Impact of Stereospecific Intramolecular Hydrogen-Bonding on Cell Permeability

Supporting Information

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Methods

Extended Computational Details

Conformations for the ammonium and neutral amines were generated using the LowModeMD method in MOE 2012, an exhaustive method that took on average 1 hour for compounds 1 and 8 using a criteria of keeping unique conformations within 5 kcal/mol (maintained throughout the simulation such that any conformations above the criterion are automatically discarded) and ended only after 50 consecutive, non-unique conformers are generated. The MMFFs force field was used for energy calculations. The conformations in the lowest 3 kcal/mol were minimized using MMFFs with GBSA and clustered using the Schrodinger Suite 2012 (Update 2) MacroModel and Canvas packages. The lowest energy conformation of each cluster and the lowest 1 kcal/mol were optimized using B3LYP/6-31G* with and without Poisson Boltzmann Finite Element (PBF) solvation. Both methods provided extremely similar geometries, particularly for the lowest energy structure.

Free energy was determined from the lowest energy conformation at B3LYP/6-31G* for the amines and the ammonium ions of 1 and 8 using B3LYP/6-31G* unscaled frequency calculations calculated at 298K. Single-point free energy of solvation was calculated on these geometries using both the Poisson Boltzmann Finite Element (PBF) and SM8 continuum solvation method as implemented in Jaguar version 8.5. The calculated values for these 4 species are given in Table SI 2 for ΔG\text{gas} and Table SI 3 for ΔG\text{solv}. Table 3 in the manuscript reflects the sum of the difference in gas phase free energy and free energy of solvation of the amine and ammonium diastereomers. A more typical thermodynamic cycle used for non-isomeric compounds is detailed in the next section. As noted in the main text, the PBF and SM8 solvation models give fairly different free energies of solvation: 3.1 kcal/mol for SM8 vs. 1.6 for PBF for the amines and -4.9 vs. -1.2 kcal/mol for the ammonium ions). This difference is consistent with previous publications (e.g. Marenich et al. J Chem. Theory Comput. 2007, 3, 2011-2033) though it would be expected to be less significant for diastereomers. The solvation energies alter the predicted pKa difference from the gas phase free energy in the same direction.
Relative pKa calculation using a typical thermodynamic cycle

A thermodynamic cycle often used for calculating pKa is the following as reviewed in Toth et al. *J. Chem. Phys.* 2001, 114, 4595-4606:

\[
\text{AH}^+ \ (\text{gas}) \rightarrow A: \ (\text{gas}) + \ H^+ \ (\text{gas}) \quad \Delta G_{\text{gas}} \\
\downarrow \Delta G_{\text{sol,AH}^+} \quad \downarrow \Delta G_{\text{sol,A:}} \quad \downarrow \Delta G_{\text{sol,H}^+} \\
\text{AH}^+ \ (\text{aq}) \rightarrow A: \ (\text{aq}) + \ H^+ \ (\text{aq}) \quad \Delta G_{\text{aq}}
\]

(1) \(\Delta G_{\text{aq}} = \Delta G_{\text{gas}} + \Delta G_{\text{sol,A:}} + \Delta G_{\text{sol,H}^+} - \Delta G_{\text{sol,AH}^+}\)

(2) \(\Delta G_{\text{gas}} = \Delta G_{\text{gas,A:}} + \Delta G_{\text{gas,H}^+} - \Delta G_{\text{gas,AH}^+}\)

(3) \(\Delta G_{\text{aq}} = -RT \ln K_a = RT \ln 10 \ pK_a = (298 \cdot 8.31 \cdot 2.3025 / 4.184 / 1000) \ pK_a = 1.36 \ \text{kcal/mol} \cdot \ pK_a\)

For relative pKa calculations, the free energy of the proton is not necessary in the calculation of the free energy cycle, which cannot be calculated using quantum mechanics calculations. For the difference in pKa between two compounds, 1 and 8, we have:

(4) \(\Delta G_{\text{aq,8}} - \Delta G_{\text{aq,1}} = (\Delta G_{\text{gas,8,amine}} - \Delta G_{\text{gas,1,amine}}) - (\Delta G_{\text{gas,8,ammonium}} - \Delta G_{\text{gas,1,ammonium}}) + (\Delta G_{\text{sol,8,amine}} - \Delta G_{\text{sol,1,amine}}) - (\Delta G_{\text{sol,8,ammonium}} - \Delta G_{\text{sol,1,ammonium}})\)

(5) \(\Delta \Delta \text{pKa (8-1)} = (\Delta G_{\text{aq,8}} - \Delta G_{\text{aq,1}}) / 1.36 \ \text{kcal/mol}\)

Using this equation, a pKa difference identical to experiment was obtained. This level of agreement was unexpected but the accuracy is greatly helped by studying diastereomers.
**Supporting Tables**

**Table SI 1:** Overview on LogD and solubility data.

| Cmpd | C8C9C25 | LogD | Solubility |
|------|---------|------|------------|
| 1    | SSS     | 4.5  | 1          |
| 2    | RRS     | 4.3  | 1          |
| 3    | SSR     | 4.5  | 2          |
| 4    | RRR     | 4.5  | 1          |
| 5    | SRR     | 3.5  | 86         |
| 6    | RSS     | 3.6  | 93         |
| 7    | RSR     | 3.8  | 98         |
| 8    | SRS     | 3.9  | 87         |
| 9    | SRS-Nmet| 3.75 | 64         |
| 10   | SSS-Nmet| 3.55 | 93         |

**Table SI 2:** Calculated values for the thermodynamic corrections for the lowest energy conformations of the amine and ammonium ions of 1 and 8 at 298K using B3LYP/6-31G* gas phase frequency calculation.

| Species  | Electronic energy | Zero point energy correction (kcal/mol) | Entropy correction (cal/mol/K) | Enthalpy correction (kcal/mol) | Free energy correction (kcal/mol) |
|----------|-------------------|----------------------------------------|------------------------------|-------------------------------|----------------------------------|
| 1, amine SSS | -1951.734437 | 428.605 | 239.284 | 25.228 | -46.115 |
| 8, amine SRS  | -1951.727094 | 428.922 | 233.708 | 24.515 | -45.165 |
| 1, ammonium  | -1952.129495 | 437.973 | 236.439 | 24.765 | -45.729 |
| 8, ammonium  | -1952.135224 | 438.010 | 231.867 | 24.666 | -44.465 |

**Table SI 3:** Calculated free energy of solvation ΔG_{sol} using continuum solvation models of the B3LYP/6-31G* optimized gas phase geometries.

| Species     | SM8 (kcal/mol) | Poisson Boltzmann Finite Element method (kcal/mol) |
|-------------|----------------|---------------------------------------------------|
| 1, amine SSS | -14.79        | -17.93                                           |
| 8, amine SRS | -17.86        | -19.54                                           |
| 1, ammonium  | -59.44        | -54.83                                           |
| 8, ammonium  | -54.54        | -53.66                                           |
Table SI 4: Overview on the Caco-2 permeability results in absorptive direction using two different apical pH 6.5 and 7.4. Average and Standarddeviation (Stdev) calculated based on 3 to 6 individual measurements.

| Cmpd | C8C9C25 | Papp AB [10⁻⁶ cm/s] (Average ± Stdev) | Mass Recovery [%] (Average ± Stdev) | pH (apical) | pH (basolateral) |
|------|---------|--------------------------------------|------------------------------------|-------------|------------------|
| 1    | SSS     | 63.8 ± 20.2                          | 81.7 ± 5.5                          | 6.5         | 7.4              |
| 1    | SSS     | 63.9 ± 15.7                          | 81.1 ± 5.2                          | 7.4         | 7.4              |
| 2    | RRS     | 63.3 ± 14.8                          | 84.6 ± 9.4                          | 6.5         | 7.4              |
| 2    | SRR     | 64.4 ± 7.7                           | 82.8 ± 3.1                          | 7.4         | 7.4              |
| 3    | SSR     | 64.6 ± 11.7                          | 82.2 ± 7.5                          | 6.5         | 7.4              |
| 3    | RSS     | 66.0 ± 10.2                          | 82.3 ± 3.1                          | 7.4         | 7.4              |
| 4    | RRR     | 65.3 ± 8.2                           | 82.8 ± 4.9                          | 6.5         | 7.4              |
| 4    | RRR     | 67.1 ± 6.7                           | 85.6 ± 4.9                          | 7.4         | 7.4              |
| 5    | SRR     | 15.5 ± 1.3                           | 75.2 ± 3.8                          | 6.5         | 7.4              |
| 5    | RRS     | 22.7 ± 1.7                           | 73.3 ± 1.2                          | 7.4         | 7.4              |
| 6    | RSS     | 20.1 ± 3.9                           | 88.3 ± 5.7                          | 6.5         | 7.4              |
| 6    | SSR     | 32.2 ± 4.0                           | 77.9 ± 4.4                          | 7.4         | 7.4              |
| 7    | RSR     | 24.1 ± 5.0                           | 83.4 ± 4.2                          | 6.5         | 7.4              |
| 7    | RSR     | 34.2 ± 1.6                           | 79.9 ± 4.0                          | 7.4         | 7.4              |
| 8    | SRS     | 21.8 ± 5.8                           | 74.4 ± 0.5                          | 6.5         | 7.4              |
| 8    | SRS     | 27.5 ± 2.5                           | 73.9 ± 1.5                          | 7.4         | 7.4              |
| 9    | SRS-Nmet | 15.2 ± 2.1                          | 74.5 ± 4.0                          | 6.5         | 7.4              |
| 9    | SRS-Nmet | 17.2 ± 4.5                          | 74.6 ± 1.8                          | 7.4         | 7.4              |
| 10   | SSS-Nmet | 15.2 ± 0.7                          | 77.6 ± 4.1                          | 6.5         | 7.4              |
| 10   | SSS-Nmet | 17.6 ± 1.8                          | 77.7 ± 1.9                          | 7.4         | 7.4              |
Table SI 5: Results of the Efflux-Ratio determination of 1-8.

| Cmpd | Efflux Ratio (Average ± Stdev) | Papp AB $[10^{-6} \text{ cm/s}]$ (Average ± Stdev) | Papp BA $[10^{-6} \text{ cm/s}]$ (Average ± Stdev) | Mass Recovery AB [%] (Average ± Stdev) | Mass Recovery BA [%] (Average ± Stdev) |
|------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| 1    | 0.36 ± 0.08                     | 56.4 ± 12.0                    | 19.1 ± 0.02                    | 49.5 ± 14.5                    | 58.5 ± 4.5                     |
| 2    | 0.1 ± 0.01                      | 70.5 ± 19.1                    | 7.1 ± 2.5                      | 70 ± 21                        | 13.5 ± 5.5                     |
| 3    | 0.42 ± 0.01                     | 26.2 ± 3.1                     | 10.9 ± 1.4                     | 35.5 ± 5.5                     | 61.5 ± 6.5                     |
| 4    | 0.31                            | 38.5                           | 10.9 ± 1.25                    | 60                             | 48 ± 5                         |
| 5    | 0.47 ± 0.04                     | 31.9 ± 0.3                     | 14.9 ± 1.4                     | 71.5 ± 2.5                     | 73.5 ± 3.5                     |
| 6    | 0.41 ± 0.02                     | 44.1 ± 0.4                     | 18.1 ± 0.6                     | 77 ± 3                         | 75.5 ± 3.5                     |
| 7    | 0.36 ± 0.03                     | 54.8 ± 2.2                     | 19.4 ± 0.5                     | 84.5 ± 2.5                     | 77.5 ± 1.5                     |
| 8    | 0.48 ± 0.07                     | 33.8 ± 1.5                     | 16.2 ± 1.7                     | 71.5 ± 1.5                     | 80 ± 3                         |
Supporting Figures

**Figure SI 1**: a) Solubility versus lipophilicity (logD) for compounds 1, 8-10. b) Permeability (Caco-2 Papp AB) versus lipophilicity (LogD) for 1, 8-10, determined with a pH gradient of 6.5 (apical) to 7.4 (basolateral, green/light blue squares) and with equal pH of 7.4 on both sides (orange/yellow diamonds), 9 and 10 are Amid-N-methylated versions of 8 and 1, respectively. Standard deviations are given as error bars.
**Figure SI 2:** a) Lipophilicity (LogD) versus solubility for compounds 1-8 (green), 2 series of reference compounds out of the Broad library (blue and yellow, *ACS Med. Chem. Lett.*, 2012, 3 (2), pp 112–117) and erythromycin. Compounds 1-4 show a significant higher LogD and lower solubility values. b) Lipophilicity (LogD) versus permeability for compounds 1-8 and the references. Compounds 1-4 show significant higher permeability and lipophilicity (Figure 1).
NMR data

Scheme SI 1: Structural formula of 1 with atom numbering used for NMR analysis.
Table SI 6: $^1$H, $^{13}$C and $^{15}$N chemical shifts of 1 and 8 in DMSO-$d_6$.

| Atom | Chemical Shift 1 | Chemical Shift 8 | $\Delta$1-8 | Atom | Chemical Shift 1 | Chemical Shift 8 | $\Delta$1-8 |
|------|------------------|------------------|-------------|------|------------------|------------------|-------------|
| C1   | 124.74           | 119.51           | 5.23       |     |                  |                  |             |
| H    | 7.25             | 6.97             | 0.28       |     |                  |                  |             |
| C2   | 123.1            | 126.3            | -3.2       |     |                  |                  |             |
| H    | 8.43             | 7.74             | 0.69       |     |                  |                  |             |
| C3   | 131.59           | 126.6            | 4.99       |     |                  |                  |             |
| C4   | 144.67           | 148.52           | -3.85      |     |                  |                  |             |
| C5   | 132.19           | 122.13           | 10.06      |     |                  |                  |             |
| C6   | 123.83           | 129.96           | -6.13      |     |                  |                  |             |
| H    | 7.1              | 7.28             | -0.18      |     |                  |                  |             |
| O7   |                  |                  |            |     |                  |                  |             |
| C8   | 85.69            | 74.56            | 11.13      |     |                  |                  |             |
| H    | 3.54             | 4.74             | -1.2       |     |                  |                  |             |
| C9   | 36.59            | 34.58            | 2.01       |     |                  |                  |             |
| H    | 1.83             | 2.12             | -0.29      |     |                  |                  |             |
| C10  | 49.63            | 47.79            | 1.84       |     |                  |                  |             |
| H2   | 3.12, 3.33       | 3.04, 3.32       | 0.08, 0.01 |     |                  |                  |             |
| C12  | 167.33           | 168.79           | -1.46      |     |                  |                  |             |
| O13  |                  |                  |            |     |                  |                  |             |
| C14  | 59.86            | 58.76            | 1.1        |     |                  |                  |             |
| H2   | 2.25, 2.70       | 2.56, 2.71       | 0.31, 0.01 |     |                  |                  |             |
| N11  | 132.93           | 126.46           | 6.47       |     |                  |                  |             |
| C15  | 33.02            | 32.94            | 0.08       |     |                  |                  |             |
| C16  | 42.94            | 42.09            | 0.85       |     |                  |                  |             |
| H3   | 1.73             | 2.09             | -0.36      |     |                  |                  |             |
| C17  | 60.9             | 61.03            | -0.13      |     |                  |                  |             |
| H2   | 3.07, 3.21       | 3.39, 3.47       | 0.32, 0.26 |     |                  |                  |             |
| C18  | 131.13           | 133.71           | -2.58      |     |                  |                  |             |
| C19  | 130.89           | 130.18           | 0.71       |     |                  |                  |             |
| H    | 7.18             | 7.17             | 0.01       |     |                  |                  |             |
| C20  | 118.31           | 118.33           | -0.02      |     |                  |                  |             |
| H    | 6.94             | 6.84             | 0.1        |     |                  |                  |             |
| C21  | 155.73           | 155.33           | 0.4        |     |                  |                  |             |
| C22  | 118.31           | 118.33           | -0.02      |     |                  |                  |             |
| C23  | 130.89           | 130.18           | 0.71       |     |                  |                  |             |
| H    | 7.18             | 7.17             | 0.01       |     |                  |                  |             |
| H2   |                  |                  |            |     |                  |                  |             |
| C18  | 131.13           | 133.71           | -2.58      |     |                  |                  |             |
| C19  | 130.89           | 130.18           | 0.71       |     |                  |                  |             |
| H    | 7.18             | 7.17             | 0.01       |     |                  |                  |             |
| C20  | 118.31           | 118.33           | -0.02      |     |                  |                  |             |
| H    | 6.94             | 6.84             | 0.1        |     |                  |                  |             |
| C21  | 155.73           | 155.33           | 0.4        |     |                  |                  |             |
| C22  | 118.31           | 118.33           | -0.02      |     |                  |                  |             |
| C23  | 130.89           | 130.18           | 0.71       |     |                  |                  |             |
| H    | 7.18             | 7.17             | 0.01       |     |                  |                  |             |
| O24  |                  |                  |            |     |                  |                  |             |
| C25  | 52.87            | 53.15            | -0.28      |     |                  |                  |             |
| H    | 4.25             | 4.51             | -0.26      |     |                  |                  |             |
| C26  | 62.38            | 62.78            | -0.4       |     |                  |                  |             |
| H2   | 3.54             | 3.48, 3.60       | 0.06, -0.06 |     |                  |                  |             |
| O27  |                  |                  |            |     |                  |                  |             |
| N28  | 122.96           | 119.78           | 3.18       |     |                  |                  |             |
| H    | 10.77            | 9.7              | 1.07       |     |                  |                  |             |
| C29  | 165.98           | 163.74           | 2.24       |     |                  |                  |             |
| O30  |                  |                  |            |     |                  |                  |             |
| C31  | 143.24           | 141.61           | 1.63       |     |                  |                  |             |
| C32  | 121.64           | 121.19           | 0.45       |     |                  |                  |             |
| H    | 7.71             | 7.74             | -0.03      |     |                  |                  |             |
| C33  | 150.24           | 150.37           | -0.13      |     |                  |                  |             |
| H    | 8.73             | 8.75             | -0.02      |     |                  |                  |             |
| C34  |                  |                  |            |     |                  |                  |             |
| C35  | 150.24           | 150.37           | -0.13      |     |                  |                  |             |
| C36  | 121.64           | 121.19           | 0.45       |     |                  |                  |             |
| H    | 7.71             | 7.74             | -0.03      |     |                  |                  |             |
| C37  | 156.59           | 156.78           | -0.19      |     |                  |                  |             |
| C38  | 118.56           | 118.32           | 0.24       |     |                  |                  |             |
| C39  | 130.01           | 129.95           | 0.06       |     |                  |                  |             |
| H    | 7.38             | 7.36             | 0.02       |     |                  |                  |             |
| C40  | 123.41           | 123.23           | 0.18       |     |                  |                  |             |
| C41  | 130.01           | 129.95           | 0.06       |     |                  |                  |             |
| C42  | 118.56           | 118.32           | 0.24       |     |                  |                  |             |
| C43  | 15.12            | 14.39            | 0.73       |     |                  |                  |             |
| H3   | 1.22             | 1.14             | 0.08       |     |                  |                  |             |
| C44  | 16.08            | 10.38            | 5.7        |     |                  |                  |             |
| H3   | 0.69             | 0.83             | -0.14      |     |                  |                  |             |
| H3   | 1.22             | 1.14             | 0.08       |     |                  |                  |             |
| C44  | 16.08            | 10.38            | 5.7        |     |                  |                  |             |
| H3   | 0.69             | 0.83             | -0.14      |     |                  |                  |             |
$^1$H-NMR spectra of 1 and 8 in DMSO-$d_6$

Spectrum SI 1: Overlay of $^1$H NMR spectra for 1 (SSS) and 8 (SRS) in DMSO-$d_6$. 
NMR spectra of 1 in DMSO-$d_6$

Spectrum SI 2: $^1$H NMR spectrum of 1 in DMSO-$d_6$.

Spectrum SI 3: $^{13}$C NMR spectrum of 1 in DMSO-$d_6$. 

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S13
Spectrum SI 4: COSY spectrum of I in DMSO-$d_6$.

Spectrum SI 5: HSQC spectrum of I in DMSO-$d_6$. 
Spectrum SI 6: HMBC spectrum of 1 in DMSO-$d_6$. 
NMR spectra of 8 in DMSO-\(d_6\)

Spectrum SI 7: \(^1\)H NMR spectrum of 8 in DMSO-\(d_6\).

Spectrum SI 8: \(^{13}\)C NMR spectrum of 8 in DMSO-\(d_6\).
Spectrum SI 9: COSY spectrum of 8 in DMSO-$d_6$.

Spectrum SI 10: HSQC spectrum of 8 in DMSO-$d_6$. 
Spectrum SI 11: HMBC spectrum of 8 in DMSO-\textit{d}_6.
NMR spectra of 1 in CDCl₃

Spectrum SI 12: $^1$H NMR spectrum of 1 in CDCl₃.

Spectrum SI 13: $^{13}$C NMR spectrum of 1 in CDCl₃.
NMR spectra of 8 in CDCl$_3$

Spectrum SI 14: $^1$H NMR spectrum of 8 in CDCl$_3$.

Spectrum SI 15: $^{13}$C NMR spectrum of 8 in CDCl$_3$. 

S20
Spectrum SI 16: Overlay of $^1$H NMR spectra observed at temperatures varying from 293 K (red) to 338 K (purple). The signals shift with increasing temperature upfield and this effect is stronger in the series of $^1$H NMR spectra for 8.
Synthesis of 9 and 10

General Methods. All oxygen and/or moisture-sensitive reactions were carried out under N₂ atmosphere in glassware that had been flame-dried under a vacuum (~0.5 mmHg) and purged with N₂ prior to use. All reagents and solvents were purchased from commercial vendors and used as received or synthesized according to the references. ¹H spectra were recorded on 300 MHz spectrometers. All chemical shifts are reported in parts per million (δ) referenced to residual non deuterated solvent. Data are reported as follows: chemical shifts, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet; coupling constant(s) in Hz; integration). Unless otherwise indicated, NMR data were collected at 25 °C. Flash chromatography was performed using 40−60 µm silica gel (60 Å mesh) with the indicated solvent. Analytical thin layer chromatography (TLC) was performed on 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and aqueous potassium permanganate or ceric ammonium molybdate stain followed by heating. High resolution mass spectra were obtained using a LC-MS coupled with a quadrupole.

Scheme S 1: Synthesis of the N-methylated compound 9.

\[ \text{N-}((2S,3R)-5-((S)-1-hydroxypropan-2-yl)-3-methyl-2-((methyl(4-phenoxybenzyl)amino)methyl)-6-oxo-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocin-10-yl)-N-methylisonicotinamide (9).} \]  
\[ \text{S2a (100.0 mg, 0.133 mmol, 1.0 equiv)} \] was dissolved in a mixture of DMF/Piperidine (4:1, 1.33 mL) and the reaction mixture was stirred at RT for 20 minutes. Solvents were removed in vacuo and the crude aniline (70.0 mg, 0.133 mmol, 1.0 equiv) was dissolved in CH₂Cl₂ (2.66 mL) and cooled to 0 °C. Then isonicotinoyl chloride hydrochloride (95.0 mg, 0.532 mmol, 4.0 equiv) and triethylamine (0.278 mL, 1.995 mmol, 15.0 equiv) were added. The reaction mixture was stirred at RT for 1 hour. The reaction was then quenched with water, and the reaction mixture was extracted with CH₂Cl₂ (x3). The combined organic layers were washed with brine and dried over Na₂SO₄. After filtration, the solvent was removed.
in vacuo to afford a crude residue, which was purified by chromatography on silica gel (gradient: 0-100% ethyl acetate in hexanes) to provide 74.0 mg (88%) of amide as a colorless oil.

To a solution of the amide (74.0 mg, 0.117 mmol, 1.0 equiv) in DMF (1.17 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 7.02 mg, 0.175 mmol, 1.5 equiv). The reaction mixture was stirred at 0 °C for 15 min before iodomethane was added (8.04 µL, 0.129 mmol, 1.1 equiv). The reaction mixture was stirred at RT for 90 min. The reaction was then quenched with a saturated solution of aqueous ammonium chloride, and the reaction mixture was extracted with CH₂Cl₂ (x3). The combined organic layers were washed with brine and dried over Na₂SO₄. After filtration, the solvent was removed in vacuo to afford a crude residue, which was pure enough to be used in the next step.

To a solution of N-Methylated compound (70.0 mg, 0.108 mmol, 1.0 equiv) in CH₂Cl₂ (2.16 mL) at 0 °C were added 2,6-dimethylpyridine (0.050 mL, 0.433 mmol, 4.0 equiv) and tert-butyldimethylsilyl trifluoromethanesulphonate (0.070 mL, 0.325 mmol, 3.0 equiv). The reaction mixture was slowly warmed to RT and stirred for 4 hours. The reaction was then quenched with a saturated solution of aqueous ammonium chloride, and the reaction mixture was extracted with ethyl acetate (x3). The combined organic layers were washed with brine and dried over Na₂SO₄. After filtration, the solvent was removed in vacuo to afford a crude residue, which was used in the next step. The TBS-ester intermediate (0.076 mg, 0.108 mmol, 1.0 equiv) was dissolved in THF (2.16 mL) and at 0 °C acetic acid (9.27 µL, 0.162 mmol, 1.50 equiv) and tetrabutylammonium fluoride (1.0M sol’n in THF, 0.162 mL, 0.162 mmol, 1.50 equiv) were added. The reaction was stirred at 0 °C for 40 min. The reaction was then quenched with a saturated solution of aqueous ammonium chloride, and the reaction mixture was extracted with ethyl acetate (x3). The combined organic layers were washed with brine and dried over Na₂SO₄. After filtration, the solvent was removed in vacuo to afford a crude residue, which was purified by chromatography on silica gel (gradient: 0-80% ethyl acetate in hexanes) to provide 44.0 mg (75%) of free amine as a colorless oil.

To a solution of free amine (44.0 mg, 0.080 mmol, 1.0 equiv) in 1,2-dichloroethane (1.61 mL) was added 4-phenoxybenzaldehyde (0.042 mL, 0.240 mmol, 3.0 equiv). The reaction was stirred at RT for 30 min before sodium triacetoxyborohydride (0.102 mg, 0.480 mmol, 6.0 equiv) was added and the reaction was stirred for an additional 30 min. The reaction was then quenched with a saturated solution of sodium bicarbonate, and the mixture was extracted with ethyl acetate (x3). The combined organic layers were washed with brine and dried over Na₂SO₄. After filtration, solvent was removed in vacuo to
afford a crude residue, which was purified by chromatography on silica gel (gradient: 0-30% CH₂Cl₂/MeOH/(7M sol’n of NH₄ in MeOH) (80:15:5) in CH₂Cl₂) to provide 47.0 mg (80%) of the tertiary amine as a colorless oil.

To a solution of tertiary amine (20.0 mg, 0.027 mmol, 1.0 equiv) in 1,2-dichloroethane (0.55 mL) was added 2,2,2-trifluoroacetic acid (0.042 mL, 0.549 mmol, 20 equiv). The reaction was stirred at RT for 30 min. The reaction was then quenched with a saturated solution of sodium bicarbonate, and the reaction mixture was extracted with CH₂Cl₂ (x3). The combined organic layers were washed with brine and dried over Na₂SO₄. After filtration, excess solvent was removed in vacuo to afford a crude residue, which was purified by chromatography on silica gel (gradient: 0-60% CH₂Cl₂/MeOH/(7M NH₄ solution in MeOH) (80:15:5) in CH₂Cl₂) to provide 10.38 mg (62%) of 9.

¹H NMR (300 MHz, CDCl₃): δ 8.48-8.37 (br m, 2H), 7.48-6.70 (m, 14H), 4.74 (br s, 1H), 3.89-3.58 (m, 4H), 3.35 (s, 2H), 3.28-3.12 (m, 3H), 2.95-2.77 (m, 2H), 2.51-2.29 (br m, 3H), 1.25-1.20 (m, 5H), 0.91-0.83 (m, 2H), 0.72-0.70 (m, 2H). LC/MS: [M+H]⁺ 609.48. HRMS (ESI) calcd for C₃₆H₄₁N₄O₅ [M + H]⁺: 609.3071. Found: 609.3099.
Spectrum SI 17: LC-MS of 9
Compound 10 was synthesized using the same protocol described above starting with S2d, the SSS stereoisomer of S2a. From 83 mg of starting material, 6.4 mg of final product 10 was obtained.

1H NMR (300 MHz, CDCl$_3$) δ 8.92-8.34 (m, 2H), 7.59-7.18 (m, 7H), 7.11 (dt, $J = 10.5$, 6.3 Hz, 2H), 7.05-6.84 (m, 5H), 4.18-3.15 (m, 10H), 3.05-2.44 (m, 3H), 2.41-2.21 (m, 3H), 1.67 (s, 1H), 1.48-1.21 (m, 4H), 0.79-0.48 (m, 3H). LC/MS: [M+H]$^+$ 609.48. HRMS (ESI) calcd for C$_{36}$H$_{41}$N$_4$O$_5$ [M + H]$^+$: 609.3071. Found: 609.3100.
Spectrum SI 19: LC-MS of 10

Spectrum SI 20: $^1$H NMR of 10
Lowest energy B3LYP/PBF/6-31G* structures in sdf format

Neutral from of 8 (SRS)
MOLSOFT 09231311203D
Structure written by MMmdl.

82 86 0 0 1 0 0 0 0 0999 V2000
9.3538 9.8705 0.7852 C 0 0 0 0 0 0 0 0 0 0 0 0 0
10.3352 9.3933 0.6477 H 0 0 0 0 0 0 0 0 0 0 0 0 0
9.1782 10.0305 1.8631 H 0 0 0 0 0 0 0 0 0 0 0 0 0
9.3868 10.8533 0.2861 H 0 0 0 0 0 0 0 0 0 0 0 0 0
8.2461 9.0060 0.1688 C 0 0 1 0 0 0 0 0 0 0 0 0 0
7.2757 9.5030 0.3358 H 0 0 0 0 0 0 0 0 0 0 0 0 0
8.3956 8.8820 -1.3756 C 0 0 0 0 0 0 0 0 0 0 0 0 0
7.7728 8.0250 -1.7200 H 0 0 0 0 0 0 0 0 0 0 0 0 0
7.1718 8.8232 -1.8558 O 0 0 0 0 0 0 0 0 0 0 0 0 0
10.0960 8.0349 -1.3875 H 0 0 0 0 0 0 0 0 0 0 0 0 0
8.1147 7.7060 0.9029 N 0 0 0 0 0 0 0 0 0 0 0 0 0
7.1376 7.6714 2.0017 C 0 0 0 0 0 0 0 0 0 0 0 0 0
7.5743 7.1323 2.8601 H 0 0 0 0 0 0 0 0 0 0 0 0 0
6.9949 8.7160 2.3294 H 0 0 0 0 0 0 0 0 0 0 0 0 0
5.7487 7.0695 1.6528 C 0 0 1 0 0 0 0 0 0 0 0 0 0
5.0598 7.4450 2.4375 H 0 0 0 0 0 0 0 0 0 0 0 0 0
5.2313 7.5565 0.2901 C 0 0 0 0 0 0 0 0 0 0 0 0 0
5.2491 8.6579 0.2333 H 0 0 0 0 0 0 0 0 0 0 0 0 0
4.1894 7.2445 0.1136 H 0 0 0 0 0 0 0 0 0 0 0 0 0
5.8535 7.1627 -0.5307 H 0 0 0 0 0 0 0 0 0 0 0 0 0
5.7267 5.5315 1.8145 C 0 0 1 0 0 0 0 0 0 0 0 0 0
5.9019 5.2976 2.8835 H 0 0 0 0 0 0 0 0 0 0 0 0 0
4.4006 4.9277 1.3423 C 0 0 0 0 0 0 0 0 0 0 0 0 0
4.3688 5.0085 0.2438 H 0 0 0 0 0 0 0 0 0 0 0 0 0
3.5550 5.5359 1.7417 H 0 0 0 0 0 0 0 0 0 0 0 0 0
4.2433 3.5084 1.6934 N 0 0 0 0 0 0 0 0 0 0 0 0 0
3.8333 3.3546 3.0955 C 0 0 0 0 0 0 0 0 0 0 0 0 0
4.5738 3.8241 3.7633 H 0 0 0 0 0 0 0 0 0 0 0 0 0
2.8399 3.8167 3.2981 H 0 0 0 0 0 0 0 0 0 0 0 0 0
3.7805 2.2838 3.3510 H 0 0 0 0 0 0 0 0 0 0 0 0 0
3.2537 2.8553 0.8195 C 0 0 0 0 0 0 0 0 0 0 0 0 0
3.0852 1.8443 1.2372 H 0 0 0 0 0 0 0 0 0 0 0 0 0
| X   | Y   | Z     | Element | Charge | X Coordinates | Y Coordinates | Z Coordinates | Bond Lengths |
|-----|-----|-------|---------|--------|----------------|----------------|----------------|--------------|
| 9.3043 | 3.1583 | 3.1469 | C       | 0       | 0              | 0              | 0              | 0            |
| 9.3880 | 2.2448 | 3.7349 | H       | 0       | 0              | 0              | 0              | 0            |
| 10.3715 | 4.0558 | 3.0451 | C       | 0       | 0              | 0              | 0              | 0            |
| 11.3072 | 5.2093 | 2.2685 | C       | 0       | 0              | 0              | 0              | 0            |
| 9.0487 | 5.5166 | 1.6262 | C       | 0       | 0              | 0              | 0              | 0            |
| 9.0650 | 6.7343 | 0.7379 | C       | 0       | 0              | 0              | 0              | 0            |
| 10.0007 | 6.8274 | -0.0850 | O       | 0       | 0              | 0              | 0              | 0            |

1 2 1 0 0 0 0
1 3 1 0 0 0 0
1 4 1 0 0 0 0
5 1 1 0 0 0 0
5 6 1 0 0 0
5 7 1 0 0 0
5 12 1 0 0 0
7 8 1 0 0 0
7 9 1 0 0 0
7 10 1 0 0 0
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12 13 1 0 0 0
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16 17 1 0 0 0
16 18 1 0 0 0
16 22 1 0 0 0
18 19 1 0 0 0
18 20 1 0 0 0
18 21 1 0 0 0
22 23 1 0 0 0
22 24 1 0 0 0
22 57 1 0 0 0
24 25 1 0 0 0
24 26 1 0 0 0
24 27 1 0 0 0
27 28 1 0 0 0
27 32 1 0 0 0
28 29 1 0 0 0
Ammonium ion form of 8 (SRS)
MOLSOFT 09231311203D
Structure written by MMmdl.
83 87 0 0 1 0 0 0 0 0 0999 V2000
  8.0539  9.3629  -0.7663 C 0 0 0 0 0 0 0 0 0 0 0 0 0
  8.3403  9.6572  0.2528 H 0 0 0 0 0 0 0 0 0 0 0 0 0
  6.9853  9.0875  -0.7750 H 0 0 0 0 0 0 0 0 0 0 0 0 0
  8.1844 10.2443  -1.4161 H 0 0 0 0 0 0 0 0 0 0 0 0 0
  8.9367  8.2199  -1.2811 C 0 0 1 0 0 0 0 0 0 0 0 0 0
  8.6106  7.9562  -2.3030 H 0 0 0 0 0 0 0 0 0 0 0 0 0
 10.4266  8.6538  -1.4165 C 0 0 0 0 0 0 0 0 0 0 0 0 0

$$$$

108.28875

0.

0

-18.974155
| X       | Y       | Z       | Element | Bond Length | Bond Angle |
|---------|---------|---------|---------|-------------|------------|
| 10.5079 | 9.2313  | -2.3544 | H       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 11.0471 | 7.7388  | -1.5411 | H       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 10.9095 | 9.4995  | -0.3946 | O       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 10.7570 | 8.9861  | 0.4368  | H       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 8.7452  | 6.9406  | -0.5175 | N       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 7.9734  | 5.8866  | -1.1692 | C       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 8.3240  | 4.9008  | -0.8196 | H       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 6.4448  | 6.0136  | -0.9352 | C       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 6.1184  | 7.0027  | -1.3112 | H       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 5.7034  | 4.9073  | -1.7008 | C       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 6.0319  | 4.8885  | -2.7532 | H       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 4.6105  | 5.0565  | -1.7158 | H       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 5.9164  | 3.9136  | -1.2703 | H       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 6.2040  | 5.9943  | 0.5870  | C       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 6.7317  | 6.8342  | 1.0704  | H       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 4.7169  | 6.0448  | 0.9900  | C       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 4.1257  | 5.3311  | 0.3979  | H       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 4.3088  | 7.0575  | 0.8539  | H       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 4.5495  | 5.6419  | 2.4491  | N       | 0 3 2 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 5.4482  | 5.1644  | 2.6718  | H       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 3.4624  | 4.6227  | 2.6382  | C       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 2.5101  | 5.0510  | 2.2940  | H       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 3.7051  | 3.7187  | 2.0608  | H       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 3.3940  | 4.3705  | 3.7064  | H       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 4.3639  | 6.8209  | 3.4450  | C       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 3.3358  | 7.1783  | 3.2701  | H       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 4.4028  | 6.3377  | 4.4360  | H       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 5.3698  | 7.9145  | 3.2951  | C       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 5.0157  | 9.1217  | 2.6537  | C       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 3.9910  | 9.2679  | 2.2901  | H       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 5.9407  | 10.1526 | 2.5086  | C       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 5.6731  | 11.0972 | 2.0272  | H       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 7.2540  | 9.9919  | 2.9979  | C       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 8.0915  | 11.0377 | 2.7662  | O       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 9.3624  | 11.0795 | 3.3742  | C       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 9.4774  | 11.2049 | 4.7636  | C       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 8.5805  | 11.2217 | 5.3906  | H       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 10.7569 | 11.3253 | 5.3226  | C       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| 10.8632 | 11.4268 | 6.4073  | H       | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |
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|  7 |  8 |  1 |  0 |  0 |  0 |  0 |
|  7 |  9 |  1 |  0 |  0 |  0 |  0 |
|  7 |10  |  1 |  0 |  0 |  0 |  0 |
|10 |11  |  1 |  0 |  0 |  0 |  0 |
|12 |13  |  1 |  0 |  0 |  0 |  0 |
|12 | 82 |  1 |  0 |  0 |  0 |  0 |
|13 |14  |  1 |  0 |  0 |  0 |  0 |
|13 |15  |  1 |  0 |  0 |  0 |  0 |
|16 |13  |  1 |  0 |  0 |  0 |  0 |
|16 |17  |  1 |  0 |  0 |  0 |  0 |
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|16 | 22 |  1 |  0 |  0 |  0 |  0 |
|18 |19  |  1 |  0 |  0 |  0 |  0 |
|18 |20  |  1 |  0 |  0 |  0 |  0 |
|18 |21  |  1 |  0 |  0 |  0 |  0 |
|22 |23  |  1 |  0 |  0 |  0 |  0 |
|22 |24  |  1 |  0 |  0 |  0 |  0 |
|22 | 58 |  1 |  0 |  0 |  0 |  0 |
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|27 |24  |  1 |  0 |  0 |  0 |  0 |
|27 |28  |  1 |  0 |  0 |  0 |  0 |
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|27 |33  |  1 |  0 |  0 |  0 |  0 |
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|29 |31  |  1 |  0 |  0 |  0 |  0 |
|29 |32  |  1 |  0 |  0 |  0 |  0 |
|33 |34  |  1 |  0 |  0 |  0 |  0 |
|33 |35  |  1 |  0 |  0 |  0 |  0 |
|33 |36  |  1 |  0 |  0 |  0 |  0 |
|36 |37  |  1 |  0 |  0 |  0 |  0 |
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|37 |39  |  2 |  0 |  0 |  0 |  0 |
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|39 |41  |  1 |  0 |  0 |  0 |  0 |
|41 |42  |  1 |  0 |  0 |  0 |  0 |
|   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|
| 41| 54| 2| 0| 0| 0| 0|
| 42| 43| 1| 0| 0| 0| 0|
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| 44| 45| 1| 0| 0| 0| 0|
| 44| 46| 2| 0| 0| 0| 0|
| 46| 47| 1| 0| 0| 0| 0|
| 46| 48| 1| 0| 0| 0| 0|
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| 54| 55| 1| 0| 0| 0| 0|
| 54| 56| 1| 0| 0| 0| 0|
| 56| 57| 1| 0| 0| 0| 0|
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| 59| 81| 2| 0| 0| 0| 0|
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| 60| 75| 2| 0| 0| 0| 0|
| 61| 62| 1| 0| 0| 0| 0|
| 61| 63| 1| 0| 0| 0| 0|
| 63| 64| 2| 0| 0| 0| 0|
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| 66| 68| 2| 0| 0| 0| 0|
| 68| 69| 1| 0| 0| 0| 0|
| 68| 70| 1| 0| 0| 0| 0|
| 70| 71| 2| 0| 0| 0| 0|
| 71| 72| 1| 0| 0| 0| 0|
| 71| 73| 1| 0| 0| 0| 0|
| 73| 74| 1| 0| 0| 0| 0|
| 75| 76| 1| 0| 0| 0| 0|
| 75| 77| 1| 0| 0| 0| 0|
| 77| 78| 1| 0| 0| 0| 0|
| 77| 79| 2| 0| 0| 0| 0|
| 79| 80| 1| 0| 0| 0| 0|
Neutral form of 1 (SSS)
MOLSOFT 09231311203D
Structure written by MMmdl.

| 79 | 81 | 1 | 0 | 0 | 0 | 0 |
|---|---|---|---|---|---|---|
| 81 | 82 | 1 | 0 | 0 | 0 | 0 |
| 82 | 83 | 2 | 0 | 0 | 0 | 0 |
M CHG 1 27 1
M END

$\text{MOE\_MMFFs\_E}$
39.823734

$\text{MOE\_MMFFs\_dE}$
0.327276

$\text{Protonated}$
1

$\text{SM8\_Solvation\_Energy\_kcal\_mol\_}$
-66.41788

$\text{MOLSOFT 09231311203D}$
$\text{Structure written by MMmdl.}$
4.6680  8.6245  2.8522 H  0  0  0  0  0  0  0  0  0  0  0  0
5.1124  7.2513  3.8985 H  0  0  0  0  0  0  0  0  0  0  0  0
3.7236  7.1180  2.7908 H  0  0  0  0  0  0  0  0  0  0  0  0
5.6835  5.4554  1.7724 C  0  0  1  0  0  0  0  0  0  0  0  0
5.7378  5.0818  2.8157 H  0  0  0  0  0  0  0  0  0  0  0  0
4.4444  4.9146  1.0504 C  0  0  0  0  0  0  0  0  0  0  0  0
3.5332  5.4633  1.3786 H  0  0  0  0  0  0  0  0  0  0  0  0
4.2785  3.4606  1.2093 N  0  0  0  0  0  0  0  0  0  0  0  0
2.5635  3.5682  2.5075 H  0  0  0  0  0  0  0  0  0  0  0  0
3.5318  2.0551  2.5977 H  0  0  0  0  0  0  0  0  0  0  0  0
3.5310  2.8675  0.0787 C  0  0  0  0  0  0  0  0  0  0  0  0
2.4950  3.2793  0.0267 H  0  0  0  0  0  0  0  0  0  0  0  0
4.2002  3.0423 -1.2717 C  0  0  0  0  0  0  0  0  0  0  0  0
4.0076  3.4437 -3.6785 C  0  0  0  0  0  0  0  0  0  0  0  0
3.4205  3.2748 -2.4196 C  0  0  0  0  0  0  0  0  0  0  0  0
2.3300  3.3442 -2.3257 H  0  0  0  0  0  0  0  0  0  0  0  0
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3.4023  3.6418 -4.5679 H  0  0  0  0  0  0  0  0  0  0  0  0
5.4037  3.3891 -3.8048 C  0  0  0  0  0  0  0  0  0  0  0  0
5.9250  3.5484 -5.0747 O  0  0  0  0  0  0  0  0  0  0  0  0
7.1583  4.1830 -5.2204 C  0  0  0  0  0  0  0  0  0  0  0  0
8.0184  3.6742 -6.2022 C  0  0  0  0  0  0  0  0  0  0  0  0
7.7177  2.7856 -6.7652 H  0  0  0  0  0  0  0  0  0  0  0  0
9.2425  4.3145 -6.4358 C  0  0  0  0  0  0  0  0  0  0  0  0
9.9184  3.9170 -7.2005 H  0  0  0  0  0  0  0  0  0  0  0  0
9.6086  5.4443 -5.6906 C  0  0  0  0  0  0  0  0  0  0  0  0
10.5722 5.9319 -5.8699 H  0  0  0  0  0  0  0  0  0  0  0  0
8.7380  5.9490 -4.7128 C  0  0  0  0  0  0  0  0  0  0  0  0
9.0090  6.8300 -4.1179 H  0  0  0  0  0  0  0  0  0  0  0  0
7.5053  5.3248 -4.4806 C  0  0  0  0  0  0  0  0  0  0  0  0
6.8168  5.7152 -3.7250 H  0  0  0  0  0  0  0  0  0  0  0  0
6.2020  3.1330 -2.6772 C  0  0  0  0  0  0  0  0  0  0  0  0
7.2901  3.0896 -2.7763 H  0  0  0  0  0  0  0  0  0  0  0  0
5.5976  2.9654 -1.4286 C  0  0  0  0  0  0  0  0  0  0  0  0
6.2345  2.8212 -0.5518 H  0  0  0  0  0  0  0  0  0  0  0  0
6.8099  4.9017  1.0333 O  0  0  0  0  0  0  0  0  0  0  0  0
7.9681  4.6430  1.7504 C  0  0  0  0  0  0  0  0  0  0  0  0
| X     | Y     | Z     | Atm  | Cols 1 | Cols 2 | Cols 3 | Cols 4 | Cols 5 | Cols 6 | Cols 7 | Cols 8 | Cols 9 | Cols 10 | Cols 11 | Cols 12 | Cols 13 |
|-------|-------|-------|------|--------|--------|--------|--------|--------|--------|--------|--------|--------|---------|---------|---------|---------|
| 8.0936| 3.4180| 2.4610| C    | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0       | 0       | 0       | 0       |
| 7.0332| 2.4949| 2.3738| N    | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0       | 0       | 0       | 0       |
| 6.2407| 2.7641| 1.7579| H    | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0       | 0       | 0       | 0       |
| 6.9276| 1.3041| 3.0749| C    | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0       | 0       | 0       | 0       |
| 7.6367| 0.9870| 4.0382| O    | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0       | 0       | 0       | 0       |
| 5.8759| 0.3496| 2.5661| C    | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0       | 0       | 0       | 0       |
| 5.5528| 0.1942| 1.2073| C    | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0       | 0       | 0       | 0       |
| 6.0300| 0.8029| 0.4338| H    | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0       | 0       | 0       | 0       |
| 4.6214|-0.7911| 0.8454| C    | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0       | 0       | 0       | 0       |
| 4.3672|-0.9406|-0.2123| H    | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0       | 0       | 0       | 0       |
| 3.9966|-1.5999| 1.7211| N    | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0       | 0       | 0       | 0       |
| 4.3276|-1.4467| 3.0197| C    | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0       | 0       | 0       | 0       |
| 3.8182|-2.1175| 3.7237| H    | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0       | 0       | 0       | 0       |
| 5.2588|-0.5135| 3.4880| C    | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0       | 0       | 0       | 0       |
| 5.5207|-0.4474| 4.5480| H    | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0       | 0       | 0       | 0       |
| 9.2995| 3.1524| 3.1428| C    | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0       | 0       | 0       | 0       |
| 9.3821| 2.2329| 3.7218| H    | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0       | 0       | 0       | 0       |
| 10.3714|4.0473| 3.0478| C    | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0       | 0       | 0       | 0       |
| 11.3050|3.8138| 3.5695| H    | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0       | 0       | 0       | 0       |
| 10.2749|5.2079| 2.2766| C    | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0       | 0       | 0       | 0       |
| 11.1284|5.8803| 2.1506| H    | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0       | 0       | 0       | 0       |
| 9.0609| 5.5227| 1.6419| C    | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0       | 0       | 0       | 0       |
| 9.0132| 6.7104| 0.7199| C    | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0       | 0       | 0       | 0       |
| 9.9114| 6.8251|-0.1422| O    | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0      | 0       | 0       | 0       | 0       |

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Ammonium ion form of 1 (SSS)

MOLSOFT 09231311203D

Structure written by MMmdl.

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8.872  9.8839  0.2615 C  0 0 0 0 0 0 0 0 0 0 0 0
9.8530  9.4600 -0.0572 H  0 0 0 0 0 0 0 0 0 0 0 0
8.9900 10.2580  1.2937 H  0 0 0 0 0 0 0 0 0 0 0 0
8.6493 10.7433 -0.3893 H  0 0 0 0 0 0 0 0 0 0 0 0
7.7865  8.8179  0.1687 C  0 0 0 0 0 0 0 0 0 0 0 0
6.8378  9.2502  0.5348 H  0 0 0 0 0 0 0 0 0 0 0 0
7.5620  8.3935 -1.3090 C  0 0 0 0 0 0 0 0 0 0 0 0
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6.8779  9.1153 -1.7841 H  0 0 0 0 0 0 0 0 0 0 0 0
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7.7247  6.4800 -1.3038 H  0 0 0 0 0 0 0 0 0 0 0 0
8.0541  7.6742  1.0741 N  0 0 0 0 0 0 0 0 0 0 0 0
7.2424  7.5893  2.2891 C  0 0 0 0 0 0 0 0 0 0 0 0
7.7730  6.9862  3.0418 H  0 0 0 0 0 0 0 0 0 0 0 0
7.1546  8.6076  2.7103 H  0 0 0 0 0 0 0 0 0 0 0 0
5.8144  7.0537  2.0382 C  0 0 2 0 0 0 0 0 0 0 0 0
5.4173  7.6185  1.1713 H  0 0 0 0 0 0 0 0 0 0 0 0
4.9220  7.3702  3.2526 C  0 0 0 0 0 0 0 0 0 0 0 0
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3.8865  7.0141  3.1175 H  0 0 0 0 0 0 0 0 0 0 0 0
4.8674  8.4590  3.4197 H  0 0 0 0 0 0 0 0 0 0 0 0
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5.5633  4.9856  2.6753 H  0 0 0 0 0 0 0 0 0 0 0 0
4.4864  5.2424  0.8360 C  0 0 0 0 0 0 0 0 0 0 0 0
3.6316  5.8303  1.2018 H  0 0 0 0 0 0 0 0 0 0 0 0
4.2089  4.1754  0.8518 H  0 0 0 0 0 0 0 0 0 0 0 0
4.7077  5.6138 -0.0230 N  0 3 0 0 0 0 0 0 0 0 0 0
5.5063  6.3120 -0.1208 H  0 0 0 0 0 0 0 0 0 0 0 0
5.1324  4.4288 -1.4439 C  0 0 0 0 0 0 0 0 0 0 0 0
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4.2902  3.7243 -1.5192 H  0 0 0 0 0 0 0 0 0 0 0 0
5.9926  3.9593 -0.9508 H  0 0 0 0 0 0 0 0 0 0 0 0
|    |        |        |   |   |   |   |   |   |   |   |   |   |
|----|--------|--------|---|---|---|---|---|---|---|---|---|---|
| 3.4597 | 6.2715 | -1.2513 | C |   |   |   |   |   |   |   |   |   |
| 3.6568 | 6.2712 | -2.3353 | H |   |   |   |   |   |   |   |   |   |
| 2.6233 | 5.5823 | -1.0489 | H |   |   |   |   |   |   |   |   |   |
| 3.2199 | 7.6570 | -0.7336 | C |   |   |   |   |   |   |   |   |   |
| 3.9594 | 8.7323 | -1.2672 | C |   |   |   |   |   |   |   |   |   |
| 4.6408 | 8.5533 | -2.1070 | H |   |   |   |   |   |   |   |   |   |
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| 2.9446 | 10.2618 | 0.3140 | C |   |   |   |   |   |   |   |   |   |
| 2.7607 | 11.4888 | 0.8850 | O |   |   |   |   |   |   |   |   |   |
| 3.7420 | 12.4745 | 0.6861 | C |   |   |   |   |   |   |   |   |   |
| 5.0259 | 13.2014 | 1.2220 | C |   |   |   |   |   |   |   |   |   |
| 5.2670 | 11.3839 | 1.7693 | H |   |   |   |   |   |   |   |   |   |
| 5.9707 | 13.3233 | 1.0657 | C |   |   |   |   |   |   |   |   |   |
| 6.9745 | 13.2022 | 1.4864 | H |   |   |   |   |   |   |   |   |   |
| 5.6282 | 14.5037 | 0.3895 | C |   |   |   |   |   |   |   |   |   |
| 6.3678 | 15.3018 | 0.2730 | H |   |   |   |   |   |   |   |   |   |
| 4.3350 | 14.6644 | -0.1270 | C |   |   |   |   |   |   |   |   |   |
| 4.0631 | 15.5875 | -0.6480 | H |   |   |   |   |   |   |   |   |   |
| 3.3805 | 13.6464 | 0.0163 | C |   |   |   |   |   |   |   |   |   |
| 2.3657 | 13.7524 | -0.3781 | H |   |   |   |   |   |   |   |   |   |
| 2.1496 | 9.2129 | 0.8159 | C |   |   |   |   |   |   |   |   |   |
| 1.4322 | 9.4299 | 1.6122 | H |   |   |   |   |   |   |   |   |   |
| 2.2909 | 7.9257 | 0.2941 | C |   |   |   |   |   |   |   |   |   |
| 1.6567 | 7.1207 | 0.6855 | H |   |   |   |   |   |   |   |   |   |
| 6.8257 | 4.9235 | 1.0153 | O |   |   |   |   |   |   |   |   |   |
| 7.9910 | 4.6471 | 1.7534 | C |   |   |   |   |   |   |   |   |   |
| 8.0924 | 3.4290 | 2.4657 | C |   |   |   |   |   |   |   |   |   |
| 7.0000 | 2.5532 | 2.3982 | N |   |   |   |   |   |   |   |   |   |
| 6.3159 | 2.7903 | 1.6808 | H |   |   |   |   |   |   |   |   |   |
| 6.7749 | 1.3881 | 3.1252 | C |   |   |   |   |   |   |   |   |   |
| 7.4740 | 1.0233 | 4.0705 | O |   |   |   |   |   |   |   |   |   |
| 5.5610 | 0.6212 | 2.6690 | C |   |   |   |   |   |   |   |   |   |
| 5.0778 | 0.6262 | 1.3464 | C |   |   |   |   |   |   |   |   |   |
| 5.6043 | 1.1555 | 0.5426 | H |   |   |   |   |   |   |   |   |   |
| 3.9409 | -0.1360 | 1.0431 | C |   |   |   |   |   |   |   |   |   |
| 3.5555 | -0.1673 | 0.0154 | H |   |   |   |   |   |   |   |   |   |
| 3.2650 | -0.8692 | 1.9452 | N |   |   |   |   |   |   |   |   |   |
| 3.7498 | -0.8801 | 3.2026 | C |   |   |   |   |   |   |   |   |   |
| 3.1941 | -1.4929 | 3.9231 | H |   |   |   |   |   |   |   |   |   |
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References

1. Chou, D. H.-C.; Duvall, J. R.; Gerard, B.; Liu, H.; Pandya, B. A.; Suh, B.-C.; Forbeck, E. M.; Faloon, P.; Wagner, B. K.; Marcaurelle, L. A., Synthesis of a novel suppressor of β-cell apoptosis via diversity-oriented synthesis. *ACS Med. Chem. Lett.* 2011, 2 (9), 698-702.