solid (182 mg, 51% yield), M.P. = 175 – 177 °C; \(^1^H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.89 (s, 1H), 8.72 (s, 1H), 8.23 (t, \(J = 6.2\) Hz, 1H), 7.64 – 7.58 (m, 1H), 7.45 (d, \(J = 5.4\) Hz, 1H), 7.35 – 7.29 (m, 8H), 7.27 – 7.19 (m, 2H), 4.38 (t, \(J = 7.8\) Hz, 1H), 4.21 – 4.13 (m, 2H); \(^1^C\) NMR (126 MHz, CDCl\(_3\)) \(\delta\) 164.7, 148.0, 144.0, 143.4, 142.2, 137.5, 130.5, 128.8, 128.2, 126.8, 122.5, 122.4, 116.7, 50.9, 44.1; HRMS (ESI) m/z calculated for C\(_{22}\)H\(_{19}\)N\(_2\)OS [M+H]\(^+\): 359.1213; found [M+H]\(^+\): 359.1212.

Methyl 6-(5,7-dimethoxyisoquinoline-3-carboxamido)hexanoate (L7)

Color-less semi-solid (94 mg, 26% yield); \(^1^H\) NMR (500 MHz, CDCl\(_3\)) \(^1^H\) NMR (500 MHz, Chloroform-d) \(\delta\) 8.94 (s, 1H), 8.83 (s, 1H), 8.15 (s, 1H), 6.83 (s, 1H), 6.67 (s, 1H), 6.37 (s, 1H), 5.95 (s, 3H), 3.66 (s, 3H), 3.55 – 3.49 (m, 2H), 2.33 (t, \(J = 7.5\) Hz, 2H), 1.74 – 1.64 (m, 4H), 1.49 – 1.41 (m, 2H); \(^1^C\) NMR (126 MHz, CDCl\(_3\)) \(\delta\) 174.2, 165.2, 160.8, 157.1, 148.9, 141.9, 131.6, 125.1, 115.4, 102.1, 96.9, 55.9, 51.7, 39.3, 34.1, 29.7, 26.7, 24.8; HRMS (ESI) m/z calculated for C\(_{19}\)H\(_{25}\)N\(_2\)O\(_5\) [M+H]\(^+\): 361.1758; found [M+H]\(^+\): 361.1756.

\(N\)-benzyl-6,7-dimethoxyisoquinoline-3-carboxamide (M17)

Grey solid (206 mg, 64% yield), M.P. = 160 – 162 °C; \(^1^H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.90 (s, 1H), 8.58 – 8.46 (m, 2H), 7.43 – 7.27 (m, 5H), 7.23 (s, 1H), 7.20 (s, 1H), 4.72 (d, \(J = 6.0\) Hz, 2H), 4.04 (s, 3H), 3.70 (s, 3H); \(^1^C\) NMR (126 MHz, CDCl\(_3\)) \(\delta\) 165.2, 153.5, 151.7, 148.5, 142.7, 138.6, 132.8, 128.8, 128.0, 127.5, 126.2, 119.3, 106.1, 105.5, 56.4, 56.3, 43.7; HRMS (ESI) m/z calculated for C\(_{19}\)H\(_{19}\)N\(_2\)O\(_3\) [M+H]\(^+\): 323.1390; found [M+H]\(^+\): 323.1390.

\(N\)-(4-chlorobenzyl)thieno[3,2-c]pyridine-6-carboxamide (N15)
White solid (129 mg, 43% yield), M.P.= 129 – 131 °C; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 8.99 (d, \textit{J} = 1.0 Hz, 1H), 8.77 (s, 1H), 8.53 (s, 1H), 7.66 (d, \textit{J} = 5.4 Hz, 1H), 7.56 – 7.46 (m, 1H), 7.32 – 7.30 (m, 4H), 4.67 (d, \textit{J} = 6.2 Hz, 2H); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) δ 164.7, 148.2, 144.0, 143.2, 137.7, 137.1, 133.3, 130.7, 130.5, 129.3, 128.9, 122.6, 122.5, 117.0, 43.0; HRMS (ESI) m/z calculated for C\textsubscript{15}H\textsubscript{12}ClN\textsubscript{2}O\textsubscript{3} [M+H]\textsuperscript{+}: 303.0353; found [M+H]\textsuperscript{+}: 303.0354.

\textit{N}-benzylthieno[3,2-c]pyridine-6-carboxamide (O11)

White solid (134 mg, 50% yield), M.P.= 100 – 102 °C; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 9.0 (d, \textit{J} = 0.9 Hz, 1H), 8.8 (s, 1H), 8.5 (s, 1H), 7.7 (d, \textit{J} = 5.4 Hz, 1H), 7.5 – 7.5 (m, 1H), 7.4 – 7.4 (m, 2H), 7.4 – 7.3 (m, 2H), 7.3 – 7.3 (m, 1H), 4.7 (d, \textit{J} = 6.1 Hz, 2H); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) δ 164.7, 148.2, 144.0, 143.5, 138.5, 137.6, 130.6, 130.4, 128.9, 128.1, 127.6, 122.6, 122.4, 117.0, 43.8; HRMS (ESI) m/z calculated for C\textsubscript{15}H\textsubscript{13}N\textsubscript{2}O\textsubscript{3} [M+H]\textsuperscript{+}: 269.0743; found [M+H]\textsuperscript{+}: 269.0743.

\textit{N}-phenethylthieno[3,2-c]pyridine-6-carboxamide (P8)

White solid (149 mg, 53% yield), M.P.= 108 – 109 °C; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 8.98 (d, \textit{J} = 0.9 Hz, 1H), 8.75 (d, \textit{J} = 1.0 Hz, 1H), 8.28 (s, 1H), 7.65 (d, \textit{J} = 5.5 Hz, 1H), 7.51 – 7.49 (m, 1H), 7.35 – 7.22 (m, 5H), 3.82 – 3.73 (m, 2H), 2.98 (t, \textit{J} = 7.3 Hz, 2H); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) δ 164.7, 148.1, 144.0, 143.6, 139.2, 137.6, 130.5, 128.9, 128.7, 126.6, 122.5, 116.7, 41.0, 36.1; HRMS (ESI) m/z calculated for C\textsubscript{16}H\textsubscript{15}N\textsubscript{2}O\textsubscript{3} [M+H]\textsuperscript{+}: 283.0900; found [M+H]\textsuperscript{+}: 283.0899.
6.3. $^1$H and $^{13}$C NMR spectra, HRMS

$N$-((1S,3s)-adamantan-1-yl)thieno[3,2-c]pyridine-6-carboxamide (A3)
Chemical Formula: C_{16}H_{28}N_{2}OS
Exact Mass: 312.1296
Molecular Weight: 312.4310
N-cyclohexylthieno[3,2-c]pyridine-6-carboxamide (A13)
18mdv071-yz478C #12 RT: 0.20842 A
T: FTMS + p ESI Full ms [220.00-1000.00]
261.10577

Chemical Formula: C_{14}H_{10}N_{2}O_{2}
Exact Mass: 260.0983
Molecular Weight: 260.3550
5,6,7-Trimethoxy-N-phenethylisoquinoline-3-carboxamide (A22)
5,7-Dimethoxy-\(N\)-phenethylisoquinoline-3-carboxamide (B5)
Chemical Formula: C_{20}H_{20}N_{2}O_{3}
Exact Mass: 336.15
Molecular Weight: 336.39
5,8-Dimethoxy-N-phenethylisoquinoline-3-carboxamide (B16)
Chemical Formula: C_{20}H_{20}N_{2}O_{3}
Exact Mass: 336.1474
Molecular Weight: 336.3910
$N$-(4-(benzyloxy)benzyl)-5,6,7-trimethoxyisoquinoline-3-carboxamide (B24)
Chemical Formula: C<sub>27</sub>H<sub>26</sub>N<sub>2</sub>O<sub>5</sub>
Exact Mass: 458.1842
Molecular Weight: 458.5140
6,7-Dimethoxy-N-phenethylisoquinoline-3-carboxamide (C2)
Chemical Formula: C20H24N2O3
Exact Mass: 336.1474
Molecular Weight: 336.3910
7,8-Dimethoxy-N-phenethylisoquinoline-3-carboxamide (C10)
Chemical Formula: C_{26}H_{28}N_{2}O_{3}
Exact Mass: 336.1474
Molecular Weight: 336.3910
$N$-phenethyl-$[1,3]$dioxolo$[4,5-f]$isoquinoline-$8$-carboxamide (D19)
Chemical Formula: C_{19}H_{16}N_{2}O_{3}
Exact Mass: 320.1161
Molecular Weight: 320.3480
$N$-(2-isopropylphenyl)-6,7-dimethoxyisoquinoline-3-carboxamide (E7)
**Chemical Formula:** C_{21}H_{25}N_{2}O_{3}  
**Exact Mass:** 350.1630  
**Molecular Weight:** 350.4180
$N$-benzyl-$5,7$-dimethoxyisoquinoline-$3$-carboxamide (E12)
Chemical Formula: C_{16}H_{18}N_2O_3

Exact Mass: 322.13
Molecular Weight: 322.36
N-(2-ethyl-6-methylphenyl)-6,7-dimethoxyisoquinoline-3-carboxamide (E17)
Chemical Formula: C₂₃H₂₃N₂O₃
Exact Mass: 350.1630
Molecular Weight: 350.4180
N-(2,2-diphenylethyl)-5,6,7-trimethoxyisoquinoline-3-carboxamide (F8)
17mdv207-yz444c #280  RT: 5.25  AV: 1  NL: 2.69E8
T: FTMS + p ESI Full ms [200.00-800.00]

Chemical Formula: C_{21}H_{24}N_{2}O_{4}
Exact Mass: 442.1893
Molecular Weight: 442.5150
$N$-((1s,3s)-adamantan-1-yl)-5,6,7-trimethoxyisoquinoline-3-carboxamide (F13)
17mdv207-yz450c #283  RT: 5.69  AV: 1  NL: 1.25E7
T: FTMS + p ESI Full ms [200.00-800.00]

Chemical Formula: C₃₅H₂₈N₂O₆
Exact Mass: 396.2049
Molecular Weight: 396.4870
N-(4-chlorobenzyl)-5,7-dimethoxyisoquinoline-3-carboxamide (F15)
Chemical Formula: C_{19}H_{17}ClN_{2}O_{3}  
Exact Mass: 356.0928  
Molecular Weight: 356.8060
N-cyclohexyl-6,7-dimethoxyisoquinoline-3-carboxamide (H13)
Chemical Formula: C_{14}H_{22}N_{2}O_{3}
Exact Mass: 314.1630
Molecular Weight: 314.3850
N-(benzo[d][1,3]dioxol-5-ylmethyl)-5,6,7-trimethoxyisoquinoline-3-carboxamide (16)
Chemical Formula: C_{21}H_{29}N_{5}O_{6}
Exact Mass: 396.1321
Molecular Weight: 396.3990
5,6,7-Trimethoxy-N-(thiophen-2-ylmethyl)isoquinoline-3-carboxamide (I17)
17mdv207-yz443c #217  RT: 4.55  AV: 1  NL: 8.98E6
T: FTMS + p ESI Full ms [200.00-800.00]

Chemical Formula: C_{18}H_{19}N_{2}O_{5}S
Exact Mass: 358.0987
Molecular Weight: 358.4120
5,6,7-Trimethoxy-N-(2,4,4-trimethylpentan-2-yl)isoquinoline-3-carboxamide (J3)
**Chemical Formula:** C_{21}H_{12}N_{2}O_{4}

**Exact Mass:** 374.2206

**Molecular Weight:** 374.4810
$N$-(tert-butyl)-6,7-dimethoxyisoquinoline-3-carboxamide (J9)
Chemical Formula: C_{14}H_{19}N_{2}O_{3}

Exact Mass: 288.1474

Molecular Weight: 288.3470
Methyl (5,6,7-trimethoxyisoquinoline-3-carbonyl)leucinate (J18)
Chemical Formula: $C_{20}H_{26}N_2O_6$

Exact Mass: 390.18

Molecular Weight: 390.44
Methyl (6,7-dimethoxyisoquinoline-3-carbonyl) glycinate (K5)
Chemical Formula: C₁₅H₁₆N₂O₅
Exact Mass: 304.11
Molecular Weight: 304.30
5,7-Dimethoxy-N-((tetrahydrofuran-2-yl)methyl)isoquinoline-3-carboxamide (K8)
N-(2,2-diphenylethyl)thieno[3,2-c]pyridine-6-carboxamide (K21)
Chemical Formula: C_{29}H_{23}N_2O_S
Exact Mass: 358.1140
Molecular Weight: 358.4590
Methyl 6-(5,7-dimethoxyisoquinoline-3-carboxamido)hexanoate (L7)
Chemical Formula: C_{19}H_{24}N_{2}O_{5}
Exact Mass: 360.17
Molecular Weight: 360.41
N-benzyl-6,7-dimethoxyisoquinoline-3-carboxamide (M17)
Chemical Formula: C_{18}H_{19}N_{2}O_{3}
Exact Mass: 322.1317
Molecular Weight: 322.3640
$N$-(4-chlorobenzyl)thieno[3,2-$c$]pyridine-6-carboxamide (N15)
Chemical Formula: C_{11}H_{11}ClN_{3}OS
Exact Mass: 302.0281
Molecular Weight: 302.7760
N-benzylthieno[3,2-c]pyridine-6-carboxamide (O11)

![Chemical Structure](image)
Chemical Formula: C_{18}H_{13}N_{2}OS
Exact Mass: 268.0670
Molecular Weight: 268.3340
N-phenethylthieno[3,2-c]pyridine-6-carboxamide (P8)
Chemical Formula: C_{14}H_{14}N_{2}OS
Exact Mass: 282.0827
Molecular Weight: 282.3610
7. Gram scale reaction procedure for the synthesis of 6,7-dimethoxy-N-phenethylisoquinoline-3-carboxamide

A round-bottomed flask (100 mL) equipped with a Teflon-coated magnetic stir bar was charged with 2,2-dimethoxyacetaldehyde (4.52 mL, 30 mmol) and 3,4-dimethoxybenzylamine (5.01 g, 30 mmol) in MeOH (20 mL). The reaction mixture was stirred at room temperature for 20 min, then, benzoic acid (3.66 g, 30 mmol) and phenylethylisocyanide (3.93 g, 30 mmol) were added. The reaction mixture was stirred at room temperature for 15 h. Upon completion, the solvent was removed under vacuum. Then, the reaction mixture was dissolved in dioxane (15 mL) and 37% HCl\textsubscript{(aq)} (15 mL) was added dropwise via a pressure equalizing dropping funnel (60 mL). The reaction mixture was stirred at room temperature for 12 h. The precipitated product was dried under vacuum. Then, it was dissolved in dichloromethane (100 mL), transferred to a separatory funnel (250 mL), washed with saturated NaHCO\textsubscript{3} solution (3 x 50 mL), water (1 x 50 mL), brine (1 x 50 mL) and dried over MgSO\textsubscript{4}. The solvent was removed under vacuum and the crude product was washed with cold tert-butyl methyl ether (7.26 g, yield: 72%, Fig. S4). The purity of the obtained product was determined by qHNMR using benzyl benzoate as internal standard.

![Fig. S4. Multi-gram synthesis.](image)

7.1. qHNMR

For the \textsuperscript{1}H NMR experiment, 42.10 mg (~1/8 mmol) of the gram scale reaction sample and 28.67 mg (~1/8 mmol) of the internal standard were dissolved in CDCl\textsubscript{3}.

The following equation was used for quantification:\textsuperscript{9}

\[
P_x = \frac{I_x N_{\text{std}}}{I_{\text{std}} N_x} \frac{M_x}{m_{\text{std}}} P_{\text{std}} = \frac{3.184336.3928.67}{3.8542122542.10} 100 = 89\%
\]

where \(I_x\) and \(I_{\text{std}}\) correspond to the integrated signal area of the NMR line of the sample and standard, respectively. \(N, M, m\) and \(P\) are number of spins (protons), molecular mass, weighed mass and the purity, respectively.
7.2. $^1$H and $^{13}$C NMR spectra of gram scale reaction
7.3. qHNMR spectrum of gram scale reaction

8. Crystal structure determination

X-ray diffraction data for single crystals of compounds A3, B5 and K21 were collected using SuperNova (Rigaku - Oxford Diffraction) four circle diffractometer with a mirror monochromator and a microfocus MoKα radiation source (λ = 0.71073 Å) which was used for monocrystals of A3 and K21. Additionally, the diffractometer was equipped with a CryoJet HT cryostat system (Oxford Instruments) allowing low temperature experiments, performed at 130(2) K. The obtained data sets were processed with CrysAlisPro software. The phase problem was solved with direct methods using SIR2004 or SUPERFLIP. Parameters of obtained models were refined by full-matrix least-squares on F² using SHELXL-2014/6. Calculations were performed using WinGX integrated system (ver. 2014.1). Figure was prepared with Mercury 3.7 software.

All non-hydrogen atoms were refined anisotropically. All hydrogen atoms attached to carbon atoms were positioned with the idealised geometry and refined using the riding model with the isotropic displacement parameter U_{iso}[H] = 1.2 U_{eq}[C]. The difference Fourier map was inspected in order to find position of hydrogens linked to nitrogen atoms. These hydrogen atoms were refined with no restraints on the isotropic displacement parameters. Crystal data and structure refinement results for presented crystal structures are shown in Table S3. The molecular geometry (asymmetric units) observed in presented crystal structures are shown in Fig. S5.
Crystals of compound A3 exhibited the twinning phenomena. Obtained data show the two-component twin with approximately 52% and 48% of component 1 and component 2, respectively. Data was processed with twin option of the CrysAlisPro software. The obtained model was refined against HKLF4.

Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos.: CCDC1828773 (B5), CCDC1827864 (K21) and CCDC1827863 (A3). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

**Fig. S5.** Molecular geometry observed in crystal structures of compounds B5, K21 and A3, showing the atom labelling scheme (here asymmetric units are presented except for B5, for which three independent molecules are observed in the asymmetric unit). Displacement ellipsoids of non-hydrogen atoms are drawn at the 30% probability level. H atoms are presented as small spheres with an arbitrary radius.
Table S3. Crystal data and structure refinement results for compounds B5, K21 and A3.

|                  | B5                      | K21                     | A3                      |
|------------------|-------------------------|-------------------------|-------------------------|
| Empirical moiety formula | 3x (C_{20}H_{20}N_{2}O_{3}) | C_{22}H_{18}N_{2}S | C_{18}H_{20}N_{2}O_{3} |
| Formula weight [g/mol]   | 336.38                  | 358.44                  | 312.42                  |
| Crystal system         | Monoclinic              | Monoclinic              | Monoclinic              |
| Space group            | P2_1/a                  | P2_1/n                  | P2_1/c                  |
| Unite cell dimensions | a = 9.3950(4) Å, b = 43.7250(14) Å, c = 12.6567(4) Å, β = 96.256(3)° | a = 8.9525(2) Å, b = 19.7350(4) Å, c = 10.1928(3) Å, β = 100.181(2)° | a = 11.8199(10) Å, b = 11.5116(6) Å, c = 11.5293(9) Å, β = 101.081(9)° |
| Volume [Å^3]          | 5168.4(3)               | 1772.48(8)              | 1539.5(2)               |
| Z                  | 12                      | 4                       | 4                       |
| D_cal [Mg/m^3]       | 1.297                   | 1.343                   | 1.348                   |
| μ [mm⁻¹]            | 0.088                   | 0.196                   | 0.214                   |
| F(000)              | 2136                    | 752                     | 664                     |
| Crystal size [mm³]   | 0.4 x 0.3 x 0.1          | 0.5 x 0.3 x 0.1          | 0.5 x 0.5 x 0.1          |
| Θ range             | 2.83° to 28.57°          | 2.90° to 28.60°         | 3.27° to 28.67°         |
| Index ranges        | -12 ≤ h ≤ 7, -57 ≤ k ≤ 54, -16 ≤ l ≤ 15 | -11 ≤ h ≤ 12, -25 ≤ k ≤ 25, -11 ≤ l ≤ 13 | -13 ≤ h ≤ 14, -15 ≤ k ≤ 9, -14 ≤ l ≤ 14 |
| Refl. collected      | 33394                   | 14761                   | 8756                    |
| Independent reflections | 12007 / [R(int) = 0.0298] | 4168 / [R(int) = 0.0370] | 2885 / [R(int) = 0.1021] |
| Completeness [%] to Θ | 99.7 (Θ 26.3°)          | 99.9 (Θ 25.2°)         | 98.7 (Θ 25.0°)          |
| Absorption correction | Multi-scan             | Multi-scan              | Multi-scan              |
| Tmin. and Tmax.      | 0.872 and 1.000          | 0.757 and 1.000         | 0.784 and 1.000         |
| Data/ restraints/parameters | 12007 / 0 / 683         | 4168 / 6 / 239          | 2885 / 0 / 203          |
| GooF on F2           | 1.062                   | 1.040                   | 1.049                   |
| Final R indices      | R1= 0.0534, wR2= 0.1157 | R1= 0.0405, wR2= 0.0860 | R1= 0.0548, wR2= 0.1388 |
| R indices (all data) | R1= 0.0777, wR2= 0.1296 | R1= 0.0667, wR2= 0.0995 | R1= 0.0629, wR2= 0.1464 |
| Δρ_{max}, Δρ_{min} [e·Å⁻³] | 0.25 and -0.20          | 0.29 and -0.30          | 0.38 and -0.45          |
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