Supporting Information

A Scaffold-Diversity Synthesis of Biologically Intriguing Cyclic Sulfonamides

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Supporting Information

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1. General Information

All commercially available compounds were used as provided without further purification unless otherwise noted. Solvents were purchased from Fisher, VWR and Acros in laboratory, reagent and anhydrous grade, as labelled by corresponding companies. If no additional information regarding treatment is given, the solvents were used directly from the container. Reagents were purchased from Alfa Aesar, Sigma Aldrich and VWR respectively. If it is stated, that a reaction was carried out under an Argon atmosphere, standard Schlenk techniques were used. Column chromatography was performed using silica gel (Acros, particle size 0.035-0.070 mm).

$^1$H, $^{13}$C and $^{19}$F-NMR were recorded on a Bruker DRX400 (400 MHz), Bruker DRX500 (500 MHz), INOVA500 (500 MHz) or Bruker Biospin AVANCE HDX-III (700 MHz) using Chloroform-$d$ (CDCl$_3$), CD$_2$Cl$_2$, (CD$_3$)$_2$CO, or (CD$_3$)$_2$SO as solvent at room temperature. $^1$H and $^{13}$C-NMR spectra were calibrated to the solvent signals of Chloroform-$d$ (7.26 and 77.16 ppm), CD$_2$Cl$_2$ (5.32 and 53.84 ppm), CD$_3$CN (1.94 and 1.32/118.26 ppm) or (CD$_3$)$_2$SO (2.50 and 39.52 ppm). The abbreviations $s$, $d$, $t$, $q$ and $m$ stand for singlet, doublet, triplet, quartet and multiplet in that order. High resolution mass spectra (HRMS) were recorded on a LTQ Orbitrap mass spectrometer coupled to an Accela HPLC-System (HPLC column: Hypersyl GOLD, 50 mm x 1 mm, particle size 1.9 μm; Ionization method: electron spray ionization). Preparative HPLC was performed using a 1260 Infinity II system by Agilent Technologies and Nucleodur C18 Gravity VP10/125 5 μm or Nucleodur C18 gravity VP21/125 5 μm columns by Macherey-Nagel.

2. Experimental section - Synthesis

2.1. Branching Pathway

2.1.1 Synthesis of Ketimines (1), Allenes (3) and Sulfonium Salts

CO$_2$Et-$^1$H-$^1$, Me-$^1$, 2-Pyr-$^4$ were synthesized according to procedures previously reported in literature. Spectral data were in accordance with reported ones.

Allenes 3-OEt, 3-OtBu and 3-OBn were synthesized according to reported literature procedures$^5$ with recorded spectral data matching previously reported ones.
Sulfonium salts (carbethoxy)methyl dimethylsulfonium bromide and benzyl dimethylsulfonium bromide were synthesized and handled according to reported literature procedures; with recorded spectral data matching previously reported ones.\textsuperscript{[7][8]}

2.1.2 Synthesis of Aziridines 2a-2h

Aziridines were synthesized according to general scheme depicted above. Observed diastereoselectivity (\textit{syn} in most examples) or lack of it in cases of 2c and 2h can be described and established by the procedure shown in Scheme S1, referring to general considerations of sulfur ylide mediated aziridination.\textsuperscript{[9]}

\textbf{Scheme S1: Model for diastereoselectivity of aziridination reaction.}

\begin{itemize}
  \item \textbf{Syn over Anti-selectivity :}
    \begin{itemize}
      \item - C-C bond rotation in betain \textit{i} gets rid of the steric interaction between aryl moiety of ketimine and that from sulfur ylide (R\textsuperscript{2}) and thus favoring a transition state leading to \textit{syn}-aziridines.
      \item - C-C bond rotation in betain \textit{ii} demands high activation energy leading to unstable crowding and steric repulsion between R\textsuperscript{1} and aryl moiety of ketimine and therefore is not favored.
      \item - in case R\textsuperscript{1} and R\textsuperscript{2} = Ar (e.g. 2c and 2h), = stacking of aryl function (R\textsuperscript{2}) and ketimine aryl function stabilize the transition state (\textit{ii}) leading to \textit{anti}-aziridine formation. However, in this case, betain \textit{i} route is equally favored (low energy barrier to rotation) and therefore \textit{syn} and \textit{anti} products are formed in similar amounts.
    \end{itemize}
\end{itemize}
Benzyl dimethylsulfonium bromide (1.4 eq., 100.0 mg, 0.43 mmol), Potassium carbonate (2.0 eq., 32.8 mg, 0.24 mmol) and 3-methylbenzo[d]isothiazole 1,1-dioxide 1-Me (1.0 eq., 21.0 mg, 0.12 mmol) were combined in Acetonitrile (970 µl). The reaction was stirred for 10 h at ambient temperature. Then, an additional 2.2 eq (157 mg, 0.68 mmol) of sulfonium salt were added to the mixture and the reaction stirred for 30 additional hours at ambient temperature. The reaction was concentrated and objected to silica gel column chromatography (7% to 14% EA/CyH) to yield 22 mg (0.08 mmol, 68%) of syn-2a and 3 mg (0.01 mmol, 9%) of anti-2a. syn-2a

![syn-2a](image)

$^1$H NMR (500 MHz, Chloroform-d) δ 7.77 (dt, $J = 7.6$, 0.9 Hz, 1H), 7.69 (td, $J = 7.6$, 1.2 Hz, 1H), 7.62 – 7.56 (m, 2H), 7.45 – 7.34 (m, 5H), 3.65 (s, 1H), 1.60 (s, 3H); $^{13}$C NMR (126 MHz, Chloroform-d) δ 141.2, 133.8, 133.7, 132.6, 130.3, 128.8, 128.7, 127.7, 124.3, 123.66, 61.6, 56.9, 13.1; HMRS (ESI): Calculated for C$_{15}$H$_{14}$O$_2$N S = [M+H]$^+$: 272.07398, found: 272.07328
\textbf{syn-2a NOESY}

\textbf{anti-2a}

$^1$H NMR (600 MHz, Chloroform-d) $\delta$ 7.73 (dt, $J = 7.8, 0.9$ Hz, 1H), 7.68 (ddd, $J = 7.8, 7.1, 1.2$ Hz, 1H), 7.46 (ddd, $J = 8.1, 7.1, 1.1$ Hz, 1H), 7.41 (dt, $J = 7.7, 1.0$ Hz, 1H), 7.15 – 7.12 (m, 1H), 7.10 – 7.06 (m, 2H), 6.93 (dq, $J = 7.3, 1.2$ Hz, 2H), 4.21 (s, 1H), 2.07 (s, 3H); $^{13}$C NMR (151 MHz, Chloroform-d) $\delta$ 137.7, 137.4, 133.4, 131.0, 130.4, 128.5, 128.3, 127.9, 125.6, 122.6, 62.2, 55.1, 19.7; HMRS (ESI): Calculated for C$_{15}$ H$_{14}$ O$_2$ N S = [M+H]$^+$: 272.07398, found: 272.07359
(±)-7b-methyl-1-carbethoxy-1,7b-dihydroazirino[1,2-b]benzo[d]isothiazole 3,3-dioxide (2b)

(Carbethoxymethyl)dimethylsulfonium bromide (1.2 eq., 99 mg, 0.43 mmol, Potassium carbonate (2.0 eq., 99.0 mg, 0.72 mmol) and 3-methylbenzo[d]isothiazole 1,1-dioxide 1-Me (1.0 eq., 65.0 mg, 0.36 mmol) were combined in Acetonitrile (1.3 ml). The reaction was concentrated and objected to silica gel column chromatography (15% to 21% EA/CyH) to yield 81.0 mg (0.30 mmol, 84%) of product aziridine.

Rf (30% EA/CyH) = 0.55; 1H NMR (400 MHz, Chloroform-d) δ 7.74 – 7.64 (m, 2H), 7.61 – 7.54 (m, 2H), 4.28 (m, 2H), 3.15 (s, 1H), 1.91 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H).

13C NMR (101 MHz, Chloroform-d) δ 164.0, 139.2, 134.0, 133.2, 130.7, 124.9, 123.3, 62.4, 55.5, 53.9, 14.1, 13.3.

HMRS (ESI): Calculated for C12 H14 O4 N S = [M+H]+: 268.06381, found: 268.06385
(+)-1,7b-diphenyl-1,7b-dihydroazirino[1,2-b]benzo[d]isothiazole 3,3-dioxide (2c)

Benzyl dimethylsulfonium bromide (2.25 eq., 112.0 mg, 0.48 mmol) was combined with Potassium carbonate (2.50 eq., 74.0 mg, 0.53 mmol) in an oven-dried schlenk tube with a magnetic stirring bar and solved in 2.28 ml DMF. After 10 min. Ketimine (1.0 eq., 52.0 mg, 0.21 mmol mg) was added to the mixture. The reaction was stirred at ambient temperature overnight. After completion of conversion (TLC analysis), the reaction was quenched by adding saturated aqueous ammonium chloride solution (4 ml). 2 ml Ethyl Acetate were added and layers were separated. The aqueous layer was extracted twice more with 2 ml each. Combined organic layers were washed with water three times (10 ml each) and brine once. Concentration delivered crude material, which was objected to silica gel column chromatography (3:2 Ethyl acetate / Cyclohexane (v/v)) to deliver 67 mg (0.20 mmol, 94%) of aziridine.

**Syn-2c**

**1H NMR** (400 MHz, Chloroform-d) δ 7.66 – 7.61 (m, 2H), 7.61 – 7.56 (m, 1H), 7.52 – 7.41 (m, 6H), 7.20 – 7.09 (m, 5H), 4.65 (s, 1H).

**13C NMR** (126 MHz, Chloroform-d) δ 137.3, 136.7, 135.1, 133.2, 131.0, 130.4, 129.5, 129.1, 128.5, 128.0, 127.9, 127.1, 122.2, 60.7, 60.2.

**HMRS (ESI):** Calculated for C<sub>20</sub>H<sub>16</sub>O<sub>2</sub>N S = [M+H]<sup>+</sup>: 334.08963, found: 334.09003
$^1$H NMR (700 MHz, Chloroform-\textit{d}) δ 7.83 – 7.80 (m, 1H), 7.59 – 7.56 (m, 2H), 7.36 – 7.33 (m, 1H), 7.31 – 7.27 (m, 5H), 7.23 – 7.16 (m, 3H), 7.12 (d, $J = 7.7$ Hz, 2H), 3.87 (s, 1H).

$^{13}$C NMR (176 MHz, Chloroform-\textit{d}) δ 140.6, 133.6, 133.2, 132.6, 130.9, 130.3, 129.3, 129.0, 128.8, 128.7, 128.3, 127.8, 125.6, 123.5, 62.4, 62.3.

HMRS (ESI): Calculated for C$_{20}$H$_{16}$O$_2$N S = [M+H]$^+$: 334.08963, found: 334.09043
To (Carbethoxymethyl)dimethylsulfonium bromide (121 mg, 0.53 mmol, 1.35 eq.) was added sodium hydride (24 mg, 60 wt.% in paraffin oil, 1.55 eq.) in 3.8 ml N,N-DMF. The mixture was stirred for 5 min at ambient temperature and 3-(phenyl) 1,2 benzothiazole 1,1-dioxide 1-Ph (1.0 eq., 95 mg, 0.39 mmol) was added in one portion. The reaction was stirred for 10 h at ambient temperature. The reaction mixture was poured into 50 ml of saturated aqueous ammonium chloride solution and extracted with 10 ml Ethyl acetate (3 times). Combined organic layers were washed with water and brine (each 15 ml), dried over anhydrous sodium sulfate and concentrated. Objection to silica gel column chromatography (Ethyl Acetate/Cyclohexane 15-25%) furnished 32 mg (0.10 mmol, 25%) of desired aziridine.


**1H NMR** (500 MHz, Chloroform-d) \( \delta \) 7.80 – 7.72 (m, 1H), 7.61 – 7.58 (m, 2H), 7.53 (dq, \( J = 5.1, 2.9 \) Hz, 2H), 7.46 – 7.40 (m, 4H), 4.10 – 3.96 (m, 2H), 3.50 (s, 1H), 0.96 (t, \( J = 7.2 \) Hz, 3H).

**13C NMR** (126 MHz, Chloroform-d) \( \delta \) 163.4, 138.4, 133.8, 132.7, 130.8, 130., 129.5, 129.0, 128.1, 126.0, 123.3, 62.1, 58.7, 56.6, 13.7.

**HMRS (ESI):** Calculated for C\(_{17}\)H\(_{16}\)O\(_4\)N S = [M+H]: 330.07946, found: 330.07993

(+)Diethyl azirino[1,2-b]benzo[d]isothiazole-1,7b(1H)-dicarboxylate 3,3-dioxide (2e)

(Carbethoxymethyl)dimethylsulfonium bromide (2.0 eq., 105 mg, 0.46 mmol) and Potassium carbonate (3.0 eq., 95.3 mg, 0.69 mmol) were combined in dry DMSO (2.3 ml) in a flame-dried 10 ml schlenk tubed equipped with a magnetic stirring bar under an Argon atmosphere. The mixture was stirred for 10 min and Ketimine 1-CO\(_2\)Et (1.0 eq., 55 mg, 230.0 \( \mu \)mol) was added as a solid. The reaction was then monitored via TLC.

After 3 h, starting material had been consumed and the reaction mixture was quenched with 2 ml saturated aqueous ammonium chloride solution and the resulting mixture was poured into 40 ml water in a separation funnel.

The mixture was extracted with Ethyl acetate (5 times with 9 ml each). Combined organic layers were washed with water and brine and dried over anhydrous sodium sulfate. Concentration delivered crude product. Objection to silica gel column chromatography (16 to 30% EA/CyH) furnished 28 mg aziridine (0.09 mmol, 37% yield).

R\(_f\) = 0.31 (30%EA/CyH); **1H NMR** (400 MHz, Chloroform-d) \( \delta \) 7.93 – 7.89 (m, 1H), 7.73 – 7.67 (m, 2H), 7.66 – 7.60 (m, 1H), 4.33 (qd, \( J = 7.1, 5.9 \) Hz, 2H), 4.24 (qd, \( J = 7.2, 0.6 \) Hz, 2H), 3.26 (s, 1H), 1.32 (t, \( J = 7.1 \) Hz, 3H), 1.28 (t, \( J = 7.1 \) Hz, 3H).

**13C NMR** (126 MHz, Chloroform-d) \( \delta \) 162.8, 162.7, 134.1, 132.9, 132.8, 131.6, 126.4, 123.4, 63.3, 62.8, 55.3, 53.8, 13.9, 13.9.

**HMRS (ESI):** Calculated for C\(_{14}\)H\(_{16}\)O\(_6\)N S = [M+H]: 326.06928, found: 326.06938

Calculated for C\(_{14}\)H\(_{15}\)O\(_6\)N Na S = [M+Na]: 348.05123, found: 348.05129
Ethyl 1-phenylazirino[1,2-b]benzo[d]isothiazole-7b(1H)-carboxylate 3,3-dioxide (2f)

To 3-carbethoxy 1,2 benzothiazole 1,1-dioxide 1-CO₂Et (1.0 eq., 24 mg, 0.10 mmol) in 0.8 ml Acetonitrile was added 2.1 eq. (benzyl)dimethylsulfonyl bromide (49.1 mg, 0.21 mmol) and Potassium carbonate (2.05 eq., 28.4 mg, 0.21 mmol). The reaction was stirred for 14 h at ambient temperature. The reaction mixture was poured into 10 ml of saturated aqueous ammonium chloride solution and extracted with 5 ml Ethyl acetate (3 times). Combined organic layers were washed with water and brine (each 15 ml), dried over anhydrous sodium sulfate and concentrated. Objection to silica gel column chromatography (11% to 29% EA/CyH) furnished 18 mg (0.05 mmol, 54%) aziridine.

¹H NMR (500 MHz, Chloroform-d) δ 8.17 (dt, J = 7.9, 0.9 Hz, 1H), 7.78 (dt, J = 7.7, 0.9 Hz, 1H), 7.73 (td, J = 7.7, 1.2 Hz, 10H), 7.65 (td, J = 7.6, 1.1 Hz, 1H), 7.51 – 7.48 (m, 2H), 7.39 – 7.35 (m, 3H), 4.16 – 4.01 (m, 2H), 3.80 (s, 1H), 1.02 (t, J = 7.1 Hz, 3H).

¹³C NMR (126 MHz, Chloroform-d) δ 163.4, 134.7, 133.8, 133.2, 131.0, 130.9, 129.3, 128.4, 127.6, 126.5, 123.4, 62.5, 61.7, 57.7, 13.8.

HMRS (ESI): Calculated for C₁₇H₁₆O₄N S = [M+H]⁺: 330.07946, found: 330.07982

(−)-Ethyl 7b-(pyridin-2-yl)-1,7b-dihydroazirino[1,2-b]benzo[d]isothiazole-1-carboxylate 3,3-dioxide (2g)

(Carbethoxymethyl)dimethylsulfonyl bromide (1.37 eq., 108 mg, 0.47 mmol), Potassium carbonate (2.0 eq., 95 mg, 0.69 mmol) and 3-methylbenzo[d]isothiazole 1,1-dioxide 1-Me (1.0 eq., 84.0 mg, 0.34 mmol) were combined in Acetonitrile (1.275 ml). The reaction was concentrated and objected to silica gel column chromatography (18% to 36% EA/CyH) to yield 103 mg (0.31 mmol, 91%) of product aziridine.
$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 8.63 (ddd, $J$ = 4.9, 1.7, 1.0 Hz, 1H), 8.04 – 7.98 (m, 1H), 7.77 – 7.67 (m, 3H), 7.59 (pd, $J$ = 7.4, 1.4 Hz, 1H), 7.31 (ddd, $J$ = 7.2, 4.9, 1.6 Hz, 1H), 4.10 – 3.92 (m, 1H), 3.48 (s, 1H), 1.00 (t, $J$ = 7.1 Hz, 2H).

$^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 163.2, 151.7, 149.5, 137.8, 137.3, 134.0, 133.0, 131.1, 127.3, 124.2, 124.1, 123.3, 62.3, 56.8, 27.1, 14.0.

HMRS (ESI): Calculated for C$_{16}$H$_{15}$O$_4$N$_2$S = [M+H]$^+$: 331.07470, found: 331.07463

(+)-1-Phenyl-7b-(pyridin-2-yl)-1,7b-dihydroazirino[1,2-b]benzo[d]isothiazole 3,3-dioxide (2h)

Benzylidemethylsulphonium bromide (1.4 eq., 100.0 mg, 0.43 mmol), Potassium carbonate (2.0 eq., 32.8 mg, 0.24 mmol ) and 2-Pyridinyl Ketimine 2-Pyr-1 (1.0 eq., 29.0 mg, 0.12 mmol) were combined in Acetonitrile (970 µl). The reaction was stirred for 10 hours at ambient temperature. Then, additional 2.2 eq (157 mg, 0.68 mmol) of sulfonium salt were added to the mixture and the reaction stirred for 30 additional hours at ambient temperature. The reaction was stopped by concentration using a rotary evaporator and objecte to silica gel column chromatography to yield 29 mg (0.09 mmol, 73%) of a 1:1 mixture of diastereomers.

anti-2h

$^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 8.53 – 8.50 (m, 1H), 8.15 (d, $J$ = 7.7 Hz, 1H), 7.81 – 7.77 (m, 1H), 7.69 – 7.55 (m, 5H), 7.23 (dd, $J$ = 6.8, 3.0 Hz, 2H), 7.16 (tt, $J$ = 4.8, 2.7 Hz, 5H), 3.98 (s, 1H).

$^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 151.5, 149.5, 138.7, 136.7, 133.5, 133.1, 131.9, 130.3, 128.5, 128.2, 127.4, 126.7, 123.8, 123.7, 123.2, 62.9, 61.3.

HMRS (ESI): Calculated for C$_{19}$H$_{15}$O$_2$N$_2$S = [M+H]$^+$: 335.08487 found: 335.08570

Calculated for C$_{19}$H$_{15}$O$_2$N$_2$NaS = [M+Na]$^+$: 357.06682 found: 357.06777
**syn-2h**

\[\text{\textsuperscript{1}H NMR (500 MHz, Chloroform-d)} \delta 8.74 \text{ (dt, } J = 5.0, 1.3 \text{ Hz, 1H}), 8.12 \text{ (d, } J = 7.9 \text{ Hz, 1H}), 7.79 \text{ (dd, } J = 7.6, 1.8 \text{ Hz, 1H}), 7.76 - 7.72 \text{ (m, 1H)}, 7.64 \text{ (td, } J = 4.9, 2.6 \text{ Hz, 1H}), 7.38 \text{ (ddd, } J = 7.6, 4.9, 1.3 \text{ Hz, 1H}), 7.20 - 7.07 \text{ (m, 5H)}, 4.70 \text{ (s, 1H).} \]

\[\text{\textsuperscript{13}C NMR (126 MHz, Chloroform-d)} \delta 154.8, 149.8, 137.6, 137.1, 135.7, 133.3, 131.1, 130.5, 128.6, 128.1, 127.9, 124.1, 122.6, 122.3, 61.9, 59.4. \]

**HMRS (ESI):** Calculated for C\textsubscript{19}H\textsubscript{15}O\textsubscript{2}N\textsubscript{2}S = [M+H]\textsuperscript{+}: 335.08487, found: 335.08470
2.1.3 Synthesis of Azetidines

Azetidines \(4a\) and \(4b\) were synthesized according to the procedure of Ye et al.\(^{[10]}\) and results were in accordance with the reported yields and spectral data. For azetidines \(4c-e\), same conditions with corresponding substrates and allenes were used.

\((\pm)\)-tert-butyl \((E)\)-2-(4,4-dioxido-8b-phenyl-1,8b-dihydro-2H-azeto[1,2-b]benzo[d]-isothiazol-2-ylidene)acetate (4b)

Yield: 742 mg, 52% (3.7 mmol scale)

\(^1\)H NMR (400 MHz, Chloroform-d) \(\delta\) 7.80 (ddd, \(J = 7.8, 1.3, 0.7 \text{ Hz}, 1\text{H})\), 7.66 – 7.61 (m, 1H), 7.60 – 7.54 (m, 3H), 7.46 – 7.38 (m, 3H), 7.37 – 7.31 (m, 1H), 5.85 (t, \(J = 2.4 \text{ Hz}, 1\text{H})\), 4.01 (dd, \(J = 17.0, 2.4 \text{ Hz}, 1\text{H})\), 3.73 (dd, \(J = 17.0, 2.4 \text{ Hz}, 1\text{H})\), 1.42 (s, 9H).

\(^{13}\)C NMR (176 MHz, Chloroform-d) \(\delta\) 165.7, 154.9, 143.3, 139.4, 136.5, 134.3, 130.2, 129.1, 128.8, 125.8, 125.0, 122.4, 106.8, 80.7, 77.1, 43.3, 28.4.

HMRS (ESI): Calculated for \(C_{21}H_{22}O_4NS = [M+H]^+\): = 384.12641, found: 384.12632
Calculated for \(C_{21}H_{22}O_4NaNS = [M+Na]^+\): = 406.10835, found: 406.10802
Calculated for \(C_{21}H_{22}O_4NKNS = [M+K]^+\): = 422.08229, found: 422.08188

\((\pm)\)-Ethyl \((E)\)-2-(4,4-dioxido-8b-(pyridin-2-yl)-1,8b-dihydro-2H-azeto[1,2-b]benzo[d]-isothiazol-2-ylidene)acetate (4c)\(^{[10]}\)

\(^1\)H NMR (400 MHz, Chloroform-d) \(\delta\) 8.66 (ddd, \(J = 4.8, 1.7, 1.0 \text{ Hz}, 1\text{H})\), 7.87 (dt, \(J = 7.8, 0.9 \text{ Hz}, 1\text{H})\), 7.78 – 7.75 (m, 1H), 7.75 – 7.72 (m, 1H), 7.37 – 7.31 (m, 1H), 5.96 (t, \(J = 2.3 \text{ Hz}, 1\text{H})\), 5.85 (t, \(J = 2.4 \text{ Hz}, 1\text{H})\), 4.76 (t, \(J = 1.1 \text{ Hz}, 1\text{H})\), 4.01 (dd, \(J = 17.0, 2.4 \text{ Hz}, 1\text{H})\), 3.73 (dd, \(J = 17.0, 2.4 \text{ Hz}, 1\text{H})\), 1.42 (s, 9H).

\(^{13}\)C NMR (176 MHz, Chloroform-d) \(\delta\) 165.7, 154.9, 143.3, 139.4, 136.5, 134.3, 130.2, 129.1, 128.8, 125.8, 125.0, 122.4, 106.8, 80.7, 77.1, 43.3, 28.4.
$^1$H NMR (400 MHz, Chloroform-d) δ 7.76 (d, $J = 7.9$ Hz, 1H), 7.72 – 7.67 (m, 1H), 7.58 (t, $J = 7.6$ Hz, 0H), 7.44 (d, $J = 7.8$ Hz, 1H), 5.87 (t, $J = 2.3$ Hz, 1H), 4.09 (q, $J = 7.1$ Hz, 2H), 3.53 (dd, $J = 17.1$, 2.3 Hz, 1H), 3.35 (dd, $J = 17.1$, 2.3 Hz, 1H), 1.90 (s, 3H), 1.22 (t, $J = 7.1$ Hz, 4H).

$^{13}$C NMR (126 MHz, Chloroform-d) δ 166.4, 156.0, 143.9, 137.2, 134.3, 130.1, 123.8, 122.3, 104.4, 73.6, 60.2, 42.6, 25.7, 14.4

HMRS (ESI): Calculated for C$_{14}$H$_{16}$O$_4$N S = [M+H]$^+$: = 294.07946, found: 294.07974

($\pm$)-ethyl (E)-2-(8b-methyl-4,4-dioxido-1,8b-dihydro-2H-azeto[1,2-b]benzo[d]isothiazol-2-ylidene)acetate (4d)

Yield: 28% (0.12 mmol scale, 10 mg)

$^1$H NMR (500 MHz, Chloroform-d) δ 7.80 (dt, $J = 7.8$, 0.9 Hz, 1H), 7.77 – 7.62 (m, 3H), 7.35 – 7.30 (m, 5H), 5.96 (t, $J = 2.3$ Hz, 1H), 5.09 (d, $J = 2.0$ Hz, 2H), 4.36 – 4.23 (m, 2H), 4.02 – 3.95 (m, 1H), 3.50 (dd, $J = 17.3$, 2.3 Hz, 1H), 1.31 (t, $J = 7.2$ Hz, 9H).

$^{13}$C NMR (126 MHz, Chloroform-d) δ 167.5, 165.8, 155.5, 155.5, 137.2, 137.2, 135.8, 134.5, 131.2, 128.7, 128.4, 125.3, 122.4, 104.9, 72.4, 66.3, 63.4, 40.9, 14.1.

HMRS (ESI): Calculated for C$_{21}$H$_{20}$O$_6$N S = [M+H]$^+$: = 414.10058, found: 414.09967
Calculated for C$_{21}$H$_{19}$O$_6$Na N S = [M+Na]$^+$: = 436.08253, found: 436.08153
Calculated for C$_{21}$H$_{19}$O$_6$K N S = [M+K]$^+$: = 452.05647, found: 452.05550

($\pm$)-Ethyl (E)-2-(2-(benzyloxy)-2-oxoethylidene)-1,2-dihydro-8bH-azeto[1,2-b]benzo[d]-isothiazole-8b-carboxylate 4,4-dioxide (4e)

Yield: 90% (0.34 mmol scale, 140 mg)

$^1$H NMR (500 MHz, Chloroform-d) δ 7.80 (dt, $J = 7.8$, 0.9 Hz, 1H), 7.77 – 7.62 (m, 3H), 7.35 – 7.30 (m, 5H), 5.96 (t, $J = 2.3$ Hz, 1H), 5.09 (d, $J = 2.0$ Hz, 2H), 4.36 – 4.23 (m, 2H), 4.02 – 3.95 (m, 1H), 3.50 (dd, $J = 17.3$, 2.3 Hz, 1H), 1.31 (t, $J = 7.2$ Hz, 9H).

$^{13}$C NMR (126 MHz, Chloroform-d) δ 167.5, 165.8, 155.5, 155.5, 137.2, 137.2, 135.8, 134.5, 131.2, 128.7, 128.4, 125.3, 122.4, 104.9, 72.4, 66.3, 63.4, 40.9, 14.1.

HMRS (ESI): Calculated for C$_{21}$H$_{20}$O$_6$N S = [M+H]$^+$: = 414.10058, found: 414.09967
Calculated for C$_{21}$H$_{19}$O$_6$Na N S = [M+Na]$^+$: = 436.08253, found: 436.08153
Calculated for C$_{21}$H$_{19}$O$_6$K N S = [M+K]$^+$: = 452.05647, found: 452.05550

S17
(±)-Ethyl (E)-2-(2-(tert-butoxy)-2-oxoethylidene)-1,2-dihydro-8bH-azeto[1,2-b]benzo[d]-
isothiazole-8b-carboxylate 4,4-dioxide (4f)

Yield: 85% (70 µmol scale, 27 mg)

\[ \text{1H NMR (500 MHz, Chloroform-d) } \delta \] 7.81 (d, J = 7.8 Hz, 1H), 7.77 – 7.64 (m, 3H), 5.82 (t, J = 2.2 Hz, 1H), 4.37 – 4.23 (m, 2H), 3.96 (dd, J = 17.2, 2.2 Hz, 1H), 3.46 (dd, J = 17.2, 2.2 Hz,
1H), 1.41 (s, 9H), 1.31 (t, J = 7.1 Hz, 3H).

\[ \text{13C NMR (126 MHz, Chloroform-d) } \delta \] 167.6, 165.1, 153.6, 137.3, 137.2, 134.3, 131.1, 125.1,
122.3, 107.1, 80.8, 72.4, 63.2, 40.7, 28.2, 14.0.

\[ \text{HMRS (ESI): Calculated for } C_{14}H_{13}O_{6}N_{S} = \text{[M-}t\text{-Bu}+H]^+ = 324.05636, \text{found: 324.05687} \]

2.1.4 Synthesis of fused Pyrrolines by Phosphine Catalysis

Ketimine substrate \[ \text{1-CO}_2\text{Et} \] (1.0 eq., 90 mg, 0.38 mmol) and \[ \text{PPh}_3 \] (0.35 eq., 34.5 mg, 0.13 mmol) were combined in dry Toluene (6 ml) in an oven-dried Schlenk tube under an Argon atmosphere. Benzylxoyallene (1.70 eq., 93.5 mg, 0.64 mmol) was added and the reaction was
stirred at same temperature and monitored by TLC. After completion of conversion (5 h), the reaction mixture was concentrated under reduced pressure.
Crude reaction mixtures was subjected to silica gel column chromatography (12% to 16% EA/CyH) to give [3+2] product in 82% yield (0.31 mmol, 128 mg).

\[ \text{1H NMR (500 MHz, Chloroform-d) } \delta 8.03 - 7.93 (m, 1H), 7.81 - 7.74 (m, 1H), 7.64 - 7.53 (m, 2H), 7.43 - 7.31 (m, 5H), 7.01 (t, } J = 2.3 \text{ Hz, 1H}), 5.29 (d, } J = 12.2 \text{ Hz, 1H}), 5.24 (d, } J = 12.2 \text{ Hz, 1H}), 4.87 (d, } J = 18.2 \text{ Hz, 1H}), 4.38 (d, } J = 18.2 \text{ Hz, 1H}), 4.21 (qd, } J = 7.1, 4.2 \text{ Hz, 2H}), 1.18 (t, } J = 7.1 \text{ Hz, 3H).} 

\[ \text{13C NMR (126 MHz, Chloroform-d) } \delta 167.9, 161.8, 141.7, 136.5, 135.2, 135.1, 133.6, 133.4, 130.6, 128.8, 128.5, 127.5, 121.4, 80.9, 67.3, 63.0, 54.8, 13.9.} 

\[ \text{HMRS (ESI): Calculated for C}_{21}H_{20}O_6NS = [M+H]^+: = 414.10058, \text{ found: 414.10013} \]

\[ \text{Calculated for C}_{21}H_{19}O_6NSNa = [M+H]^+: = 436.08253, \text{ found: 436.08184} \]

\[ \text{Calculated for C}_{21}H_{19}O_6NSK = [M+H]^+: = 452.05593, \text{ found: 452.05647} \]

2.1.5 Diels-Alder reaction of Ketimines with Danishefsky's diene

![General Reaction Scheme](image)

**General procedure:**

To a solution of Ketimine 1 (1.0 eq) in Toluene or N,N-DMF in a 35 ml microwave tube equipped with a magnetic stirring bar, Danishefsky's diene was added, the vessel was flushed with Argon, closed and heated in a microwave at corresponding maximum temperature at 250 W for 45 min. After reaction, 8 ml of saturated aqueous NH\textsubscript{4}Cl solution was added and the mixture was extracted with Ethyl acetate (three times 5 ml). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated using a rotary evaporator. The crude material was objected to silica gel flash chromatography.

\[ \text{(+)-10,10a-dihydro-9H-benzo[4,5]isothiazolo[2,3-a]pyridin-9-one 5,5-dioxide (6a)} \]
Conditions:
Ketimine (1.0 eq., 148 mg, 0.89 mmol) in 3 ml Toluene (to give 0.30 M solution)
Danishefsky’s diene (1.4 eq., 240 µl, 1.24 mmol)
Conditions: 140 °C (250 W) for 30 min
Silica gel flash chromatography (EA/ CyH 18%-26%) to furnish 200 mg of Sulfonamide (96%, 0.85 mmol).

\(^1\)H NMR (500 MHz, Chloroform-\(d\)) \(\delta\) 7.89 (dt, \(J = 7.9, 0.9\) Hz, 1H), 7.76 (td, \(J = 7.6, 1.1\) Hz, 1H), 7.67 (d, \(J = 7.8\) Hz, 1H), 7.64 (d, \(J = 7.9\) Hz, 1H), 7.47 (d, \(J = 7.8\) Hz, 1H), 5.58 (dd, \(J = 8.0, 1.1\) Hz, 1H), 5.35 (dd, \(J = 15.2, 4.3\) Hz, 1H), 3.06 (ddd, \(J = 16.0, 4.3, 1.1\) Hz, 1H), 2.72 (dd, \(J = 16.0, 15.2\) Hz, 1H).

\(^13\)C NMR (126 MHz, Chloroform-\(d\)) \(\delta\) 190.8, 138.1, 134.8, 134.4, 134.2, 130.6, 123.7, 122.1, 108.4, 57.3, 41.1.

HMRS (ESI): Calculated for \(C_{11}H_{10}O_3NS = [M+H]^+ = 236.03759\) found: 236.03744

(\(\pm\))-10a-phenyl-10,10a-dihydro-9H-benzo[4,5]isothiazolo[2,3-a]pyridin-9-one 5,5-dioxide (6b)

Conditions:
Ketimine (1.0 eq., 400 mg, 1.64 mmol) in 3.5 ml Toluene (to give a 0.45 M solution),
Danishefsky’s diene (1.25 eq., 398 µl, 2.06 mmol),
Conditions: 180 °C (250 W) for 45 min,
Silica gel flash chromatography (EA/ CyH 20%-34%) to furnish 315 mg of sulfonamide (62%, 1.01 mmol).

\(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 7.91 – 7.88 (m, 1H), 7.66 (td, \(J = 7.6, 1.4\) Hz, 1H), 7.61 (td, \(J = 7.6, 1.2\) Hz, 1H), 7.56 (d, \(J = 7.8\) Hz, 1H), 7.52 – 7.48 (m, 3H), 7.39 – 7.28 (m, 7H), 5.53 (dd, \(J = 7.8, 1.1\) Hz, 2H), 3.66 (dd, \(J = 16.1, 1.1\) Hz, 1H), 3.05 (d, \(J = 16.1\) Hz, 1H).
$^{13}$C NMR (101 MHz, Chloroform-d) δ 190.4, 140.5, 137.9, 136.8, 134.8, 132.2, 130.4, 129.5, 129.3, 126.3, 124.2, 122.1, 109.9, 69.3, 46.4.

HMRS (ESI): Calculated for $C_{17}H_{14}O_3NS = [M+H]^+ = 312.06889$, found: 312.06872

(+)-10a-(pyridin-2-yl)-10,10a-dihydro-9H-benzo[4,5]isothiazolo[2,3-a]pyridin-9-one 5,5-dioxide (6c)

Conditions:
Ketimine (1.0 eq., 240 mg, 0.98 mmol) in 4 ml Toluene:N,N DMF 7:1 (v/v, as Ketimine is not soluble in neat toluene, to give 0.25 M solution)
Danishefsky's diene (1.5 eq., 285 µl, 1.47 mmol)
Conditions: 140 °C (250 W) for 45 min
Silica gel flash chromatography (EA/ CyH 20%-32%) to furnish 238 mg of Sulfonamide (78%, 0.76 mmol).

$^1$H NMR (500 MHz, Chloroform-d) δ 8.62 (d, $J = 4.8$ Hz, 1H), 7.85 (d, $J = 7.8$ Hz, 1H), 7.75 (d, $J = 7.9$ Hz, 1H), 7.70 – 7.58 (m, 4H), 7.53 (d, $J = 8.1$ Hz, 1H), 5.52 (dd, $J = 7.9$, 1.0 Hz, 1H), 4.23 (dd, $J = 15.7$, 1.1 Hz, 1H), 2.93 (d, $J = 15.7$ Hz, 1H).

$^{13}$C NMR (126 MHz, Chloroform-d) δ 190.6, 156.6, 150.0, 139.0, 137.7, 136.5, 134.7, 132.1, 130.5, 125.0, 123.6, 121.7, 119.8, 109.7, 69.8, 46.1.

HMRS (ESI): Calculated for $C_{17}H_{16}O_3N_2S = [M+H]^+ = 313.06414$, found: 316.06401

(+)-10a-ethyl-10,10a-dihydro-9H-benzo[4,5]isothiazolo[2,3-a]pyridin-9-one 5,5-dioxide-carbon dioxide (6d)

Conditions:
Ketimine $1$-CO$_2$Et (1.0 eq., 248 mg, 1.00 mmol) in 3.4 ml Toluene (0.29 M),
Danishefsky's diene (1.4 eq., 271 µl, 1.40 mmol),
Conditions: 140 °C (250 W) for 45 min,
Silica gel flash chromatography (EA/ CyH 20%-34%) to furnish 290 mg of desired sulfonamide (94%, 0.94 mmol)

\(^1\)H NMR (400 MHz, Chloroform-d) \(\delta\) 7.89 (d, \(J = 7.6\) Hz, 1H), 7.77 (t, \(J = 7.6\) Hz, 1H), 7.74 – 7.62 (m, 3H), 5.58 (d, \(J = 8.0\) Hz, 1H), 4.28 – 4.12 (m, 2H), 3.61 (d, \(J = 16.1\) Hz, 1H), 2.83 (d, \(J = 16.1\) Hz, 1H), 1.21 (t, \(J = 7.1\) Hz, 3H).

\(^1^3\)C NMR (176 MHz, Chloroform-d) \(\delta\) 194.8, 169.8, 164.2, 137.1, 135.7, 133.7, 130.8, 124.3, 122.0, 104.9, 65.6, 63.5, 58.0, 14.1.

HMRS (ESI): Calculated for C\(_{14}\)H\(_{14}\)O\(_3\)N S = [M+H]\(^+\): = 308.05872, found: 308.05897

(+)-10a-methyl-10,10a-dihydro-9H-benzo[4,5]isothiazolo[2,3-a]pyridin-9-one 5,5-dioxide (6e)

\[
\begin{align*}
\text{Conditions:} \\
\text{Ketimine (1.0 eq., 200.0 mg, 1.10 mmol) in 5 ml Toluene (to give 0.22 M solution)} \\
\text{Danishefsky’s diene (1.25 eq., 267 µl, 1.38 mmol)} \\
\text{Conditions: 140 °C (250 W) for 30 min} \\
\text{Silica gel flash chromatography (EA/ CyH 22%-34%) to furnish 19 mg of Sulfonamide (7% yield, 0.08 mmol)}
\end{align*}
\]

\(^1\)H NMR (700 MHz, Chloroform-d) \(\delta\) 7.87 (d, \(J = 7.8\) Hz, 1H), 7.76 (t, \(J = 7.6\) Hz, 1H), 7.65 (t, \(J = 7.6\) Hz, 1H), 7.57 (d, \(J = 7.9\) Hz, 1H), 7.43 (d, \(J = 7.8\) Hz, 1H), 5.58 (d, \(J = 7.9\) Hz, 1H), 2.88 (d, \(J = 15.7\) Hz, 1H), 2.81 (d, \(J = 15.7\) Hz, 1H), 1.71 (s, 3H).

\(^1^3\)C NMR (176 MHz, Chloroform-d) \(\delta\) 190.7, 141.3, 136.7, 134.6, 133.2, 130.4, 130.3, 122.8, 122.1, 106.9, 64.1, 47.3, 24.3.

HMRS (ESI): Calculated for C\(_{12}\)H\(_{12}\)O\(_3\)N S = [M+H]\(^+\): = 250.05324 found: 250.05298
2.1.6 [3+2] Cycloaddition of Ketimines with Azomethine ylides

![General Reaction Scheme](image)

**General procedure for synthesis of fused imidazolidines 8a-e**

N-(Methoxymethyl)-N-(trimethylsilylmethyl)benzylamine (82.0 µl, 0.30 mmol) and corresponding imine (0.10 mmol) were combined in CH₂Cl₂ (0.7 mL) in an oven-dried Schlenk tube and a mixture of TFA and CH₂Cl₂ (10% v/v in 36 µl DCM, 0.5 eq.) was added via syringe. The resultant mixture was stirred at 0°C (ice-water bath) for 1 h. The crude reaction mixture was purified by flash chromatography on silica gel (EtOAc/Petroleum Ether) to afford corresponding tricyclic sulfonamides.

*(+)-2-benzyl-1,2,3,9b-tetrahydrobenzo[d]imidazo[1,5-b]isothiazole 5,5-dioxide (8a)*

![Image](image)

Yield: 37%, 11 mg, 0.04 mmol

**¹H NMR** (500 MHz, Chloroform-d) δ 7.78 (d, J = 7.6 Hz, 1H), 7.63 (td, J = 7.6, 1.1 Hz, 1H), 7.57 – 7.52 (m, 1H), 7.33 (dd, J = 7.7, 1.0 Hz, 1H), 7.30 – 7.22 (m, 4H), 7.18 (d, J = 7.2 Hz, 1H), 5.07 (dd, J = 7.0, 2.8 Hz, 1H), 4.74 (d, J = 8.6 Hz, 1H), 3.87 (d, J = 8.6 Hz, 1H), 3.60 (d, J = 13.2 Hz, 1H), 3.52 (d, J = 13.2 Hz, 1H), 3.22 (dd, J = 10.5, 2.8 Hz, 1H), 3.17 (dd, J = 10.5, 7.0 Hz, 1H).

**¹³C NMR** (126 MHz, Chloroform-d) δ 139.9, 137.3, 136.2, 133.4, 129.6, 128.5, 128.5, 127.5, 123.8, 121.6, 71.0, 63.2, 58.0, 57.2.

**HMRS (ESI):** Calculated for C₁₆H₁₇O₂N₂S = [M+H]⁺: 301.10053, found: 301.10053
(+)-2-benzyl-9b-phenyl-1,2,3,9b-tetrahydrobenzo[d]imidazo[1,5-b]isothiazole 5,5-dioxide (8b)

Yield: 83%, 73 mg, 0.19 mmol

$^1$H NMR (400 MHz, Chloroform-d) δ 7.74 (d, $J = 7.7$ Hz 1H), 7.66 (d, $J = 7.9$ Hz, 2H), 7.56 (t, $J = 8.0$ Hz, 1H), 7.49 (d, $J = 7.4$ Hz, 1H), 7.45 (d, $J = 8.5$, 1H), 7.36 (t, $J = 7.3$ Hz, 2H), 7.32 – 7.22 (m, 4H), 7.14 (d, $J = 6.8$ Hz, 2H), 4.98 (d, $J = 9.0$ Hz, 1H), 3.92 (d, $J = 8.9$ Hz, 1H), 3.84 (d, $J = 10.1$ Hz, 1H), 3.59 (d, $J = 13.2$ Hz, 2H), 3.50 (d, $J = 13.2$ Hz, 2H), 3.30 (d, $J = 10.2$ Hz, 2H).

$^{13}$C NMR (126 MHz, Chloroform-d) δ 144.0, 142.7, 137.7, 135.4, 133.8, 129.7, 129.0, 128.7, 128.6, 128.2, 127.7, 125.9, 124.3, 121.3, 77.4, 71.6, 66.4, 56.7.

HMRS (ESI): Calculated for C$_{22}$H$_{21}$O$_2$N$_2$S = [M+H]$^+$: = 377.13183, found: 377.13178

(+)-2-benzyl-9b-(pyridin-2-yl)-1,2,3,9b-tetrahydrobenzo[d]imidazo[1,5-b]isothiazole 5,5-dioxide (8c)

Yield: 67%, 28 mg, 74 μmol

$^1$H NMR (500 MHz, Chloroform-d) δ 8.57 (ddd, $J = 4.9$, 1.8, 0.9 Hz, 1H), 7.95 (dt, $J = 8.0$, 1.1 Hz, 1H), 7.85 (dt, $J = 7.9$, 0.9 Hz, 1H), 7.72 (dt, $J = 7.7$, 0.9 Hz, 1H), 7.65 (td, $J = 7.8$, 1.8 Hz, 1H), 7.57 (td, $J = 7.6$, 1.2 Hz, 1H), 7.50 (td, $J = 7.5$, 1.1 Hz, 1H), 7.28 – 7.21 (m, 3H), 7.18 (dd, $J = 7.5$, 4.8 Hz, 1H), 7.14 – 7.09 (m, 2H), 4.96 (dd, $J = 9.0$, 1.3 Hz, 1H), 3.97 (d, $J = 9.0$ Hz, 1H), 3.88 (dd, $J = 11.0$, 1.3 Hz, 1H), 3.58 (d, $J = 13.3$ Hz, 1H), 3.46 (d, $J = 13.3$ Hz, 1H).

$^{13}$C NMR (126 MHz, Chloroform-d) δ 161.0, 149.5, 142.8, 137.5, 137.4, 134.7, 133.6, 129.7, 128.7, 128.5, 127.5, 125.3, 122.8, 121.1, 120.2, 77.4, 72.0, 65.7, 57.1.

HMRS (ESI): Calculated for C$_{21}$H$_{20}$O$_2$N$_3$S = [M+H]$^+$: = 378.12707, found: 378.12685
(+)-2-benzyl-9b-methyl-1,2,3,9b-tetrahydrobenzo[d]imidazo[1,5-b]isothiazole 5,5-dioxide (8d)

Yield: 48%, 18 mg, 0.05 mmol

$^1$H NMR (400 MHz, Chloroform-d) $\delta$ 7.74 – 7.70 (m, 1H), 7.63 – 7.51 (m, 3H), 7.24 – 7.16 (m, 3H), 7.08 – 7.04 (m, 2H), 4.76 (dd, $J = 9.1, 0.5$ Hz, 1H), 4.18 (tq, $J = 7.1, 3.6$ Hz, 2H), 4.01 (d, $J = 9.1$ Hz, 1H), 3.52 (d, $J = 13.1$ Hz, 1H), 3.41 (d, $J = 9.1$ Hz, 1H), 3.39 (s, 1H), 1.20 (t, $J = 7.1$ Hz, 3H).

$^{13}$C NMR (126 MHz, Chloroform-d) $\delta$ 169.7, 138.2, 137.1, 135.7, 133.7, 130.6, 128.6, 128.6, 127.7, 124.7, 121.7, 75.2, 72.1, 63.0, 62.7, 57.2, 14.0.

HMRS (ESI): Calculated for C$_{19}$H$_{21}$O$_4$N$_2$S = [M+H]$^+$: = 373.12165, found: 373.12118

Calculated for C$_{19}$H$_{20}$O$_4$N$_2$Na S = [M+H]$^+$: = 395.10360, found: 395.10346

(+)-2-benzyl-9b-methyl-1,2,3,9b-tetrahydrobenzo[d]imidazo[1,5-b]isothiazole 5,5-dioxide (8e)

Yield: 73%, 23 mg, 0.07 mmol

$^1$H NMR (500 MHz, Chloroform-d) $\delta$ 7.75 (dt, $J = 7.8, 0.9$ Hz, 1H), 7.62 (td, $J = 7.5, 1.2$ Hz, 1H), 7.52 (td, $J = 7.6, 1.0$ Hz, 1H), 7.31 (dt, $J = 7.8, 0.9$ Hz, 1H), 7.27 – 7.21 (m, 3H), 7.11 (dd, $J = 7.9, 1.7$ Hz, 2H), 4.75 (dd, $J = 8.6, 1.1$ Hz, 1H), 3.83 (d, $J = 8.6$ Hz, 1H), 3.57 – 3.44 (m, 2H), 3.38 (dd, $J = 10.0, 1.2$ Hz, 1H), 2.78 (d, $J = 10.0$ Hz, 1H), 1.71 (s, 3H).

$^{13}$C NMR (126 MHz, Chloroform-d) $\delta$ 145.0, 137.3, 136.0, 133.6, 129.3, 128.5, 128.5, 127.5, 122.9, 121.4, 72.1, 71.1, 65.3, 56.7, 27.3.

HMRS (ESI): Calculated for C$_{17}$H$_{19}$O$_2$N$_2$S = [M+H]$^+$: = 315.11618, found: 315.11605
2.1.7 Reaction of Pyruvate derived α-silyl imines with Ketimines

\[
\text{S}\quad \overset{\text{N}}{\text{O}} \quad \text{CO}_2\text{Et} \quad \text{CO}_2\text{Et} \\
\text{AgOAc/PPh}_3 \quad \text{TMS} \quad \text{MeCN} \\
\text{General Reaction Scheme}
\]

\((\pm)-\text{diethyl-1-methyl-2,3-dihydrobenzo[d]imidazo[1,5-b]isothiazole-1,9b(1H)-dicarboxylate 5,5-dioxide (10)}\)

**Condition A** (affording ~ 1:1 d.r.)

To a solution of ketimine \(1\text{-CO}_2\text{Et}\) (19 mg, 80 \(\mu\)mol, 1.0 equiv.) in 500 \(\mu\)l dry \(\text{Et}_2\text{O}\) was added silylimine (365.470 \(\mu\)l, 90 mg per ml in diethyl ether solution, 158.83 \(\mu\)mol, 2.0 equiv.) followed by the addition of AgOAc (30mol%, 4.0 mg, 23.82 \(\mu\)mol) and PPh\(_3\) (30mol%, 6.3 mg, 23.82 \(\mu\)mol). The reaction was stirred at 21° C and monitored via TLC for completion. The reaction mixture was then quenched by the addition of brine and transferred to a separation funnel. EA was added and layers were separated. The aqueous layer was extracted twice more with EA. Combined organic layers were washed with water and brine once more each and dried over \(\text{Na}_2\text{SO}_4\). The solvent was removed \textit{in vacuo} and the residue was objected to silica gel column chromatography (25% to 27% to 29% to 32% to 39% \(\text{EA/Me}_2\text{CO}\), 1 CV each) to elute two products \textit{syn-10} and \textit{anti-10} in 38% (11 mg, 0.03 mmol) and 31% (9 mg, 0.02 mmol) yield, respectively.

**Optimized Condition B** (affording 100:15 d.r.)

AgNO\(_3\) (20mol%, 9.9 mg, 58.5 \(\mu\)mol) and tri(4-trifluoromethylphenyl)phosphine (20mol% 27 mg, 58.5 \(\mu\)mol, ) were combined in 1.84 ml dry \(\text{MeCN}\) at 0 °C. Ketimine \(1\text{-CO}_2\text{Et}\) (70 mg, 293 \(\mu\)mol, 1.0 equiv.) and silylimine (2.0 eq., 585.16 \(\mu\)l, 585.16 \(\mu\)mol, 1 mM in diethyl ether) were subsequently added. The reaction was stirred at 0° C for 2 h and monitored \textit{via} TLC for completion. HCl (20 \(\mu\)l) was added to the reaction mixture and stirred for 20 more minutes. The reaction mixture was then quenched by the addition of 50 \(\mu\)l 1 M aq. HCl. The mixture was concentrated and redissolved in Chloroform/Ethanol (9:1) and passed through a short pad of silica gel. The crude material was then analyzed by proton NMR to show a diastereomeric ratio of 100:15 in favor of \textit{syn-10}. Objection to silica gel column chromatography (using gradient 25% to 27% to 29% to 32% to 39% \(\text{EA/Me}_2\text{CO}\)) then furnished 57 mg (154.7 \(\mu\)mol, 53% combined yield) of fused imidazoline.
**syn-10**

**$^{1}$H NMR** (500 MHz, Chloroform-$d$) δ 7.96 (d, J = 7.8 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.69 (td, J = 7.6 Hz, 1H), 7.64 (td, J = 7.6 Hz, 1H), 4.75 (d, J = 8.5 Hz, 1H), 4.59 (d, J = 8.5 Hz, 1H), 4.33 (qd, J = 7.2, 3.2 Hz, 2H), 4.18 (tq, J = 7.1, 3.6 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H), 1.23 (d, J = 7.1 Hz, 3H), 0.95 (s, 3H).

**$^{13}$C NMR** (126 MHz, Chloroform-$d$) δ 171.3, 136.6, 133.3, 133.3, 131.1, 127.4, 121.4, 80.4, 72.0, 63.2, 62.8, 62.7, 20.2, 14.2, 14.0.

**HMRS (ESI)**: Calculated for C$_{16}$H$_{21}$O$_6$N$_2$S = [M+H]$^+$ = 369.11148, found: 369.11103
Calculated for C$_{16}$H$_{20}$O$_6$N$_2$NaS = [M+H]$^+$ = 391.09343, found: 391.09237
Calculated for C$_{16}$H$_{20}$O$_6$N$_2$K$S = [M+H]$^+$ = 407.06737, found: 407.06662

**Xray Deposition number at the Cambridge Crystallographic Data Centre**: CCDC 1910465
anti-10

$^1$H NMR (500 MHz, Chloroform-d) δ 7.79 (d, $J = 7.9$ Hz, 1H), 7.69 (d, $J = 7.3$ Hz, 1H), 7.63 – 7.56 (m, 2H), 5.14 (d, $J = 9.8$ Hz, 1H), 4.43 (d, $J = 9.8$ Hz, 1H), 4.30 (qd, $J = 7.2$, 1.6 Hz, 2H), 3.83 – 3.74 (m, 1H), 3.72 – 3.63 (m, 1H), 1.63 (s, 3H), 1.35 (t, $J = 7.2$ Hz, 3H), 0.97 (t, $J = 7.2$ Hz, 3H).

$^{13}$C NMR (126 MHz, Chloroform-d) δ 169.4, 168.1, 135.6, 133.2, 132.6, 130.8, 127.4, 120.9, 80.4, 74.7, 65.2, 62.9, 62.1, 20.2, 14.1, 13.5.

HMRS (ESI): Calculated for C$_{16}$H$_{21}$O$_6$N$_2$S = [M+H]$^+$: = 369.11148, found: 369.11134

Calculated for C$_{16}$H$_{20}$O$_6$N$_2$NaS = [M+H]$^+$: = 391.09343, found: 391.09284

Calculated for C$_{16}$H$_{20}$O$_6$N$_2$K S = [M+H]$^+$: = 407.06737, found: 407.06702

Table S1: Conditions for optimizations of diastereoselectivity in 3+2 cyclization of $N$-sulfonyl ketimines (1) with $\alpha$-silyl imines (9). Diastereoselectivity was determined by integration of peaks in $^1$H-NMR spectra of crude reaction mixtures

| Condition # | Phosphine                        | Solvent | T/°C  | Scale / mmol | d.r.   |
|-------------|----------------------------------|---------|--------|--------------|--------|
| 1           | Triphenylphosphine               | DCM     | -40 to 21 | 0.09         | n.d.   |
| 2           | Tri-o-tolylphosphine             | Et$_2$O | 21     | 0.08         | 24:10  |
| 3           | Triphenylphosphine               | Et$_2$O | 21     | 0.08         | 19:10  |
| 4           | Tricyclohexylphosphine           | Et$_2$O | 21     | 0.08         | 10:9.2 |
| 5           | Tri(4-CF$_3$)-phenylphosphine    | Et$_2$O | 21     | 0.08         | 22:10  |
| 6           | XPhos                            | Et$_2$O | 21     | 0.08         | 11:10  |
| 7           | Tri-o-tolylphosphine             | MeCN    | 21     | 0.08         | 5:1    |
| 8           | iPhox                            | MeCN    | 21     | 0.08         | 100:17 |
| 9           | (Sa,S)-DTB-Bn-SIPHOSX            | MeCN    | 21     | 0.08         | 100:23 |
| 10          | Tri(4-CF$_3$)-phenylphosphine    | MeCN    | 0      | 0.08         | 100:16 |
| 11          | Tri(4-CF$_3$)-phenylphosphine    | MeCN    | 0      | 0.3          | 100:15 |
2.2. Vinylogous Addition of Silyl Enol Ether to Ketimines (12a)

The proposed structures were based on evaluation of 1D –NOE NMR experiments (see below).

To 239 mg (1.0 eq, 1.00 mmol) of 3-carbethoxy 1,2 benzothiazole 1,1 dioxide (1-CO$_2$Et) and AgOAc in dry DCM (3.7 ml) under an Argon atmosphere in an oven-dried Schlenk flask, Silyl Enol Ether (1.6 eq, 312 µl, 1.60 mmol) was added at -78°C (Acetone-dry ice bath). The reaction was stirred at same temperature and monitored by TLC. After completion of reaction (10 min), sat. aqueous NaHCO$_3$ solution was added and stirred for 5 min at 0 °C, then transferred to a separation funnel and 8 ml of Ethyl acetate were added. Layers were separated and the aqueous layer was extracted two more times (8 ml Ethyl Acetate each). The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. After removal of solvent, the residue was purified using silica gel flash column chromatography (22% EA/CyH to 35% EA/CyH) to yield product in 89% yield (300 mg, 0.89 mmol) and 86:14 d.r.

(+)-Ethyl 3-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (1 or syn 12a)

$^1$H NMR (400 MHz, Chloroform-d) δ 7.95 – 7.91 (m, 1H), 7.74 – 7.71 (m, 1H), 7.67 – 7.61 (m, 3H), 6.15 (s, 1H), 5.84 (d, J = 5.7 Hz, 1H), 4.52 – 4.39 (m, 2H), 1.61 (s, 3H), 1.42 (t, J = 7.1 Hz, 3H); $^{13}$C NMR (126 MHz, Chloroform-d) δ 171.8, 167.9, 157.6, 135.8, 133.9, 132.2, 131.6,
127.5, 123.1, 121.7, 89.6, 71.6, 64.9, 20.8, 14.2; **HMRS (ESI):** Calculated for $\text{C}_{15}\text{H}_{16}\text{O}_{6}\text{N}\text{S} = [\text{M+H}]^+ = 338.06928$, found: 338.06994

Calculated for $\text{C}_{15}\text{H}_{15}\text{O}_{6}\text{N}\text{Na}\text{S} = [\text{M+H}]^+ = 360.05123$, found: 360.05266

**l-12a 1D NOE-experiments**

Irradiation of methyl group (1.6 ppm) shows NOE with sulfonamide amine N-H (6.15 ppm) and aromatic proton at ~7.6 ppm.

*syn-12a or l-12a*
Irradiation of lactone proton in α carbonyl position (5.8 ppm) shows NOE to aromatic proton at roughly 7.6 ppm. Both observations lead us to conclude that we this is in fact diastereomer in conformation depicted in structure below.

(±)-Ethyl 3-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (anti or l-12a)

$^1$H NMR (500 MHz, Chloroform-d) δ 8.17 (dt, $J = 8.0, 0.9$ Hz, 1H), 7.82 – 7.79 (m, 1H), 7.75 (td, $J = 7.6, 1.3$ Hz, 1H), 7.69 (td, $J = 7.6, 1.1$ Hz, 1H), 7.57 (d, $J = 5.7$ Hz, 1H), 6.20 (d, $J = 5.6$ Hz, 1H), 6.09 (s, 1H), 4.29 – 4.16 (m, 2H), 1.37 (s, 3H), 1.29 (t, $J = 7.1$ Hz, 3H).

$^{13}$C NMR (126 MHz, Chloroform-d) δ 171.1, 167.7, 157.7, 136.3, 133.9, 132.4, 131.6, 128.7, 123.3, 121.6, 90.4, 72.0, 60.5, 19.6, 13.9.

HMRS (ESI): Calculated for C$_{15}$H$_{16}$O$_6$N S = [M+H]$^+$: = 338.06928, found: 338.06966
Calculated for C$_{15}$H$_{15}$O$_6$N Na S = [M+H]$^+$: = 360.05123, found: 360.05123
Aromatic proton shows weak NOE of methyl group (1.4 ppm) with aromatic proton at 7.8 ppm, hinting towards conformation depicted below.
Irradiation of 7' (8.15 ppm) shows NOE with not only neighbouring aromatic proton (~7.6 ppm) but also weak effect with methyl group (1.37 ppm).
2.2.1 Screening conditions for improvement of 12a diastereomeric ratio

Table S1: Screening conditions to improve d.r. of vinylogous addition to ketimines.

| Condition # | Catalyst      | Solvent           | d.r.                |
|-------------|---------------|-------------------|---------------------|
| 1           | Ti(O\text{Pr})_4 | DCM               | 1:2                 |
| 2           | Zn(OTf)_2     | DCM               | n.d. Complex mixture|
| 3           | Cu(OTf)_2     | DCM               | 3:1                 |
| 4           | Dy(OTf)_3     | DCM               | n.d. – Complex mixture|
| 5           | AgOAc         | Et\text{2}O       | 2:1 (f2:f1)         |
| 6           | AgOAc         | THF               | 10:13               |
| 7           | AgOAc         | DCM + TMEDA       | 10:6.8              |
| 8           | AgOAc         | DCM               | 93:7                |

(\(+\)-3-ethyl-1,1-dioxido-2,3-dihydrobenzo[d]isothiazol-3-yl)-5-methylidihydrofuran-2(3H)-one-carbon dioxide (\textit{syn or I}-12b)

\[
\begin{align*}
\text{Pd/C/H}_2 & \quad \text{MeOH} \\
\text{General Reaction Scheme}
\end{align*}
\]

Sulfonamide \textit{syn}-12a (62 mg, 183.8 µmol) and Pd on Carbon (10 wt.%, 22.5 mg, 21.14 µmol) were dissolved in EtOH (1.4 ml) in a 10 ml Schlenk tube and stirred at ambient temperature (21 °C). The vessel was evacuated and refilled with hydrogen. This was repeated two times. The mixture was allowed to come to ambient temperature and stirred under an hydrogen atmosphere for 3 h. Then, reaction mixture was filtered over celite, concentrated and objected to silica gel column chromatography (25% to 35% EA/CyH) to yield 39 mg (0.11 mmol, 63%) of product sulfonamide and recover 28 mg (0.07 mmol, 37%) of starting material.

\textbf{\textsuperscript{1}H NMR} (700 MHz, Chloroform-\textit{d}) \(\delta\) 8.02 – 7.99 (m, 1H), 7.81 – 7.78 (m, 1H), 7.69 – 7.65 (m, 2H), 6.05 (s, 1H), 4.44 – 4.32 (m, 2H), 2.51 – 2.45 (m, 1H), 2.16 – 2.11 (m, 1H), 2.07 – 1.98 (m, 2H), 1.52 (s, 3H), 1.37 (t, \(J = 7.1\) Hz, 3H).

\textbf{\textsuperscript{13}C NMR} (176 MHz, Chloroform-\textit{d}) \(\delta\) 175.9, 168.4, 136.4, 133.7, 132.4, 131.4, 128.3, 121.7, 87.4, 72.7, 64.4, 29.8, 28.0, 23.8, 14.0.

\textbf{HMRS (ESI)}: Calculated for C\textsubscript{15} H\textsubscript{18} O\textsubscript{6} N S = [M+H]\textsuperscript{+}: = 340.08493, found: 340.08524

Calculated for C\textsubscript{15} H\textsubscript{17} O\textsubscript{6} N Na S = [M+H]\textsuperscript{+}: = 362.06688, found: 362.06717
2.3 Folding Pathway

2.3.1 Hydrogenolysis of Aziridines

\((\pm)\)-4-methyl-3-carbethoxy-3,4-dihydro-2H-benzo[e][1,2]thiazine 1,1-dioxide (13a)

Sulfonamide 2b (1.0 eq., 40 mg, 0.15 mmol) and Palladium on carbon (10 wt.%, 0.1 eq., 8.0 mg, 0.05 mmol) were dissolved in 1 ml Ethanol in a 10 ml tube equipped with a stirring bar. The vessel was evacuated and refilled with hydrogen using a balloon. This was repeated twice and the reaction was left stirring at 21 °C under an hydrogen atmosphere for 4 h. Then, it was filtered using a syringe filter and concentrated under reduced pressure to give 24 mg (0.09 mmol, 60% yield) product.

\(^1\)H NMR (700 MHz, Chloroform-\(d\)) \(\delta \) 7.81 (dq, \(J = 7.9, 1.4 \) Hz, 1H), 7.50 (tt, \(J = 7.6, 1.3 \) Hz, 1H), 7.41 (tq, \(J = 7.6, 1.2 \) Hz, 1H), 7.28 (dd, \(J = 8.0, 1.2 \) Hz, 1H), 5.36 – 5.27 (m, 1H), 4.84 (ddd, \(J = 10.4, 3.7, 1.0 \) Hz, 1H), 4.32 (qt, \(J = 7.2, 1.2 \) Hz, 2H), 3.39 (qd, \(J = 7.2, 3.7 \) Hz, 1H), 1.35 (td, \(J = 7.2, 1.2 \) Hz, 3H), 1.23 (d, \(J = 7.2 \) Hz, 3H).

\(^{13}\)C NMR (176 MHz, Chloroform-\(d\)) \(\delta \) 168.3, 139.2, 136.4, 132.6, 129.4, 128.2, 124.1, 62.4, 57.8, 34.7, 17.5, 14.2.

HMRS (ESI): Calculated for \(\text{C}_{12}\text{H}_{16}\text{O}_4\text{N}_2\text{S} [\text{M+H}]^{+} = 270.07946 \), found: 270.07923
Sulfonamide 2d (1.0 eq., 17 mg, 51.61 µmol) was combined with Pd/C (10 wt.%, 4.4 mg, 4.13 µmol) in a 10 ml Schlenk tube and dissolved in 500 µl of a Ethanol/Ethyl acetate mixture (2:1 v/v). The reaction vessel was carefully evacuated under stirring and refilled with hydrogen. This was repeated twice and the reaction was allowed to stir at 21 °C under an hydrogen atmosphere. After completion of conversion, the reaction mixture was filtered using a syringe filter and concentrated to give 16 mg (0.05 mmol, quantitative) of desired product.

**1H NMR** (700 MHz, Chloroform-d) δ 7.95 – 7.90 (m, 1H), 7.49 – 7.41 (m, 2H), 7.31 – 7.22 (m, 3H), 7.12 (d, J = 7.6 Hz, 1H), 6.96 (dd, J = 7.3, 2.2 Hz, 2H), 5.11 (d, J = 11.7 Hz, 1H), 5.04 (dd, J = 11.7, 3.8 Hz [syn], 1H), 4.58 (d, J = 3.8 Hz [syn], 1H), 4.15 – 4.03 (m, 2H), 1.16 (t, J = 7.1 Hz, 3H).

**13C NMR** (176 MHz, Chloroform-d) δ 167.1, 137.4, 137.2, 136.7, 132.9, 130.9, 129.2, 129.0, 128.9, 128.4, 124.3, 62.3, 58.8, 46.0, 14.1.
Sulfonamide 2e (1.0 eq., 20 mg, 61.47 µmol ) and Palladium on carbon (10 wt.%, 0.1 eq., 6.5 mg, 0.01 mmol) were dissolved in 650 µl of a 3:1 Ethanol/Ethyl Acetate (v/v) mixture in a 10 ml Schlenk tube equipped with a stirring bar. The vessel was evacuated and refilled with hydrogen using a balloon. This was repeated twice and the reeaction was left stirring at 21 °C under an hydrogen atmosphere. After completion of conversion, filtration using a syringe filter and concentration delivered desired 8 mg (0.02 mmol, 40% yield) of desired sulfonamide as one diastereomer.

^{1}H NMR (400 MHz, Chloroform-d) δ 7.91 – 7.87 (m, 1H), 7.60 – 7.48 (m, 3H), 5.84 (d, J = 12.4 Hz, 1H), 4.85 (dd, J = 12.4, 3.9 Hz [syn], 1H), 4.31 (qd, J = 7.1, 1.1 Hz, 2H), 4.27 (d, J = 3.9 Hz [syn], 1H), 4.17 (qd, J = 7.1, 3.3 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-d) δ 170.8, 168.1, 137.3, 132.8, 130.8, 130.7, 129.9, 125.1, 63.0, 62.8, 56.5, 44.8, 14.4, 14.3.

HMRS (ESI): Calculated for C_{17} H_{18} O_{4} N S = [M+H]^+ = 332.09511, found: 332.09556

(±)-syn- Diethyl 3,4-dihydro-2H-benzo[e][1,2]thiazine-3,4-dicarboxylate 1,1-dioxide (13c)

(±)-Ethyl (syn)-C4-(pyridin-2-yl)phenylalaninate 1,1-dioxide (13d)
Palladium on carbon (0.1 eq., 6.4 mg, 6.05 µmol) and Sulfonamide 2g (1.0 eq., 20 mg, 60.54 µmol) were combined in 600 µl Ethanol/Ethyl Acetate (3:1 v/v) in a 10 ml Schlenk tube equipped with a magnetic stirring bar. The vessel was evacuated and refilled with hydrogen. This procedure was repeated 2 times. The mixture was kept stirring for 4 h. Then, it was filtered using a syringe filter and concentrated to give product 6 mg sulfonamide (0.02 mmol, 30%).

**1H NMR** (400 MHz, Chloroform-d) δ 8.43 (ddd, J = 4.9, 1.9, 0.9 Hz, 1H), 7.95 – 7.89 (m, 1H), 7.68 (td, J = 7.7, 1.8 Hz, 1H), 7.44 – 7.40 (m, 2H), 7.33 – 7.28 (m, 1H), 7.25 – 7.21 (m, 1H), 7.18 (ddd, J = 7.7, 4.9, 1.1 Hz, 1H), 5.12 (dd, J = 12.2, 4.1 Hz, 1H), 4.56 (d, J = 4.1 Hz, 1H), 4.06 (qd, J = 7.1, 2.5 Hz, 2H), 1.08 (t, J = 7.1 Hz, 3H).

**13C NMR** (126 MHz, Chloroform-d) δ 168.0, 159.2, 149.9, 137.7, 137.1, 136.1, 132.4, 130.0, 128.8, 124.9, 123.3, 123.2, 62.0, 58.9, 45.6, 14.1.

**HMRS (ESI)**: Calculated for C_{16}H_{17}O_{4}N_{2}S = [M+H]^+ = 333.09035, found: 333.09018

(±)-4-methyl-3-phenyl-3,4-dihydro-2H-benzo[e][1,2]thiazine 1,1-dioxide (14a)

Sulfonamide 2a (1.0 eq., 20 mg, 73.71 µmol) and Palladium on carbon (10 wt.%, 0.1 eq., 7.8 mg, 0.01 mmol) were dissolved in 750 µl of a 3:1 (v/v) Ethanol/Ethyl Acetate Mixture in a 10 ml tube equipped with a stirring bar. The vessel was evacuated and refilled with hydrogen using a balloon. This was repeated twice and the reaction was left stirring at 21 °C under an hydrogen atmosphere for 16 h. Then it was filtered using a syringe filter and concentrated under reduced pressure to give 22 mg (0.08 mmol, 69%) of sulfonamide.
**1H NMR** (500 MHz, Chloroform-d) δ 7.76 (dt, J = 7.8, 1.0 Hz, 1H), 7.65 (td, J = 7.6, 1.1 Hz, 1H), 7.54 (td, J = 7.6, 1.0 Hz, 1H), 7.36 (dt, J = 7.8, 0.9 Hz, 1H), 7.35 – 7.27 (m, 3H), 7.23 – 7.18 (m, 2H), 4.69 (s, 1H), 3.18 (d, J = 13.6 Hz, 1H), 3.03 (d, J = 13.6 Hz, 1H), 1.57 (s, 3H).

**13C NMR** (126 MHz, Chloroform-d) δ 144.9, 135.5, 135.3, 133.3, 130.9, 129.5, 128.6, 127.5, 123.5, 121.6, 63.6, 47.8, 26.7.

**HMRS (ESI)**: Calculated for C_{15}H_{15}O_{2}N S = [M+H]^+: C_{15}H_{16}O_{2}N S = 274.08963, found: 274.08965

(±)-3-benzyl-3-methyl-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide (14b)

[Sulfonamide 2c (1.0 eq., 20 mg, 0.06 mmol) and Palladium on carbon (10 wt.%, 0.1 eq., 6.4 mg, 0.01 mmol) were dissolved in 600 µl Ethanol/Ethyl Acetate (3:1 v/v) in a 10 ml tube equipped with a stirring bar. The vessel was evacuated and refilled with hydrogen using a balloon. This was repeated twice and the reaction was left stirring at 21 °C under an hydrogen atmosphere for 4 h. Then, it was filtered using a syringe filter and concentrated under reduced pressure to give 6 mg (0.02 mmol, 30% yield) product.]

**1H NMR** (500 MHz, Chloroform-d) δ 7.74 – 7.66 (m, 3H), 7.63 (ddd, J = 8.2, 7.2, 1.2 Hz, 1H), 7.52 (ddd, J = 8.5, 7.7, 1.2 Hz, 2H), 7.42 – 7.37 (m, 2H), 7.35 – 7.30 (m, 1H), 7.24 – 7.15 (m, 3H), 6.94 (dt, J = 6.6, 1.6 Hz, 2H), 4.88 (s, 1H), 3.77 (d, J = 14.0 Hz, 1H), 3.59 (d, J = 14.0 Hz, 1H).

**13C NMR** (126 MHz, Chloroform-d) δ 143.2, 141.8, 134.7, 134.5, 133.3, 130.6, 129.6, 129.1, 128.8, 128.4, 127.8, 126.4, 125.0, 121.7, 68.8, 46.6

**HMRS (ESI)**: Calculated for C_{20}H_{18}O_{2}N S = [M+H]^+: C_{15}H_{16}O_{2}N S = 336.10528, found: 336.10549

(±)-Ethyl 3-benzyl-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (14c)
Ethyl 1-phenylazirino[1,2-b]benzo[d]isothiazole-7b(1H)-carboxylate 3,3-dioxide 2f (1.0 eq., 23 mg, 69.83 µmol) was combined with Palladium on Carbon (10 wt.%, 0.1 eq., 7.4 mg, 0.01 mmol) in a 10 ml Schlenk tube and dissolved in 700 µl of a Ethanol/Ethyl acetate mixture (5:1 v/v). The reaction vessel was carefully evacuated under stirring and refilled with hydrogen. This was repeated twice and the reaction was allowed to stir at 21 °C under an hydrogen atmosphere. The reaction was monitored via TLC. After completion of conversion, reaction mixture was filtered using a syringe filter and concentrated to give 12 mg sulfonamide product (0.04 mmol, 66%).

$^1$H NMR (500 MHz, Chloroform-d) $\delta$ 7.74 – 7.66 (m, 3H), 7.63 (ddd, $J$ = 8.2, 7.2, 1.2 Hz, 1H), 7.52 (ddd, $J$ = 8.5, 7.7, 1.2 Hz, 2H), 7.42 – 7.37 (m, 2H), 7.35 – 7.30 (m, 1H), 7.24 – 7.15 (m, 3H), 6.94 (dt, $J$ = 6.6, 1.6 Hz, 2H), 4.88 (s, 1H), 3.77 (d, $J$ = 14.0 Hz, 1H), 3.59 (d, $J$ = 14.0 Hz, 1H).

$^{13}$C NMR (126 MHz, Chloroform-d) $\delta$ 143.6, 141.8, 134.7, 134.5, 133.3, 130.6, 129.6, 129.1, 128.8, 128.4, 127.8, 126.4, 125.0, 121.7, 68.8, 46.6,

HMRS (ESI): Calculated for C$_{17}$H$_{18}$O$_4$N S = [M+H]$^+$: = 332.09511, found: 332.09535
Calculates for C$_{17}$H$_{17}$O$_4$Na S = [M+H]$^+$: = 354.07705, found: 354.07723

(+)-3-benzyl-3-(pyridin-2-yl)-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide(14d)

1-phenyl-7b-(pyridin-2-yl)-1,7b-dihydroazirino[1,2-b]benzo[d]isothiazole 3,3-dioxide 2h (1.0 eq., 10 mg, 29.90 µmol) was combined with Pd/C (10 wt.%; 0.15 eq., 4.7 mg, 4.49 µmol) and dissolved in 500 µl Ethanol/Ethyl Acetate (2:1) in a 10 ml round bottom flask equipped with a magnetic stirring bar and a septum. The mixture was carefully evacuated and refilled with hydrogen (using a hydrogen-filled balloon). This procedure was repeated twice and the reaction was stirred under an hydrogen atmosphere at 21 °C and monitored by TLC. After 15
h, the reaction mixture was filtered. Concentration delivered crude reaction mixture. Silica gel column chromatography yielded 5 mg (0.01 mmol, 50%) of product sulfonamide.

$^1$H NMR (400 MHz, Chloroform-d) δ 8.63 (ddd, $J$ = 4.8, 1.8, 1.0 Hz, 1H), 7.97 (dt, $J$ = 8.0, 0.9 Hz, 1H), 7.73 (d, $J$ = 7.76 Hz), 7.70 – 7.61 (m, 2H), 7.53 (dd, $J$ = 7.6, 1.0 Hz, 1H), 7.22 (ddd, $J$ = 7.3, 4.8, 1.2 Hz, 1H), 7.20 – 7.13 (m, 3H), 6.99 – 6.94 (m, 2H), 5.83 (s, 1H), 4.10 (d, $J$ = 13.8 Hz, 1H), 3.44 (d, $J$ = 13.8 Hz, 1H).

$^{13}$C NMR (126 MHz, Chloroform-d) δ 158.9, 148.9, 142.5, 137.5, 135.2, 134.5, 133.4, 130.5, 129.8, 128.7, 127.6, 125.5, 123.1, 121.4, 121.0, 69.5, 46.9.

HMRS (ESI): Calculated for C$_{19}$H$_{17}$O$_2$N$_2$S = [M+H]$^+$: = 337.10053, found: 337.10054

### 2.3.2 Hydrogenolysis of Azetidines 15

![General Reaction Scheme](image)

(+)-Ethyl (E)-2-(1,1-dioxido-5-phenyl-4,5-dihydrobenzo[f][1,2]thiazepin-3(2H)-ylidene)-acetate (15a')

Sulfonamide 4a (1.0 eq., 350 mg, 0.98 mmol) was dissolved in 10 ml Ethyl acetate and 83 mg (10wt.% Pd/C, 8 mol%, 78 µmol) and charged with 8 atm hydrogen in a high pressure cylinder and was stirred for 60 h at 21 °C. Eight drops of glacial AcOH were added and the reaction was placed again under 7.5 atm of hydrogen and stirred at that temperature. After 20 h, almost no conversion could be determined and another 6 mol% of Pd/C were added (by that time, it contained 141 mg, 0.14 eq.,0.13 mmol of Pd/C in total). It was stirred for 18 additional hours. As no further conversion (TLC, U-HPLC-MS analysis) could be observed, reaction mixture was filtered over celite and concentrated. Silica gel column chromatography
(12% to 15% EA/CyH) yielded Products 15a’ and 15a in 49% (173mg, 0.48 mmol) and 51% (179 mg, 0.50 mmol) yield.

$^1$H NMR (700 MHz, Chloroform-d) δ 11.02 (s, 1H), 7.38 (td, J = 7.5, 1.6 Hz, 1H), 7.34 (td, J = 7.6, 1.4 Hz, 1H), 7.29 (td, J = 7.3, 6.6, 1.2 Hz, 2H), 7.24 – 7.21 (m, 1H), 7.18 – 7.15 (m, 2H), 7.14 (dt, J = 7.6, 1.0 Hz, 1H), 4.93 (s, 1H), 4.59 (dd, J = 10.0, 5.2 Hz, 1H), 4.12 (qd, J = 7.1, 1.9 Hz, 2H), 3.73 (t, J = 12.6 Hz, 1H), 3.24 – 3.17 (m, 1H), 1.23 (t, J = 7.1 Hz, 3H).

$^{13}$C NMR (176 MHz, Chloroform-d) δ 168.9, 152.2, 144.4, 139.4, 139.3, 134.1, 132.7, 129.1, 128.3, 127.3, 127.0, 125.8, 96.4, 60.3, 50.8, 38.4, 14.3.

HMRS (ESI): Calculated for C$_{19}$H$_{20}$O$_4$N S = [M+H]$^+$: = 358.11076, found: 358.11134
Calculated for C$_{19}$H$_{19}$O$_4$N Na S = [M+H]$^+$: = 380.09270, found: 380.09279

(+)-Ethyl 2-((syn)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepin-3-yl)acetate (15a)

$^1$H NMR (400 MHz, Chloroform-d) δ 8.09 – 8.04 (m, 1H), 7.45 – 7.37 (m, 2H), 7.34-7.27 (m, 3H), 7.25 – 7.22 (m, 2H), 6.66 – 6.61 (m, 1H), 6.67 – 6.59 (m, 1H), 5.40 (d, J = 9.6 Hz, 1H), 5.11 (dd, J = 5.8, 2.5 Hz, 1H), 4.41 – 4.31 (m, 1H), 4.21 – 4.08 (m, 2H), 2.79 (dd, J = 16.6, 4.9 Hz, 1H), 2.59 (dd, J = 16.6, 4.9 Hz, 1H), 2.31-2.25 (m, 2H), 1.28 – 1.24 (t, J = 7.04 Hz, 3H).

$^{13}$C NMR (101 MHz, Chloroform-d) δ 171.7, 143.4, 142.8, 141.2, 132.8, 129.7, 129.2, 129.1, 127.8, 127.4, 126.8, 61.4, 53.3, 46.6, 39.7, 39.1, 14.3.

HMRS (ESI): Calculated for C$_{19}$H$_{22}$O$_4$N S = [M+H]$^+$: = 360.12641, found: 360.12695

Xray Deposition number at the Cambridge Crystallographic Data Centre: CCDC 1910510
(†)-Tert-butyl 2-((syn)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepin-3-yl)acetate (15b)

59% yield (0.64 mmol, 274 mg)

$^1$H NMR (600 MHz, Chloroform-d) $\delta$ 8.10 – 8.06 (m, 1H), 7.45 – 7.42 (m, 2H), 7.37 – 7.34 (m, 1H), 7.33 – 7.30 (m, 2H), 7.28 – 7.26 (m, 2H), 6.67 – 6.64 (m, 1H), 5.50 (d, $J = 9.5$ Hz, 1H), 5.13 (d, $J = 9.9$ Hz, 1H), 4.37 – 4.30 (m, 1H), 2.76 (dd, $J = 16.7$, 4.7 Hz, 1H), 2.51 (dd, $J = 16.7$, 4.9 Hz, 1H), 2.36 – 2.25 (m, 2H), 1.46 (s, 9H).

$^{13}$C NMR (151 MHz, Chloroform-d) $\delta$ 171.0, 143.3, 142.7, 141.0, 132.5, 129.4, 129.0, 128.9, 127.6, 127.1, 126.6, 53.3, 46.5, 40.4, 38.8, 28.1, 26.9.

HMRS (ESI): Calculated for $\text{C}_{21}\text{H}_{26}\text{O}_4\text{N}\text{S} = [\text{M+Na}]^+$ = 411.14748, found: 411.14993

(†)-4-(3-(ethoxycarbonyl)-1,1-dioxido-2,3-dihydrobenzo[d]isothiazol-3-yl)butanoic acid (16)
Pearlman's catalyst (20wt%, 9mol%, 7.2 mg, 0.01 mmol) and 4d (1.0 eq., 50 mg, 0.12 mmol) were dissolved in a 3:1 (v/v) Methanol/Ethyl Acetate Mixture (1.250) in a 10 ml tube equipped with a stirring bar. The vessel was placed in a high-pressure reactor, which was then sealed and charged with Hydrogen (9 atm). The reactor was placed on a stirring plate and left there for 2 h. Then, reaction mixture was filtered to furnish 37 mg (0.11 mmol, 93% yield) of (+)-4-(3-(ethoxycarbonyl)-1,1-dioxido-2,3-dihydrobenzo[d]isothiazol-3-yl)butanoic acid 16.

\[ ^1H \text{ NMR} (700 \text{ MHz}, \text{Chloroform-d}) \delta 7.76 (d, J = 7.7 \text{ Hz}, 1\text{H}), 7.72 (d, J = 7.9 \text{ Hz}, 1\text{H}), 7.66 (t, J = 7.7 \text{ Hz}), 7.60 (dd, J = 11.1, 3.9 \text{ Hz}, 1\text{H}), 5.83 (s, 1\text{H}), 4.37 – 4.28 (m, 2\text{H}), 2.43 (dt, J = 16.7, 7.0 \text{ Hz}, 1\text{H}), 2.36 (dt, J = 16.7, 7.3 \text{ Hz}, 1\text{H}), 2.29 (ddd, J = 13.7, 11.5, 4.8 \text{ Hz}, 1\text{H}), 2.05 (ddd, J = 13.7, 11.7, 4.8 \text{ Hz}, 1\text{H}), 1.76 – 1.64 (m, 2\text{H}), 1.36 (t, J = 7.1 \text{ Hz}, 3\text{H}). \]

\[ ^{13}C \text{ NMR} (176 \text{ MHz}, \text{Chloroform-d}) \delta 178.3, 169.9, 137.9, 135.4, 133.6, 130.6, 124.9, 121.5, 69.0, 63.8, 39.3, 33.1, 19.7, 14.1. \]

HMRS (ESI): Calculated for C_{14}H_{18}O_{6}N_{5}S = [M+H]^+: 328.08493, found: 328.08477

2.3.2.1 Hydrolysis of Esters 15

\[ (+)-2-((\text{syn})-1,1\text{-dioxido-5-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepin-3-yl})\text{acetic acid (17)} \]

By hydrolysis from Ethyl Ester 15a

Sulfonamide 15a (1.0 eq. 252 mg, 701.09 µmol) was dissolved in 9.16 ml THF/MeCN 4:1 v/v mixture. Then, 2.92 ml water and aqueous 2 M NaOH (974 µl) was added to the solution. The resulting mixture was stirred at ambient temperature stirred for 19 hours. The reaction was quenched by addition of 1 M HCl (2.103 ml, 2.10 mmol) and concentrated under reduced pressure. Silica gel column chromatography (20% to 40% EA/CyH to 10% EtOH/EA) delivered 217 mg (0.65 mmol, 93%) free acid as a white solid.
By hydrolysis of tert-butyl ester 15b
Tert-butyl Ester 15b (1.0 eq., 145 mg, 374.20 µmol) was dissolved in 3.2 ml THF/1 M aq. HCl (3:1 v/v) in a 30 ml microwave tube. The vessel was sealed and irradiated at 100 °C/250 W for 45 min using a microwave synthesizer. The reaction was quenched by addition of aqueous 2 M NaOH and extracted using Ethyl acetate (3 x 5 ml). Concentration and silica gel column chromatography (20% to 40% to 10% EtOH/EA) delivered free acid (24 mg, 0.07 mmol, 19%) delivered free acid (24 mg, 0.07 mmol, 19%) and allowed recovery of unreacted starting material (81 mg, 0.21 mmol, 56%).

$^1$H NMR (500 MHz, Acetonitrile-d$_3$) δ 7.99 – 7.95 (m, 1H), 7.43 (t, $J = 7.5$ Hz, 2H), 7.38 – 7.32 (m, 2H), 7.29 – 7.25 (m, 2H), 6.63 – 6.59 (m, 1H), 5.51 (d, $J = 9.9$ Hz, 1H), 5.05 (d, $J = 10.6$ Hz, 1H), 4.36-4.27 (m, 1H), 2.59 (dd, $J = 16.1$, 5.6 Hz, 1H), 2.51 (dd, $J = 16.1$, 7.8 Hz, 1H), 2.32 (d, $J = 14.0$, 1.5 Hz, 1H), 2.08 (dd, $J = 14.0$, 2.4 Hz, 1H).

$^{13}$C NMR (126 MHz, CD$_3$CN) δ 172.3, 144.5, 143.9, 142.3, 133.5, 130.1, 129.8, 129.8, 128.1, 127.9, 127.5, 54.4, 47.3, 40.2, 40.1.

HMRS (ESI): Calculated for $C_{17}H_{18}O_4N$ S = [M+H]$^+$: = 332.09511, found: 332.09543

2.3.2.2 Synthesis of Amides 18a-c
To a solution of 40 mg of carboxylic acid 17 (1.0 eq., 120.70 µmol) in chloroform (0.9 ml) was added oxalyl chloride (1.15 eq., 238 µl, 5% solution in DCM). The vial was heated gently and dissolved after a few minutes. It was then heated at 60 °C overnight. The reaction was allowed to cool to room temperature and then concentrated under reduced pressure to remove any excess oxalyl chloride. Then, the reaction mixture was redissolved in THF (0.9 ml) and diethylamine (4.0 eq., 50 µl, 483 µmol) was added dropwise at 0 °C. After completion of conversion, reaction mixture was concentrated under reduced pressure, dried in vacuo and purified by preparative HPLC (C18, 25% to 80% MeCN/H2O (+0.1% v/v HCOOH)) to yield 27 mg (0.07 mmol, 58%).

1H NMR (600 MHz, Chloroform-d) δ 8.08 – 8.02 (m, 1H), 7.40 (t, J = 7.5 Hz, 2H), 7.34 – 7.31 (m, 1H), 7.27 – 7.23 (m, 4H), 6.64 – 6.59 (m, 1H), 5.09 (d, J = 10.8 Hz, 1H), 4.36 – 4.29 (m, 1H), 3.38 (dt, J = 14.1, 7.0 Hz, 1H), 3.32-3.20 (m, 3H), 2.80 (dd, J = 16.7, 4.5 Hz, 1H), 2.64 – 2.58 (m, 2H), 2.14 (ddd, J = 13.9, 2.3, 1.0 Hz, 1H), 1.17 (t, J = 7.1 Hz, 3H), 1.10 (t, J = 7.1 Hz, 3H).

13C NMR (151 MHz, Chloroform-d) δ 170.0, 143.8, 142.8, 141.3, 132.5, 129.5, 129.1, 129.0, 127.9, 127.2, 126.6, 54.0, 46.9, 42.3, 40.5, 38.7, 37.3, 14.3, 13.1.

HMRS (ESI): Calculated for C21 H27 O3 N S = [M+H]+: 387.17369, found: 387.17375
Calculated for C21 H26 O3 N Na S = [M+H]+: 409.15563, found: 409.15560

(+)-2-((syn)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepin-3-yl)-1-morpholinoethan-1-one (18b)
To a solution of Acid 17 (1.0 eq., 25 mg, 76 µmol) in chloroform (1 ml) was added thionyl chloride (1.20 eq., 7.5 µl, 90 µmol, as 5% solution in CHCl₃). The vial was heated gently and dissolved after a few minutes. It was then heated at 40° C for 16 h. The reaction was allowed to cool to room temperature and then concentrated under reduced pressure to remove any excess thionyl chloride. Crude acyl chloride was then dissolved in 500 µl THF in an oven-dried Schlenk tube equipped with a magnetic stirring bar under Argon atmosphere. Then, 5.0 eq. morpholine (29 µl, 0.34 mmol) was added and the reaction was kept stirring overnight. Then, it was concentrated, dried and purified by preparative HPLC to deliver 14 mg (7.49 µmol, 10% yield) of product sulfonamide.

Purification by preparative HPLC (C18, 35% to 90% MeCN/H₂O (+0.1% v/v TFA))

¹H NMR (400 MHz, Chloroform-d) δ 8.08 – 8.02 (m, 1H), 7.40 (t, J = 7.4 Hz, 2H), 7.35 – 7.30 (m, 1H), 7.29 – 7.23 (m, 4H), 6.65 – 6.61 (m, 1H), 6.17 (d, J = 9.6 Hz, 1H), 5.07 (d, J = 10.8 Hz, 1H), 4.37 (m, 1H), 3.77 – 3.61 (m, 5H), 3.53 – 3.40 (m, 3H), 2.79 (dd, J = 16.7, 4.8 Hz, 1H), 2.70 – 2.55 (m, 2H), 2.16 (d, J = 12.7 Hz, 1H).

¹³C NMR (176 MHz, Chloroform-d) δ 167.3, 141.6, 140.7, 139.2, 130.5, 127.5, 127.1, 127.0, 125.8, 125.2, 124.6, 64.8, 64.5, 51.7, 45.0, 44.0, 39.8, 36.9, 35.4.

HMRS (ESI): Calculated for C₂₁H₂₅O₄N₂S = [M+H]⁺: = 401.15218, found: 401.15295
Calculated for C₂₁H₂₄O₄N₂NaS = [M+H]⁺: = 423.13490 found: 423.13396

(+)-2-((syn)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepin-3-yl)-N-propylacetamide (18c)

To a solution of Acid 17 (1.0 eq., 25 mg, 76 µmol) in chloroform (1 ml) was added thionyl chloride (1.20 eq., 7.5 µl, 90 µmol, as 5% solution in CHCl₃). The vial was heated gently and dissolved after a few minutes. It was then heated at 40° C for 16 h. The reaction was allowed to cool to room temperature and then concentrated under reduced pressure to remove any excess thionyl chloride. Crude acyl chloride was then dissolved in 500 µl THF in an oven-dried
Schlenk tube equipped with a magnetic stirring bar under Argon atmosphere. Then, 5.0 eq. n-propylamine (28 µl, 0.34 mmol) was added and the reaction was kept stirring overnight. Then, it was concentrated, dried and purified by preparative HPLC to deliver 14 mg (0.04 mmol, 50% yield) of product sulfonamide.

Purification by preparative HPLC (C18, 35% to 90% MeCN/H2O (+0.1% v/v TFA))

$^1$H NMR (500 MHz, Chloroform-\textit{d}) $\delta$ 8.04 (dd, $J = 5.5$, 2.0 Hz, 1H), 7.40 (t, $J = 7.5$ Hz, 2H), 7.35 – 7.30 (m, 1H), 7.29 – 7.27 (m, 1H), 7.24 (ddd, $J = 8.0$, 3.5, 2.0 Hz, 3H), 6.63 – 6.58 (m, 1H), 6.31 (s, 1H), 5.59 (d, $J = 6.0$ Hz, 1H), 5.09 (d, $J = 10.6$ Hz, 1H), 4.30 (s, 1H), 3.23 – 3.13 (m, 2H), 2.76 (dd, $J = 15.6$, 4.3 Hz, 1H), 2.41 – 2.32 (m, 2H), 2.23 – 2.17 (m, 1H), 1.52 (h, $J = 7.1$ Hz, 2H), 0.92 (t, $J = 7.4$ Hz, 3H).

$^{13}$C NMR (126 MHz, Chloroform-\textit{d}) $\delta$ 170.8, 143.6, 142.6, 141.2, 132.5, 129.5, 129.1, 127.8, 127.2, 126.7, 53.7, 46.5, 41.4, 40.5, 38.7, 22.9, 11.5

$^2$HMRS (ESI): Calculated for C$_{20}$H$_{25}$O$_3$N$_2$S = [M+H]$^+$:  = 373.15804, found: 373.15774
Calculated for C$_{20}$H$_{24}$O$_3$N$_2$NaS = [M+H]$^+$:  = 395.13998 found: 395.13907

2.3.3 Synthesis of fused Pyrrolines by Reduction

$[-]$-Ethyl 9b-phenyl-1,2,3,9b-tetrahydrobenzo[d]pyrrolo[1,2-b]isothiazole-1-carboxylate 5,5-dioxide (19a)

To 23 mg Pyrroline 5a (1.0 eq., 0.06 mmol) in 1.5 ml of a Methanol/Ethyl Acetate Mixture (5:1) was added 3.2 mg Pearlman's Catalyst (20wt.%, 4mol%, 2.26 µmol,) in a Schlenk tube. The mixture was cooled to 0°C, degassed and refilled with hydrogen, again degassed, once more refilled with hydrogen using a balloon and stirred at rt. After 40 min, TLC (Ethyl Acetate/CyH 1:3) showed complete conversion of starting material ($rf$ = 0.33) to a product ($rf$ = 0.24). The mixture was filtered through a syringe filter and the
solvent was removed under reduced pressure to obtain crude product, which was purified using silica gel column chromatography (14%-20% EA/CH) to yield 12a in 95% yield (22 mg, 0.06 mmol).

$^1$H NMR (600 MHz, Chloroform-d) δ 8.05 (d, J = 7.9 Hz, 1H), 7.73 – 7.67 (m, 2H), 7.59 – 7.53 (m, 3H), 7.33 – 7.27 (m, 2H), 7.27 – 7.21 (m, 1H), 3.94-3.73 (m, 4H), 3.60 (t, J =7.6 Hz, 1H), 2.49 (m, 1H), 2.15 (m, 1H), 1.0 (t, J = 7.1 Hz, 3H).

$^{13}$C NMR (151 MHz, Chloroform-d) δ 170.2, 143.6, 139.1, 135.9, 133.1, 129.7, 128.2, 128.1, 126.8, 125.6, 121.7, 78.2, 61.3, 56.7, 48.4, 28.9, 13.7

HMRS (ESI): Calculated for C$_{19}$H$_{20}$O$_4$N S = [M+H]$^+$:  = 358.11076, found: 358.11092
Calculated for C$_{19}$H$_{19}$O$_4$N Na S = [M+H]$^+$:  = 380.09270, found: 380.09282

19a NOESY

![19a NOESY](image)
Structure of lowest energy conformation of substrate hints that addition leading to anti-pyrrolidine may be preferred, as the most probable structure (deduced via NOE interactions) suggests.

(+)-9b-(ethoxycarbonyl)-1,2,3,9b-tetrahydrobenzo[d]pyrrolo[1,2-b]isothiazole-1-carboxylic acid 5,5-dioxide (19b)
Structure assigned in analogy to 19a.

Pearlman’s catalyst (10 mol%, 8.4 mg, 0.01 mmol) and 5b (1.0 eq., 50.0 mg, 0.12 mmol) were dissolved in a 3:1 Methanol/Ethyl Acetate (3:1 v/v) mixture in a 10 ml glass tube equipped with a stirring bar. The open vessel was placed in a high-pressure reactor, which was then sealed and charged with Hydrogen (9 atm). The reactor was placed on a stirring plate and left there for 3 h. Then, reaction mixture was filtered using a syringe filter. Concentration of filtrate delivered 19b in 92% yield (36 mg, 0.11 mmol).

$^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 7.94 (d, $J = 7.8$ Hz, 1H), 7.77 (d, $J = 7.65$ Hz, 1H), 7.68 (td, $J = 7.6$, 1.3 Hz, 1H), 7.63 (ddd, $J = 7.6$, 1.1 Hz, 1H), 4.21 (m, 2H), 3.89 (dt, $J = 10.7$, 7.6 Hz, 1H), 3.68 (dd, $J = 10.7$, 7.6, 4.6 Hz, 1H), 3.27 (t, $J = 8.4$ Hz, 1H), 2.67 (m, 1H), 2.42 (m, 1H), 1.26 (t, $J = 7.1$ Hz, 2H).

$^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 175.7, 168.7, 136.7, 135.1, 133.7, 130.9, 126.4, 121.5, 63.0, 60.6, 53.7, 46.5, 30.1, 13.9.

HMRS (ESI): Calculated for C$_{14}$H$_{16}$O$_6$N S = [M+H]$^+$: = 326.06928, found: 326.06963
Calculated for C$_{14}$H$_{15}$O$_6$Na S = [M+H]$^+$: = 348.05123, found: 348.05164

2.3.4 Ring modulation reaction of cycloadduct 8a
(+)-3-(aminomethyl)-2-methyl-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide (20)

Sulfonamide 8a (1.0 eq., 55 mg, 0.18 mmol) was dissolved in 1.8 ml in a 10 ml glass vial equipped with a magnetic stirring bar. Pd/C (10 wt.%, 0.1 eq., 19.5 mg, 0.02 mmol) was added and the open vial was placed in a high-pressure reactor, which was charged with 7 atm of hydrogen. The reactor was placed on a stirring plate and the reaction was stirred at ambient temperature for 16 h. Then, it was filtered over celite and concentrated. Purification by preparative HPLC (C18, 10% to 50% MeCN/H₂O (+0.1% v/v TFA)) delivered unstable Product 20 in 87% yield (34 mg, 0.16 mmol).

¹H NMR (500 MHz, Acetonitrile-d₃) δ 7.75 – 7.73 (d, J = 8.1 Hz, 1H), 7.67 – 7.65 (m, 1H), 7.57 (t, J = 7.9 Hz, 2H), 4.77 (dd, J = 8.8, 4.9 Hz, 1H), 2.70 (dd, J = 12.6, 4.9 Hz, 1H), 2.54 (dd, J = 12.6, 8.8 Hz, 1H), 2.28 (s, 3H).

¹³C NMR (126 MHz, CD₃CN) δ 139.8, 136.6, 133.6, 130.2, 125.7, 121.3, 118.0, 64.1, 55.8, 45.4.

HMRS (ESI): Calculated for C₉H₁₃O₂N₂S = [M+H]⁺:  = 213.06922, found: 213.06943

(+)-2-methyl-1,9b-dihydrobenzo[d]imidazo[1,5-b]isothiazol-3(2H)-one 5,5-dioxide (21)

Crude sulfonamide 20 (1.0 eq., 33 mg, 109.86 µmol) was dissolved in 1.0 ml MeOH in a 10 ml glass vial equipped with a magnetic stirring bar. Pd/C (10 wt.% , 0.1 eq., 19.5 mg, 0.02 mmol) was added and the open vial was placed in a high-pressure reactor, which was charged with 7 atm of hydrogen. The reactor was placed on a stirring plate and the reaction was stirred at ambient temperature for 16 h. Then, it was filtered over celite and concentrated. It was dissolved in 2 ml dry acetonitrile and triethylamine (2.30 eq., 35 µl, 252.7 µmol) and CDI (1.15 eq., 20.5 mg, 0.13 mmol) were added and the reaction stirred at 21° C for 16 h. Then, it was
stopped by addition of 1 M aqueous HCl (50 µl) and concentrated. The residue was purified by preparative HPLC (C18, 10% to 60% MeCN/H2O (+0.1% v/v TFA)) to yield 6 mg (23%, 0.03 mmol) of 21.

\[ \text{H NMR} \quad (500 \text{ MHz, Chloroform-d}) \quad \delta \quad 7.84 (d, J = 7.8, 1H), \quad 7.71 (t d, J = 7.6, 1.0 \text{ Hz, } 1H), \quad 7.62 \quad (t, \quad J = 7.7, 1H), \quad 7.42 (d q, \quad J = 7.8, \quad 0.7 \text{ Hz, } 1H), \quad 5.40 (d d, \quad J = 9.3, \quad 4.5 \text{ Hz, } 1H), \quad 4.01 (t, \quad J = 9.3 \text{ Hz, } 1H), \quad 3.67 (d d, \quad J = 9.1, \quad 4.5 \text{ Hz, } 1H), \quad 2.89 (s, \quad 3H). \]

\[ \text{C NMR} \quad (126 \text{ MHz, Chloroform-d}) \quad \delta \quad 152.5, \quad 136.9, \quad 135.3, \quad 132.9, \quad 129.5, \quad 122.5, \quad 121.2, \quad 53.9, \quad 49.3, \quad 29.9. \]

\[ \text{HMRS (ESI)} : \text{ Calculated for } C_{10} H_{11} O_3 N_2 S = [M+H]^+ : 239.04849, \text{ found: } 239.04863 \]

\[ \text{Calculated for } C_{10} H_{11} O_3 N_2 Na S = [M+Na]^+ : 261.03043, \text{ found: } 261.03012 \]

2.3.5 Synthesis of tetrahydropyridones 22a-d

![General Reaction Scheme]

\[ (+)-7,8,10,10a\text{-tetrahydro-9H}\text{-benzo}[4,5]\text{isothiazolo}[2,3-a]\text{pyridin-9-one} \quad 5,5\text{-dioxide (22a)} \]

Enamide 6a (1.0 eq., 195 mg, 0.83 mmol) was combined with Pd/C (10wt%, 0.1 eq., 88 mg, 82.89 µmol) and dissolved in 16 ml EtOH/Ethyl Acetate 1:1 (v/v). The mixture was stirred in a high-pressure reactor 18 h under 8 atm of hydrogen pressure. Then, reaction mixture was filtered over celite and concentrated. The main component of reaction mixture was alcohol. Crude reaction mixture was dissolved in 22 ml DCM and solid sodium bicarbonate (6.25 eq., 435 mg, 0.01 mol) was added. The reaction mixture was cooled down to 0° C (ice-water bath) and DMP (2.5 eq., 879 mg, 2.07 mmol) was carefully added portionwise over 10 min under a stream of Argon. The reaction was monitored via TLC. After completion of conversion (3 h) 50 ml of aqueous sodium thiosulfate solution was added and the reaction mixture was transferred to a separation funnel. Layers were separated and the aqueous layer was extracted twice.
more with 40 ml DCM each. Combined organic layers were washed with brine (25 ml each) and dried over anhydrous sodium sulfate. Concentration delivered crude product, which was objected to silica gel flash column chromatography (29% to 35% EA/CyH) to yield tetrahydropyridin-4-one 22a in 59% yield (117 mg, 0.49 mmol).

\[^1\text{H NMR}\ (400\ \text{MHz, Chloroform-}\text{d})\ \delta\ 7.89 - 7.85\ (m, 1H), 7.67\ (td, J = 7.6, 1.3\ \text{Hz, 1H}), 7.63 - 7.58\ (m, 1H), 7.41 - 7.34\ (m, 1H), 4.66\ (dd, J = 12.0, 3.7\ \text{Hz, 1H}), 4.19\ (ddd, J = 13.3, 7.3, 2.1\ \text{Hz, 1H}), 3.40\ (ddd, J = 13.2, 12.0, 3.7\ \text{Hz, 1H}), 2.97\ (ddd, J = 14.1, 3.7, 1.7\ \text{Hz, 1H}), 2.83\ (ddd, J = 14.8, 12.0, 7.3, 0.8\ \text{Hz, 1H}), 2.63 - 2.54\ (m, 2H).

\[^{13}\text{C NMR}\ (126\ \text{MHz, Chloroform-}\text{d})\ \delta\ 204.4, 136.6, 134.5, 133.3, 129.9, 123.3, 121.6, 58.1, 45.9, 39.4, 38.4.

\text{HMRS (ESI): Calculated for C}_{11}\text{H}_{12}\text{O}_{3}\text{N S} = [M+H]^+: 238.05324 \text{ found: 238.05324}

(+)-10a-phenyl-7,8,10a-tetrahydro-9H-benzo[4,5]isothiazolo[2,3-a]pyridin-9-one 5,5-dioxide (22b)

Tricyclic sulfonamide 6b (307 mg, 986.01 µmol) and Pd on Carbon (10 wt%, 74 mg, 69.02 µmol) were dissolved in Ethanol (18 ml) in a 100 ml Schlenk flask equipped with a magnetic stirring bar. The mixture stirred at ambient temperature with a balloon filled with hydrogen attached. The reaction was monitored by TLC. After 3 h, TLC analysis had implicated complete conversion of starting material and the mixture was filtered over celite and solvent was evaporated under reduced pressure to give crude reaction product, which was purified by silica gel column chromatography (18% to 32% EA/CyH) to give product sulfonamide 22b in 90% yield (278 mg, 0.89 mmol).

\[^1\text{H NMR}\ (400\ \text{MHz, Chloroform-}\text{d})\ \delta\ 7.92 - 7.89\ (m, 1H), 7.59 - 7.51\ (m, 2H), 7.44 - 7.29\ (m, 6H), 7.03 - 6.98\ (m, 1H), 4.18\ (ddd, J = 14.7, 7.6, 1.5\ \text{Hz, 1H}), 3.55\ (dd, J = 14.4, 1.6\ \text{Hz, 1H}), 3.13\ (ddd, J = 14.7, 12.3, 3.8\ \text{Hz, 1H}), 2.96 - 2.84\ (m, 3H), 2.34 - 2.25\ (m, 1H).

\[^{13}\text{C NMR}\ (101\ \text{MHz, Chloroform-}\text{d})\ \delta\ 204.5, 142.8, 137.8, 133.8, 132.7, 129.8, 129.5, 129.1, 127.5, 124.0, 121.8, 69.1, 49.6, 39.1, 36.1.

\text{HMRS (ESI): Calculated for C}_{17}\text{H}_{16}\text{O}_{3}\text{N}_{2}\text{S} = [M+H]^+: 314.08454, \text{ found: 314.08470}

S55
(+)-10a-(pyridin-2-yl)-7,8,10,10a-tetrahydro-9H-benzo[4,5]isothiazolo[2,3-a]pyridin-9-one 5,5-dioxide (22c)

Sulfonamide 6c (1.0 eq., 220 mg, 704.35 µmol) and Pd/C (0.12 eq., 90 mg, 84.52 µmol) were combined in a 35 ml reaction tube equipped with a magnetic stirring bar. 7 ml of Ethyl Acetate/EtOH (15:7 v/v) were added and the vessel was placed in a high-pressure reactor. The reactor was charged with 7 atm of hydrogen pressure and stirred for 16 h at 22 °C. Then reaction mixture was filtered over celite and concentrated. Silica gel column chromatography (19 to 23% EA/CyH) delivered desired product in 24% yield (54 mg, 0.17 mmol) and recovered starting material. Corresponding alcohol or other side products could not be detected.

$^1$H NMR (700 MHz, Chloroform-d) δ 8.67 – 8.62 (m, 1H), 7.92 – 7.88 (m, 1H), 7.65 (td, $J = 7.7, 1.8$ Hz, 1H), 7.60 – 7.59 (m, 2H), 7.31 (ddt, $J = 10.2, 8.0, 0.8$ Hz, 2H), 7.26 – 7.24 (m, 1H), 4.20 (ddd, $J = 14.3, 7.4, 2.4$ Hz, 1H), 4.00 (dd, $J = 14.5, 1.6$ Hz, 1H), 3.25 (ddd, $J = 14.3, 11.4, 4.1$ Hz, 1H), 2.80 (ddd, $J = 15.4, 11.4, 7.4, 0.8$ Hz, 1H), 2.70 (dd, $J = 14.4, 0.8$ Hz, 1H), 2.38 (dd, $J = 15.4, 4.0, 2.4, 1.5$ Hz, 1H).

$^{13}$C NMR (176 MHz, Chloroform-d) δ 201.8, 155.4, 147.3, 138.8, 135.9, 131.8, 130.9, 128.1, 122.1, 121.6, 119.7, 119.3, 67.7, 47.2, 36.6, 34.3.

HMRS (ESI): Calculated for C$_{16}$H$_{15}$O$_{3}$N$_{2}$S = [M+H]$^+$: = 315.07979 found: 315.07962

(+)-ethyl 9-oxo-7,8,9,10-tetrahydro-10aH-benzo[4,5]isothiazolo[2,3-a]pyridine-10a-carboxylate 5,5-dioxide (22d)
Sulfonyl enamide 6d (1.0 eq., 150 mg, 0.49 mmol) was dissolved in 9ml EtOH and 26 mg (5mol%, 10wt.% content, 24.40 µmol) of Pd/C was added to the mixture. The reaction vessel (35 ml tube containing magnetic stirring bar) was placed in a high-pressure reactor that was charged with 7 bars of hydrogen and placed on a stirring plate. The reaction was stirred at 20° C and monitored by TLC.

The crude reaction mixture was filtered over celite, concentrated and the residue objected to silica gel flash column chromatography (25 to 28 to 32 % EA/CyH) to yield tetrahydropyridin-4one 22c in 97% yield (146 mg 0.47 mmol).

\[ ^1H \text{ NMR (500 MHz, Chloroform-}d\text{)} \delta 7.91 – 7.85 \text{ (m, } 1\text{H}), 7.73 – 7.63 \text{ (m, } 2\text{H}), 7.58 – 7.53 \text{ (m, } 1\text{H}), 4.30 – 4.17 \text{ (m, } 3\text{H}), 3.62 \text{ (ddd, } J = 14.0, 11.6, 4.1 \text{ Hz, } 1\text{H}), 3.36 \text{ (dd, } J = 14.4, 1.6 \text{ Hz, } 1\text{H}), 2.76 \text{ (dddd, } J = 15.0, 11.6, 7.6, 0.7 \text{ Hz, } 1\text{H}), 2.62 \text{ (dd, } J = 14.5, 0.7 \text{ Hz, } 1\text{H}), 2.51 \text{ (ddt, } J = 15.0, 4.0, 1.9 \text{ Hz, } 1\text{H}), 1.24 \text{ (t, } J = 7.1 \text{ Hz, } 3\text{H}). \]

\[ ^{13}C \text{ NMR (126 MHz, Chloroform-}d\text{)} \delta 202.7, 168.1, 135.9, 133.7, 133.5, 130.8, 123.8, 121.9, 68.3, 63.5, 48.9, 38.8, 37.1, 14.1. \]

**HMRS (ESI):** Calculated for C\textsubscript{14}H\textsubscript{16}O\textsubscript{5}N S = [M+H]\textsuperscript{+}: \ = 310.07437 found: 310.07468

### 2.3.6 Synthesis of tricyclic sulfonamides 23a-e via reductive amination
(±)-Ethyl 9-morpholino-7,8,9,10-tetrahydro-10aH-benzo[4,5]isothiazolo[2,3—a]pyridine-10a-carboxylate 5,5-dioxide (23a)

Morpholine (1.2 eq., 6.7 µl, 0.08 mmol) was added dropwise via syringe to a solution of 22d (1.0 eq., 20 mg, 64.7 µmol) with 2-Ethylhexanoic acid (1.25 eq., 12.9 µl, 0.08 mmol) in DCM (0.6 ml) and stirred for 20 min. Then, in situ generated NaBH(OEh)₃ (1.25 eq., 12.9 µl, 0.08 mmol) was added and the reaction stirred overnight. Then, solvents were removed and the residue purified by silica gel column chromatography (30% to 45% EA/CyH) to yield 16 mg (0.04 mmol, 65%) of amine product.

**¹H NMR** (400 MHz, Chloroform-d) δ 7.81 (d, J = 7.7 Hz, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.66 – 7.54 (m, 2H), 4.27 (dq, J = 10.8, 7.3 Hz, 1H), 4.16 (dq, J = 10.8, 7.1 Hz, 1H), 3.80 (ddd, J = 14.0, 4.9, 2.0 Hz, 1H), 3.75 – 3.62 (m, 4H), 3.50 (td, J = 13.7, 2.6 Hz, 1H), 3.15 (ddd, J = 14.2, 3.3, 2.0 Hz, 1H), 2.66 (s, 2H), 2.50 (p, J = 3.1 Hz, 1H), 2.40 (s, 2H), 2.04 (dt, J = 15.1, 2.6 Hz, 1H), 1.88 – 1.75 (m, 1H), 1.65 – 1.58 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H).

**¹³C NMR** (101 MHz, Chloroform-d) δ 170.4, 137.5, 133.3, 133.2, 130.2, 124.4, 121.5, 67.1, 64.2, 62.5, 56.7, 51.4, 36.6, 33.9, 25.5, 14.1.

**HMRS (ESI):** Calculated for C₁₈ H₂₅ O₅ N₂ S = [M+H]^+: 381.14787 found: 381.14779
Calculated for C₁₈ H₂₄ O₅ N₂ Na S = [M+H]^+: 403.12981 found: 403.12960
Calculated for C₁₈ H₂₄ O₅ N₂ K S = [M+H]^+: 419.10375 found: 419.10375
NOE experiment shows NOE between Morpholine H and CH$_2$-group of ethyl ester.

(+)-9-morpholino-8,9,10,10a-tetrahydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridine 5,5-dioxide (23b)

![Chemical structure](image)

22a (1.0 eq., 16 mg, 67.43 µmol), morpholine (1.25 eq., 145 µl, 84.3 µmol, as 5% v/v solution in 1,2-DCE) and powdered 4 A molecular sieves were combined in dry 1,2 DCE (800 µl) in a two-necked round bottom flask under an Argon atmosphere and stirred for 12 h at ambient temperature. Then, sodium triacetoxyborohydride (1.4 eq., 20 mg, 94.40 µmol) and glacial acetic acid (1.05 eq., 4 µl, 70.80 µmol) were added and the reaction stirred at ambient temperature overnight. Then, it was concentrated in vacuo and the residue purified (C18, 10% to 38% MeCN/H$_2$O (+0.1% v/v TFA)) yield 7.0 mg (0.02 mmol, 34%) of product sulfonamide.
**$^1$H NMR** (700 MHz, Chloroform-$d$) $\delta$ 7.81 (d, $J = 7.7$ Hz, 1H), 7.65 (t, $J = 7.4$ Hz, 1H), 7.57 (t, $J = 7.6$ Hz, 1H), 7.47 (d, $J = 7.7$ Hz, 1H), 5.06 (dd, $J = 9.4$, $J = 4.1$ Hz, 1H), 4.02 (d, $J = 4.7$ Hz, 4H), 3.61 (ddt, $J = 25.0$, $J = 13.2$, 7.3 Hz, 2H), 3.33 – 2.99 (m, 6H), 2.69 (dt, $J = 14.2$, 5.3 Hz, 1H), 2.28 (h, $J = 5.6$, 4.3 Hz, 1H), 2.25 – 2.15 (m, 3H).

**$^{13}$C NMR** (176 MHz, Chloroform-$d$) $\delta$ 137.5, 134.8, 133.6, 130.0, 124.2, 122.1, 64.3, 60.1, 54.5, 50.4, 36.9, 29.6, 23.3.

**HMRS (ESI):** Calculated for C$_{15}$H$_{21}$O$_3$N$_2$S = [M+H]$^+$ = 381.12674 found: 381.12676

In NOESY experiment, no NOE between benzylic proton and the other tertiary proton can be established. For the other amines, in contrast, such an NOE could be found. Consequently, we suggest that we isolated above depicted stereoisomer.
(+)-9-(propylamino)-8,9,10,10a-tetrahydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridine 5,5-dioxide (23c)

\[ \text{SO}_3 \]
\[ \text{H} \]
\[ \text{NH} \]

22a (1.0 eq., 28 mg, 110.93 µmol), n-propylamine (1.25 eq., 11 µl, 138.66 µmol) and powdered 4 A molecular sieves were combined in dry 1,2 DCE (800 µl) in a 10 ml oven-dried Schlenk tube under an Argon atmosphere and sodium triacetoxyborohydride (1.4 eq., 33 mg, 155.30 µmol) and glacial acetic acid (1.05 eq., 6.6 µl, 116.47 µmol) were added and the reaction stirred at ambient temperature overnight. The reaction was concentrated and the crude reaction material was purified by preparative HPLC (C18, 3% to 7% MeCN/H\textsubscript{2}O (+0.1% v/v TFA)) Lyophilization then delivered product amine 23c (9.4 mg, 0.03 mmol, 30%) and alcohol side product 24 (11 mg, 0.05 mmol, 41%).

Mixture of diastereomers, ~10:9 syn:anti (see NOESY)

\(^1\text{H NMR}\) (500 MHz, Chloroform-\text{d}) \( \delta \) 7.77 (d, \( J = 7.7 \) Hz, 1H, \text{major}), 7.72 (d, \( J = 7.7 \) Hz, 1H, \text{minor}), 7.60 (td, \( J = 7.6, 1.1 \) Hz, 1H), 7.55 – 7.50 (m, 2H), 7.47 – 7.38 (m, 3H), 5.15 (dd, \( J = 12.2, 3.1 \) Hz, 1H, \text{minor}), 4.25 (dd, \( J = 11.7, 2.9 \) Hz, 1H, \text{major}), 3.99 (ddd, \( J = 14.4, 12.8, 3.4 \) Hz, 1H), 3.91 (ddd, \( J = 13.5, 4.9, 2.0 \) Hz, 1H), 3.77 (ddd, \( J = 14.2, 5.6, 2.2 \) Hz, 1H), 3.55 (t, \( J = 3.5 \) Hz, 1H, \text{minor}), 3.42 (tt, \( J = 12.1, 3.6 \) Hz, 1H, \text{major}), 3.14 – 2.86 (m, 7H), 2.32 (d, \( J = 12.5 \) Hz, 1H, \text{major}), 2.19 (d, \( J = 14.9 \) Hz, 1H), 2.10 (ddd, \( J = 18.7, 9.2, 4.2 \) Hz, 1H), 2.06 (s, 0H), 1.89 (q, \( J = 7.8 \) Hz, 2H), 1.81 (dd, \( J = 13.5, 10.0 \) Hz, 1H), 0.94 (td, \( J = 7.4, 3.5 \) Hz, 6H).

\(^{13}\text{C NMR}\) (126 MHz, Chloroform-d) \( \delta \) 137.3, 136.4, 134.9, 134.6, 133.3, 133.2, 129.9, 129.6, 123.9, 123.4, 121.6, 121.4, 56.9, 54.8, 52.8, 49.0, 46.0, 37.9, 35.0, 32.6, 32.1, 26.5, 24.5, 20.0, 19.6, 11.4, 11.4.

\( \text{HMRS (ESI)} \): Calculated for C\textsubscript{14} H\textsubscript{21} O\textsubscript{2} N\textsubscript{2} S = [M+H]\textsuperscript{+} = 281.13183 found: 281.13189
23c gHSQC

23c NOESY
(+)-9-hydroxy-8,9,10,10a-tetrahydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridine 5,5-dioxide (24)

This product was isolated from reductive amination reaction towards 23c in significant amount (see procedure above). Only by preparative HPLC, the product mixture could be purified and we found quite some amount of alcohol 24.

$^1$H NMR (500 MHz, Chloroform-d) $\delta$ 7.80 (dd, $J = 7.9, 1.1$ Hz, 1H), 7.61 (td, $J = 7.6, 1.2$ Hz, 1H), 7.54 (t, $J = 7.6$ Hz, 1H), 7.38 (dd, $J = 7.6, 1.0$ Hz, 1H), 4.31 (dd, $J = 11.9, 3.1$ Hz, 1H), 4.00 – 3.88 (m, 2H), 3.08 (td, $J = 13.1, 3.0$ Hz, 1H), 2.54 (dddd, $J = 12.2, 4.6, 3.2, 1.8$ Hz, 1H), 2.10 (dq, $J = 12.5, 2.4$ Hz, 1H), 1.68 (tdd, $J = 12.7, 11.2, 5.1$ Hz, 1H), 1.45 (q, $J = 11.8$ Hz, 1H).

$^{13}$C NMR (126 MHz, Chloroform-d) $\delta$ 137.5, 135.2, 132.9, 129.5, 123.1, 121.6, 68.4, 57.5, 39.2, 37.9, 33.4.

HMRS (ESI): Calculated for $\text{C}_{11}\text{H}_{14}\text{O}_3\text{N} \cdot \text{S} = \text{[M+H]}^+ = 240.06889$ found: 240.06871
(+)-9-morpholino-10a-phenyl-8,9,10,10a-tetrahydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridine 5,5-dioxide (23d)

22b (1.0 eq., 25 mg, 71.8 µmol), morpholine (1.25 eq., 8 µl, 89.8 µmol) and powdered 4 A molecular sieves were combined in dry 1,2 DCE (600 µl) in a two-necked round bottom flask under an Argon atmosphere and sodium triacetoxyborohydride (1.4 eq., 21 mg, 100.5 µmol) and glacial acetic acid (1.05 eq., 4.3 µl, 75.4 µmol) were added and the reaction stirred at ambient temperature. After 16 h additional 2.3 eq. of morpholine (14 µl, 165.14 µmol) and an additional 1.4 eq. of sodium acetoxyborohydride (21 mg, 100.52 µmol) were added to the mixture. After 6 h of additional stirring, the reaction was quenched by addition of 3 ml sat. aq. ammonium chloride solution. The mixture was transferred to a separation funnel, diluted with water (15 ml) and extracted with 3 x 4 ml ethyl acetate. Combined organic layers were washed with brine and dried over anhydrous sodium sulfate. Concentration yielded crude product which was purified by preparative HPLC (10 to 38% Acetonitrile/water (+0.1 % HCOOH)). Lyophilization then delivered product (7.7 mg, 0.02 mmol, 28%).

1H NMR (500 MHz, Chloroform-d) δ 7.71 (d, J = 7.8 Hz, 1H), 7.60 – 7.55 (m, 2H), 7.54 – 7.47 (m, 2H), 7.44 (ddd, J = 8.1, 6.8, 1.5 Hz, 1H), 7.27 (dd, J = 8.5, 6.9 Hz, 2H), 7.20 (d, J = 6.2 Hz, 2H), 3.89 (ddd, J = 15.4, 8.6, 1.4 Hz, 1H), 3.82 (s, 4H), 3.20 (dd, J = 15.3, 9.9, 7.3 Hz, 1H), 2.97 – 2.59 (m, 2H), 2.54 (tdd, J = 12.0, 8.4, 2.5 Hz, 1H), 2.43 (dq, J = 16.6, 8.5, 7.8 Hz, 1H), 1.84 (dt, J = 12.5, 8.3 Hz, 1H).

13C NMR (126 MHz, Chloroform-d) δ 142.7, 141.4, 134.1, 132.6, 129.9, 129.1, 128.3, 125.3, 124.6, 121.4, 69.0, 64.6, 57.9, 49.6, 35.3, 35.2, 23.4.

HMRS (ESI): Calculated for C21H22O3N2S = [M+H]+: = 385.15804 found: 385.15842
(±)-10a-phenyl-9-(propylamino)-8,9,10a-tetrahydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridine 5,5-dioxide (23e)

22b (1.0 eq., 25 mg, 71.80 µmol), n-propylamine (1.25 eq., 7.43 µl, 89.75 µmol) and powdered 4 Å molecular sieves were combined in dry 1,2 DCE (600 µl) in a two-necked round bottom flask under an Argon atmosphere and sodium triacetoxyborohydride (1.4 eq., 21 mg, 100.52 µmol) and glacial acetic acid (1.05 eq., 4.312 µl, 75.39 µmol) were added and the reaction stirred at ambient temperature. After 16 h, additional 2.5 eq. of n-propylamine (15 µl, 179.50 µmol) and an additional 1.4 eq. of sodium acetoxyborohydride (21 mg, 100.52 µmol) were added to the mixture. After 1 d of additional stirring, reaction was concentrated under reduced pressure and the residue was purified by preparative HPLC (C18, 10% to 38% MeCN/H₂O (+0.1% v/v TFA)) to yield 5 mg (20%, 14.03 µmol) of product amine.

**¹H NMR** (500 MHz, Chloroform-d) δ 7.77 (dd, J = 7.7, 1.2 Hz, 1H), 7.61 (dd, J = 7.8, 1.6 Hz, 2H), 7.53 (td, J = 7.6, 1.5 Hz, 1H), 7.48 (td, J = 7.5, 1.0 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.34 (t, J = 7.5 Hz, 2H), 7.28 (d, J = 7.2 Hz, 1H), 3.92 – 3.85 (m, 1H), 3.30 – 3.21 (m, 1H), 2.90 (q, J = 9.7, 8.2 Hz, 3H), 2.70 – 2.51 (m, 2H), 2.48 – 2.36 (m, 1H), 1.78 (dd, J = 13.3, 6.6 Hz, 1H), 1.56 – 1.43 (m, 2H), 0.79 (t, J = 7.4 Hz, 3H).

**¹³C NMR** (126 MHz, Chloroform-d) δ 142.1, 133.8, 132.5, 129.8, 129.3 (3 C), 128.5, 125.4, 124.5, 121.5, 57.5, 50.0, 47.6, 37.9, 37.1, 34.4, 25.8, 11.4.

**HMRS (ESI):** Calculated for C₂₀H₂₅O₂N₂S = [M+H]^+ = 357.16313 found: 357.16270
3. Cheminformatic Evaluation of compound Collection

3.1 Distribution of compound collection over chemical space (PMI)

Nelson's group developed the LLAMA platform which allows scientists to evaluate compounds according to their suitability for medicinal chemistry research after different parameters.\cite{11} They also offer a principal moment of inertia (PMI) plot. Making use of this feature we could generate Supp. Figure 1 by overlay of different compounds. Position of different members of compound collection displays, in how far its three-dimensional structure resembles either rod (top left), sphere (top right) or disk (bottom).
Figure S1: PMI plot of Compound collection. “+” denotes averaged center position in PMI plot.[11] Black squares show relative positions of compounds in comparison to commonly known bioactive sulfonamides (green, see also examples in Figure 1 of paper). Aziridines and azetidines, in particular are denoted by blue and light-blue squares, respectively. Azetidines are highlighted in margenta while their ring-expansion and derivatization products are depicted as orange squares.
3.2 Predicted molecular properties of compounds

Figure S2: 3D Scatter Plot of clogp, tPSA and molweight as parameters that may be beneficial for bioavailability.

The figure shows synthesized compounds as dots according to their projective molecular properties: topological polar surface area (tPSA, should be less than 140 or 90, if availability to central nervous system is required), clogp (should be roughly between -1 and 4), both displaying a degree of how well compounds pass through plasma membrane and molecular weight, which should be generally less than 500 Da. All of compounds fit these requirements.
4. Biological Evaluation

4.1 Supporting Figures

Figure S3: Activity (induction) of benzosulfonamides in the cell painting assay. Compounds were subjected to Cell painting assay performed in U2OS cells at a concentration of 10 µM. The induction is a measure of biological activity and is determined as the ratio of the number of parameters significantly different from the control vs. the total number of parameters.
Figure S4. Structures of fenbendazole\textsuperscript{[13]} (a), tubulexin A\textsuperscript{[14]} (b) and the PLK1 inhibitor\textsuperscript{[15]} (c).

Figure S5. Fingerprint comparison for 5b (10 µM) with the fingerprint for a PLK1 inhibitor (PLK1 inh. 2 µM).

Figure S6. Benzosulfonamides 4a and 5b lead to accumulation of round cells. U2OS cells were treated with the compounds or DMSO followed by live-cell imaging. Images of cell after 24 h of treatment with 4a, 5b or DMSO as a control are shown. Scale bar: 300 µm.
Figure S7. Benzosulfonamides 4a and 5b lead to accumulation of phospho-histone 3-positive cells. U2OS cells were treated with the compounds or DMSO for 24 h prior to staining for phospho-histone 3 as a marker for mitotic arrest and DNA using DAPI. Scale bar: 50 µm.
4.2 Experimental section - Biology

Reagents

DAPI (4′,6-Diamidino-2-phenylindol, #10236276001), anti-tubulin FITC (Cat# F2168;) and Hoechst 33342 (Cat. No. B2261-25mg) were purchased from Sigma Aldrich. Anti-phospho-histone3 antibody was obtained from Abcam (Cat# ab5176). Tubulin purified from porcine brain was purchased from Cytoskeleton, Inc (#T240). Human bone osteosarcoma epithelial cells U2OS were obtained from CLS (Cat# 300364; RRID: CVCL_0042). DMEM, sodium pyruvate and non-essential amino acid obtained from PAN Biotech, and fetal bovine serum (FBS) was purchased from Gibco. Mito Tracker Deep Red (Cat. No. M22426), Phalloidin (A12381), Concanavalin A (Cat. No. C11252), WGA-Alexa594 conjugate (Cat. No. W11262) and µl/ml SYTO 14 solution (Cat. No. S7576) were obtained from Thermo Fisher Scientific.

Cell culture

U2OS cells were maintained in DMEM medium supplemented with 10 % fetal bovine serum (FBS) at 37 °C and 5% CO₂ in a humidified atmosphere. Cells were regularly assayed for mycoplasma contamination and were always confirmed to be free of mycoplasma.

Cell painting assay

The cell painting assay\textsuperscript{[12]} was carried out as described by and Bray et al.\textsuperscript{[17]} with some modifications\textsuperscript{[18]}. Initially, 5 µl U2OS medium were added to each well of a 384-well plate (PerkinElmer CellCarrier-384 Ultra). Subsequently, 1600 U2OS cells were seeded per well in 20 µl medium. The plate was incubated for 10 min at the room temperature prior to incubation for 4 h at 37 °C. Compounds were then added with the Echo 520 acoustic dispenser (Labcyte) and cells were incubation for 20 h at 37 °C. Subsequently, mitochondria were stained with Mito Tracker Deep Red for 30 min in the dark at 37 °C. Cells were fixed using 3.7 % formaldehyde (in PBS) for 20 min in the dark at 37 °C prior to permeabilization Triton X-100
for 15 min 37 °C in the dark. After three washing steps, cells were stained with Alexa Fluor 594 Phalloidin, Concanavalin A Alexa Fluor 488, Hoechst 33342, WGA-Alexa594 conjugate and SYTO 14. The plate was incubated for 30 min at 37 °C in the dark and washed three times with PBS. After the final washing step, the PBS was not aspirated. The plates were sealed and centrifuged for 1 min at 500 rpm.

The plates were prepared in triplicates with shifted layouts to reduce plate effects and imaged using a Micro XL High-Content Screening System (Molecular Devices) in 5 channels (DAPI: Ex350-400/ Em410-480; FITC: Ex470-500/ Em510-540; Spectrum Gold: Ex520-545/ Em560-585; TxRed: Ex535-585/ Em600-650; Cy5: Ex605-650/ Em670-715) with 9 sites per well and 20x magnification (binning 2).

**Figure S8:** Image generation from Cell painting Assay.

The generated images were processed with the CellProfiler package (https://cellprofiler.org/) on a computing cluster of the Max Planck Society to extract 1716 cell features (parameters). The data was then further aggregated as medians per well (9 sites -> 1 well), then over the three replicates.
Further analysis was performed with custom Python (https://www.python.org/) scripts using the Pandas (https://pandas.pydata.org/) and Dask (https://dask.org/) data processing libraries (separate publication to follow).

From the total set of 1716 parameters a subset of highly reproducible and robust parameters was determined using the procedure described by Woehrmann et al.\textsuperscript{[19]} in the following way:

Two biological repeats of one plate containing reference compounds were analysed. For every parameter, its full profile over each whole plate was calculated. If the profiles from the two repeats showed a similarity $\geq 0.8$ (see below), the parameter was added to the set.

This procedure was only performed once and resulted in a set of 579 robust parameters out of the total of 1716 that was used for all further analyses.

**Determination of reproducible Parameters**

| 1716 | Determined by CellProfiler |
|------|----------------------------|
|      | Keep parameters that have a minimum correlation of 0.80 between repeats for all cpds. |
| 579  | Final set of relevant parameters. Used for all further analyses |

**Figure S9**: Determination of reproducible parameters in cell painting assay.

To determine the phenotypic profiles for each test compound Z-scores were then calculated for each parameter as how many times the Median Absolute Deviation (MAD) of the controls the measured parameter value of a test compound deviates from the Median of the controls:
The phenotypic compound profile is then determined as the list of z-scores of all parameters for one compound.

In addition to the phenotypic profile, an induction value was determined for each compound as the fraction of significantly changed parameters, in percent:

\[
\text{Induction} \ [\%] = \frac{\text{number of parameters with abs. values} > 3}{\text{total number of parameters}}
\]

Similarities of phenotypic profiles were calculated from the correlation distances between two profiles (https://docs.scipy.org/doc/scipy/reference/generated/scipy.spatial.distance.correlation.html; Similarity = 1 - Correlation Distance) and the compounds with the most similar profiles were determined from a set of 3000 reference compounds that was also measured in the assay.

An example for two compounds with highly similar profiles (96% similarity):

An example for two compounds with low similarity profiles (0% similarity):

Each colored band represents one Z-score of a parameter.
**Immunocytochemistry**

U2OS cells were seeded per well in a 96-well plate and incubated overnight. Cells were treated with compounds or DMSO as a control for 24 hours. Cells were then fixed using 3.7% paraformaldehyde in phosphate-buffered saline. PBS and permeabilized with 0.1% Triton X-100 (in PBS) prior to staining with DAPI to visualize DNA and anti-tubulin-FITC antibody or anti-phosphor-Histone3 antibody antibodies overnight at 4℃. Images were acquired using Observer Z1 (Carl Zeiss, Germany) using 20X and 40X objectives (LD Plan-Neofluar). Automated image analysis to quantify the percentage of phospho-histone3-positive cells was performed using the DAPI stain to assess the total number of cells and the software MetaMorph. Using GraphPad Prism 5, one-way analysis of variance (ANOVA) plus T-test were performed to check the significance of data represented in Figure 1f (***, P-value < 0.0001).

**In vitro tubulin polymerization assay:**

*In vitro* tubulin polymerization assay was performed as described previously.[14] Briefly, porcine α/β-tubulin was diluted in a general buffer containing 80 mM PIPES (pH 6.9), 2 mM MgCl$_2$ and 0.5 mM EGTA. Next, 10 µM of α/β-tubulin was added to a solution containing MgCl$_2$ and glutamate with a final concentration of 0.88 µM and 0.8 mM, respectively, and added to a 96-well plate. Afterwards, compounds at a final concentration 20 µM were added to the tubulin solution and incubated at room temperature for 20 min. The plate was then incubated on ice for another 20 min prior to addition of GTP to a final concentration of 500 µM. Tubulin polymerization was monitored for 60 min by means of turbidity measurements at 340 nm.

**Real-time live-cell analysis**

Cell growth was monitored by means of real-time live-cell analysis using the IncuCyte S3 (Essen Bioscience). For this, 4000 U2OS cells were seeded per well in 96-well plate and incubated overnight. The medium was then exchanged for fresh medium that contained the compounds or DMSO as a control. Cells were incubated for 48 h and cell growth were imaged
every two hours using in the bright-field mode. Cell confluence was quantified as a measure of cell growth using the IncuCyte S3 2019A software.
5. X-Ray Structures of Compounds 15a and syn-10

Crystal data and structure refinement for 15a.

| Parameter                   | Value                        |
|-----------------------------|------------------------------|
| Identification code         | pbca                         |
| Empirical formula           | C_{19}H_{21}NO_{4}S          |
| Formula weight              | 359.43                       |
| Temperature/K               | 100                          |
| Crystal system              | orthorhombic                 |
| Space group                 | Pbc                         |
| a/Å                         | 16.4445(14)                  |
| b/Å                         | 9.7793(8)                    |
| c/Å                         | 21.9616(18)                  |
| α/°                         | 90                           |
| β/°                         | 90                           |
| γ/°                         | 90                           |
| Volume/Å³                   | 3531.8(5)                    |
| Z                           | 8                            |
| ρ_{calc}/g/cm³              | 1.352                        |
| μ/mm⁻¹                      | 0.207                        |
| F(000)                      | 1520.0                       |
| Crystal size/mm³            | 0.277 × 0.116 × 0.059        |
| Radiation                   | MoKα (λ = 0.71073)           |
| 2Θ range for data collection/° | 6.104 to 53.998             |
| Index ranges                | -21 ≤ h ≤ 21, -12 ≤ k ≤ 12, -28 ≤ l ≤ 28 |
| Reflections collected       | 82730                        |
| Independent reflections     | 38522 [R_{int} = 0.0453, R_{sigma} = 0.0160] |
| Data/restraints/parameters  | 3852/0/251                   |
| Goodness-of-fit on F²       | 1.075                        |
| Final R indexes [I>2σ (I)]  | R₁ = 0.0417, wR₂ = 0.0946    |
| Final R indexes [all data]  | R₁ = 0.0493, wR₂ = 0.0985    |
| Largest diff. peak/hole / e Å⁻³ | 0.49/-0.50             |
Crystal data and structure refinement for syn-10a.

| Property                        | Value                                      |
|---------------------------------|--------------------------------------------|
| Identification code            | C0076_0m                                   |
| Empirical formula              | C_{16}H_{20}N_{2}O_{6}S                    |
| Formula weight                 | 368.40                                     |
| Temperature/K                  | 100.0                                      |
| Crystal system                 | monoclinic                                 |
| Space group                    | P2_1/n                                     |
| a/Å                            | 7.7558(3)                                  |
| b/Å                            | 10.0904(4)                                 |
| c/Å                            | 22.1316(10)                                |
| α/°                            | 90                                         |
| β/°                            | 98.937(2)                                  |
| γ/°                            | 90                                         |
| Volume/Å³                      | 1710.97(12)                                |
| Z                              | 4                                          |
| ρ_{calc}/g/cm³                 | 1.430                                      |
| μ/mm⁻¹                         | 0.225                                      |
| F(000)                         | 776.0                                      |
| Crystal size/mm³               | 0.937 × 0.388 × 0.274                      |
| Radiation                      | MoKα (λ = 0.71073)                         |
| 2Θ range for data collection/° | 5.494 to 77.996                            |
| Index ranges                   | -13 ≤ h ≤ 13, -17 ≤ k ≤ 17, -39 ≤ l ≤ 39  |
| Reflections collected          | 83416                                      |
| Independent reflections        | 9831 [R_{int} = 0.0298, R_{sigma} = 0.0188]|
| Data/restraints/parameters     | 9831/0/234                                 |
| Goodness-of-fit on F²          | 1.094                                      |
| Final R indexes [I>2σ (I)]     | R₁ = 0.0294, wR₂ = 0.0828                  |
| Final R indexes [all data]     | R₁ = 0.0317, wR₂ = 0.0848                  |
| Largest diff. peak/hole / e Å⁻³ | 0.68/-0.43                                |
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