

Supporting Information

On the development of selective chelators for cadmium; synthesis, structure and chelating properties of 3-((5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)amino)benzo[*d*]isothiazole 1,1-dioxide, a novel thiadiazolyl saccharinate.

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1. Structure analysis

1.1 1D and 2D NMR of 3-((5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)amino)benzo[d]isothiazole 1,1-dioxide

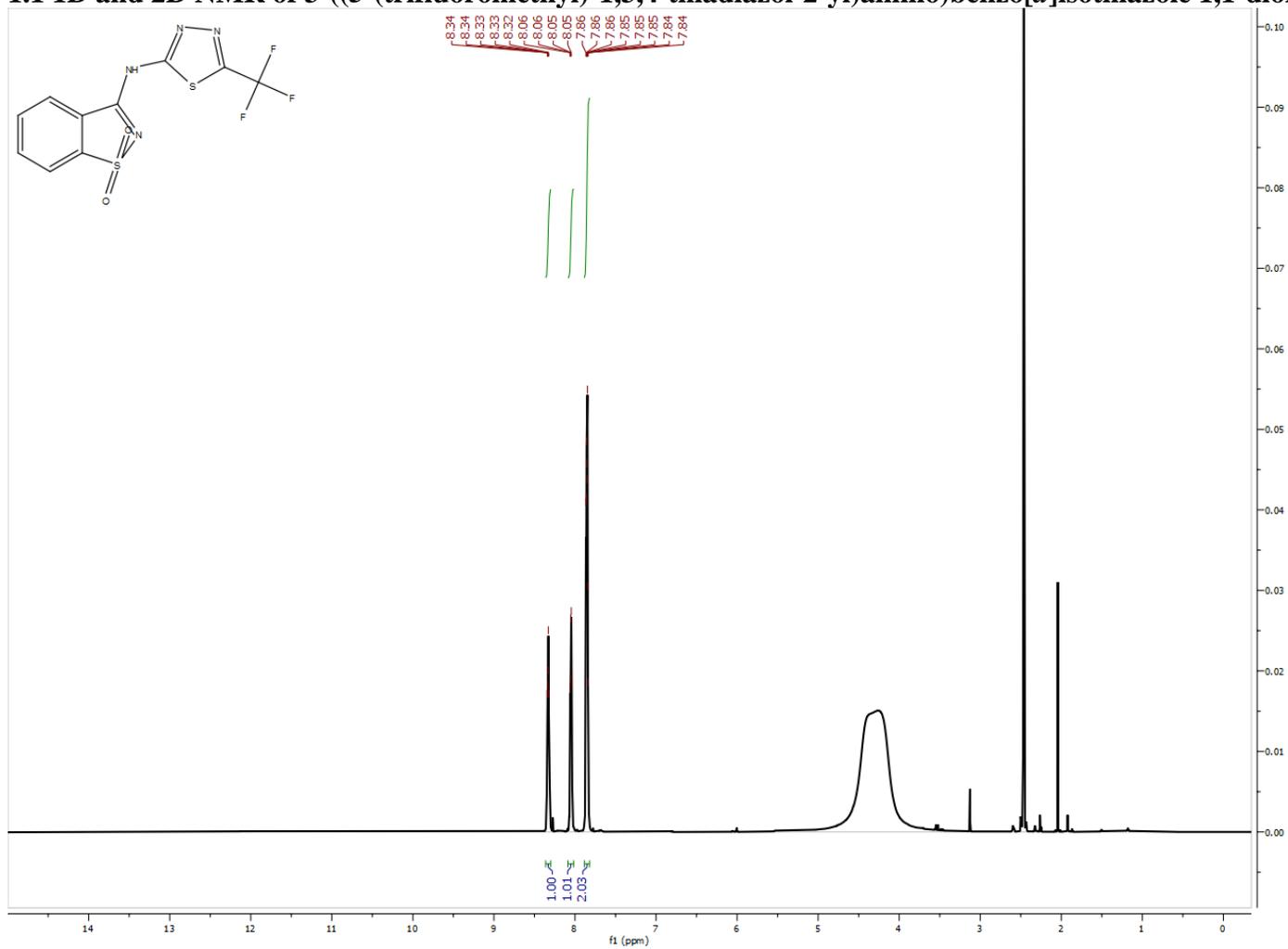


Figure S1. ¹H NMR spectra of 3-((5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)amino)benzo[d]isothiazole 1,1-dioxide (**AL14**) in DMSO-*d*₆.

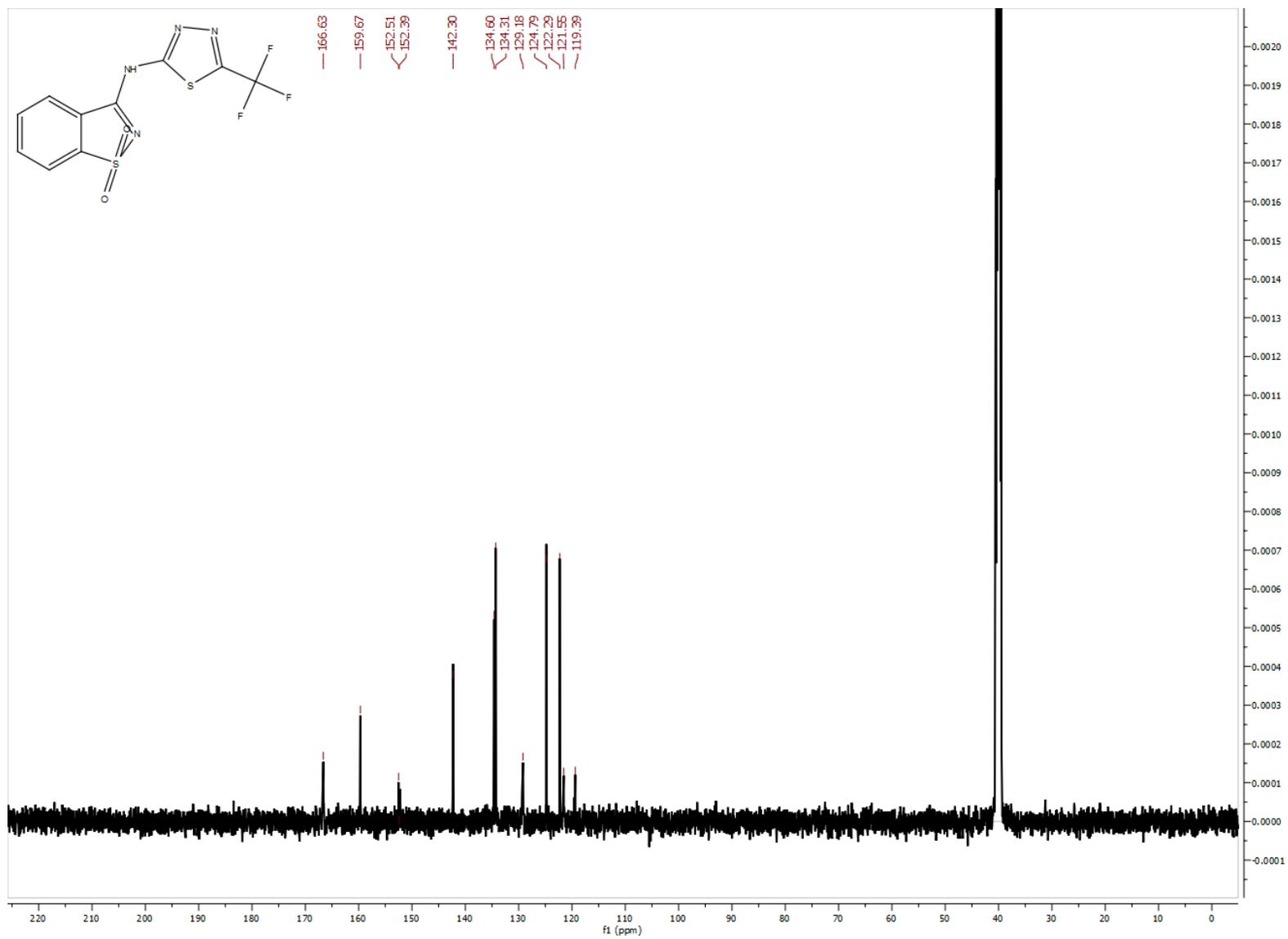


Figure S2. ¹³C NMR spectra of 3-((5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)amino)benzo[d]isothiazole 1,1-dioxide (AL14) in DMSO-*d*₆.

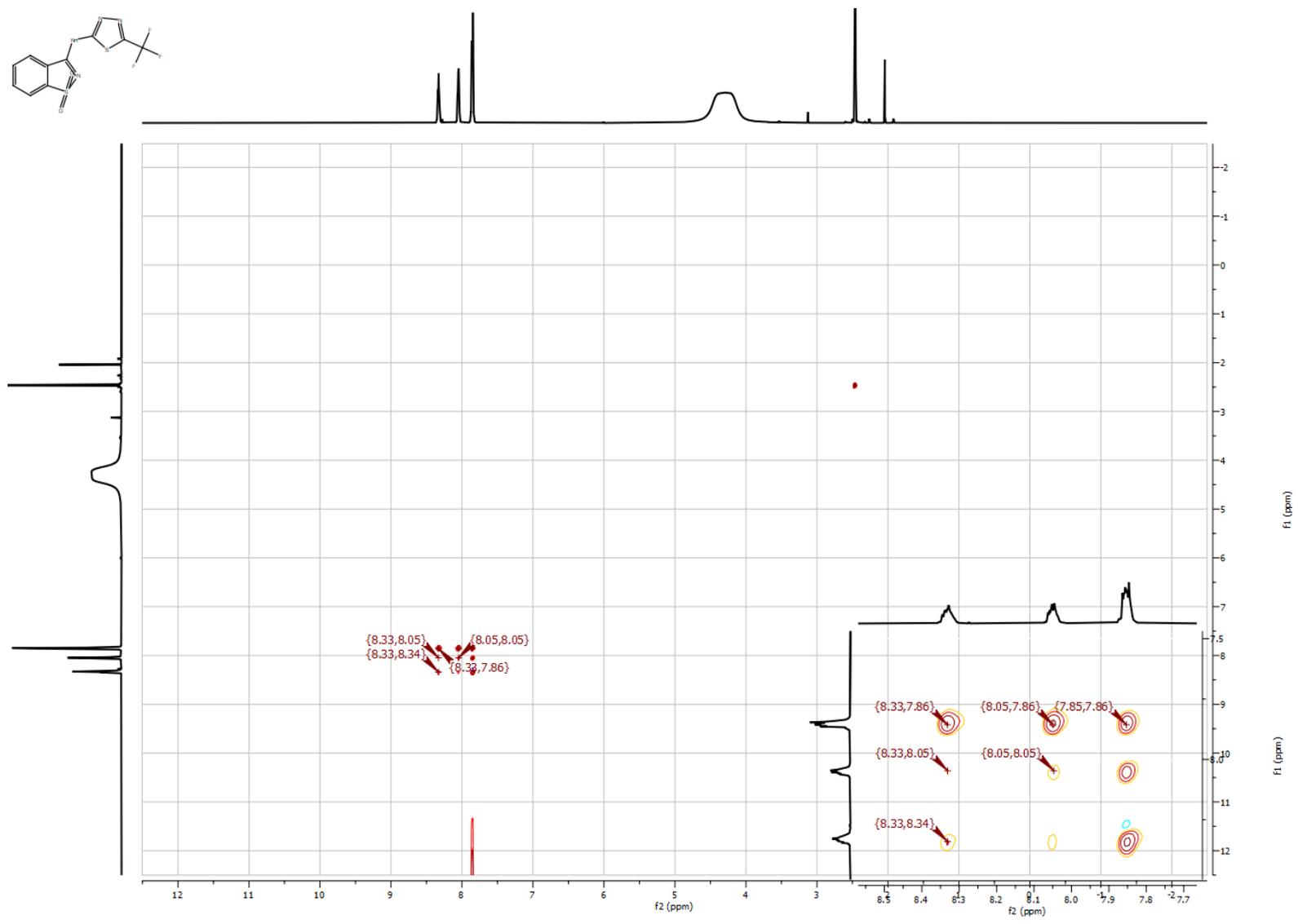


Figure S3. TOCSY spectra of 3-((5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)amino)benzo[d]isothiazole 1,1-dioxide (AL14) in DMSO-*d*₆.

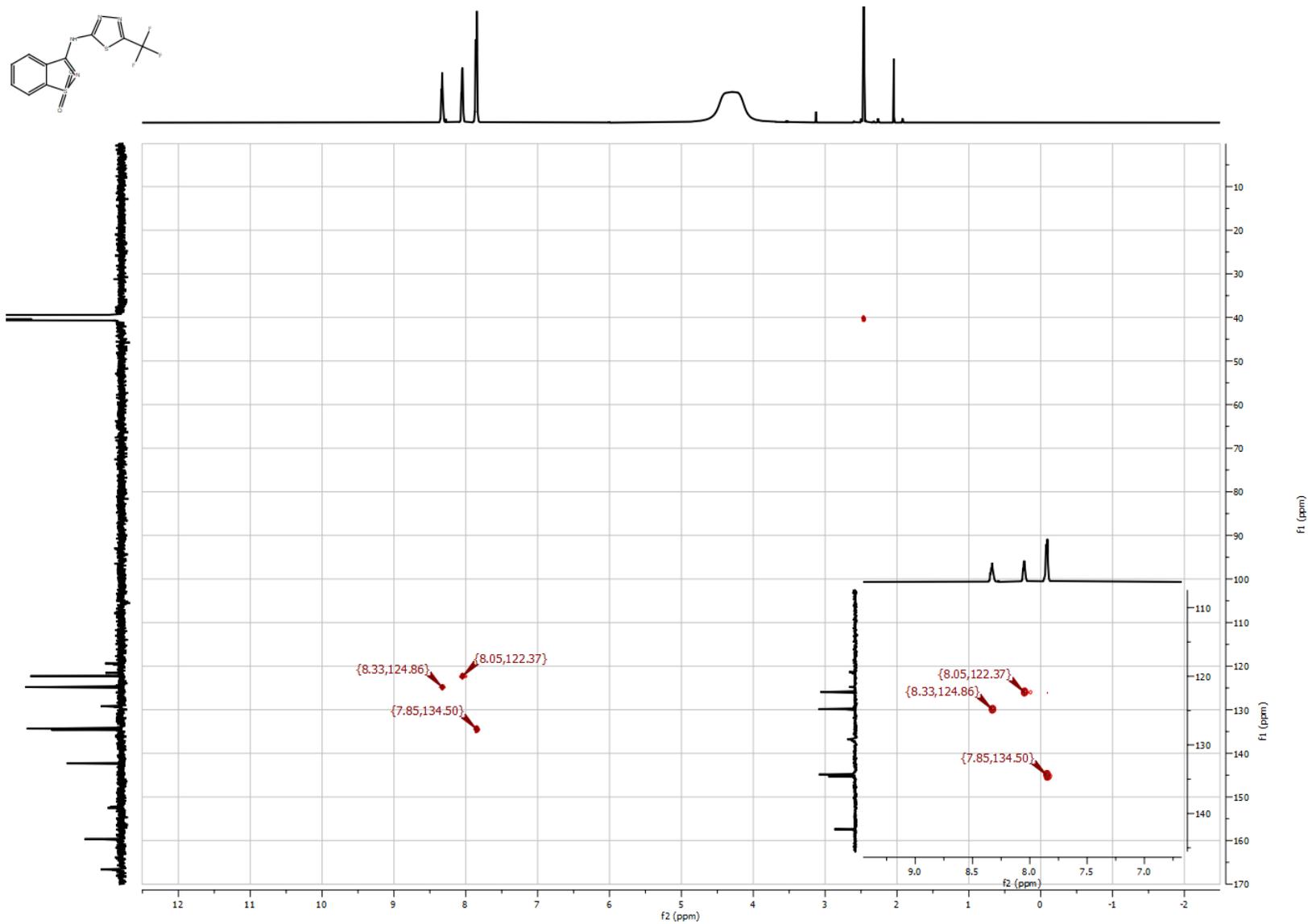


Figure S4. HSQC spectra of 3-((5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)amino)benzo[d]isothiazole 1,1-dioxide (AL14) in DMSO- d_6 .

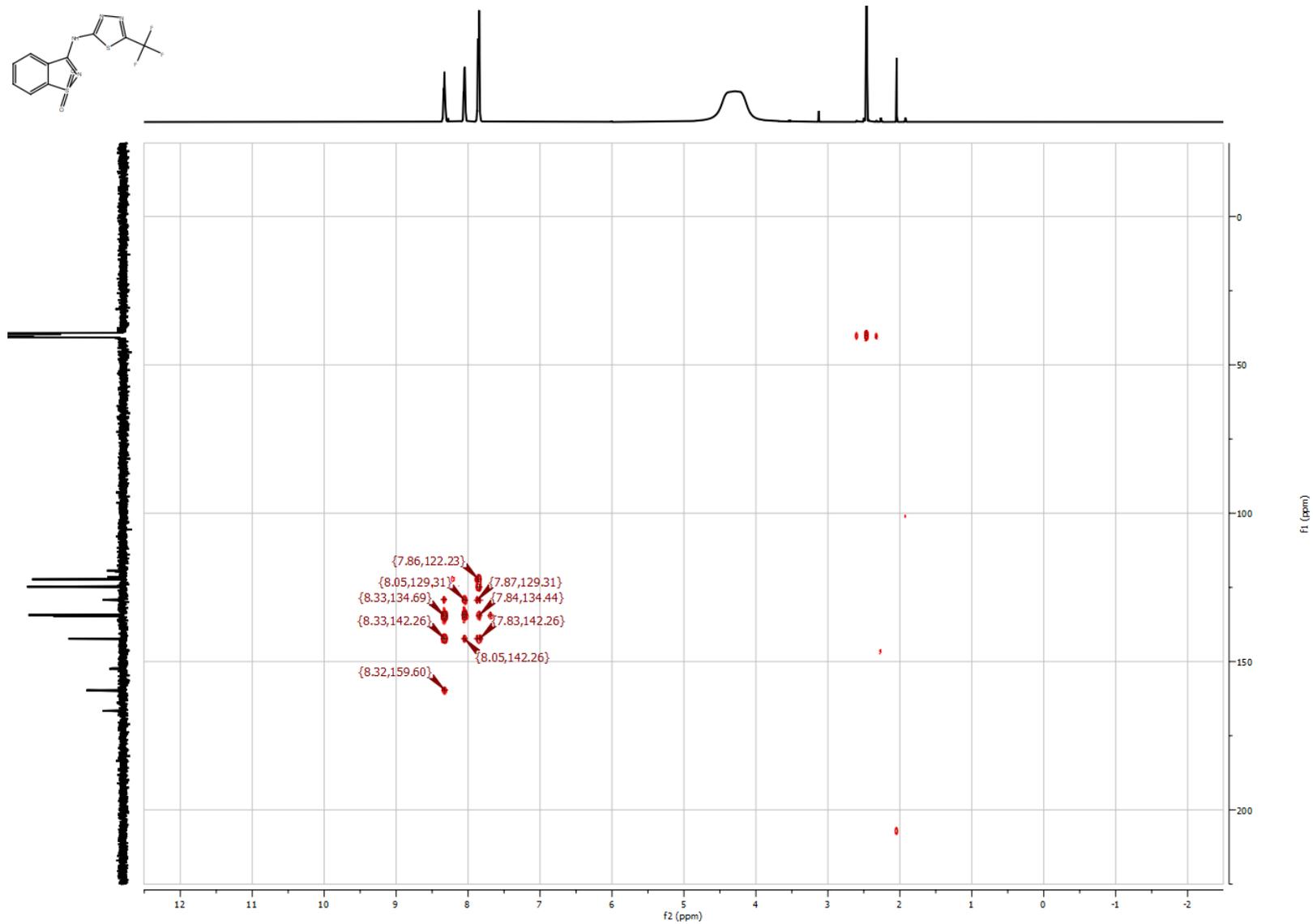


Figure S5. HMBC spectra of 3-((5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)amino)benzo[*d*]isothiazole 1,1-dioxide (AL14) in DMSO-*d*₆.

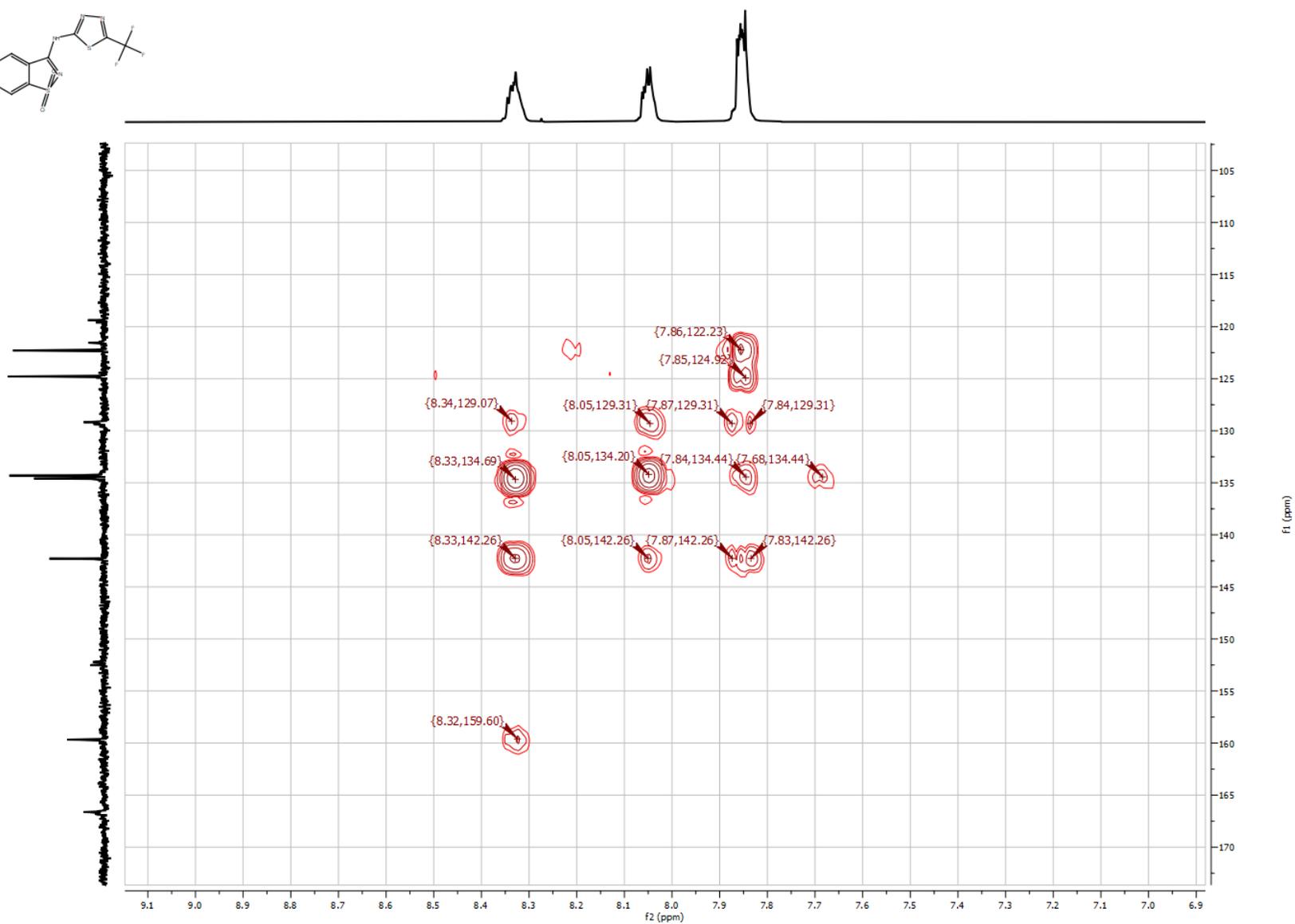
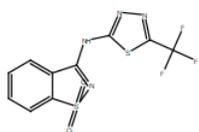


Figure S6. HMBC (expanded) spectra of 3-((5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)amino)benzo[d]isothiazole 1,1-dioxide (AL14) in DMSO-*d*₆.

1.2. Mass Spectra of 3-((5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)amino)benzo[d]isothiazole 1,1-dioxide

AL-14 pos_210123125005 #18 RT: 0.26 AV: 1 NL: 1.25E7
T: FTMS + p ESI Full ms [100.00-400.00]

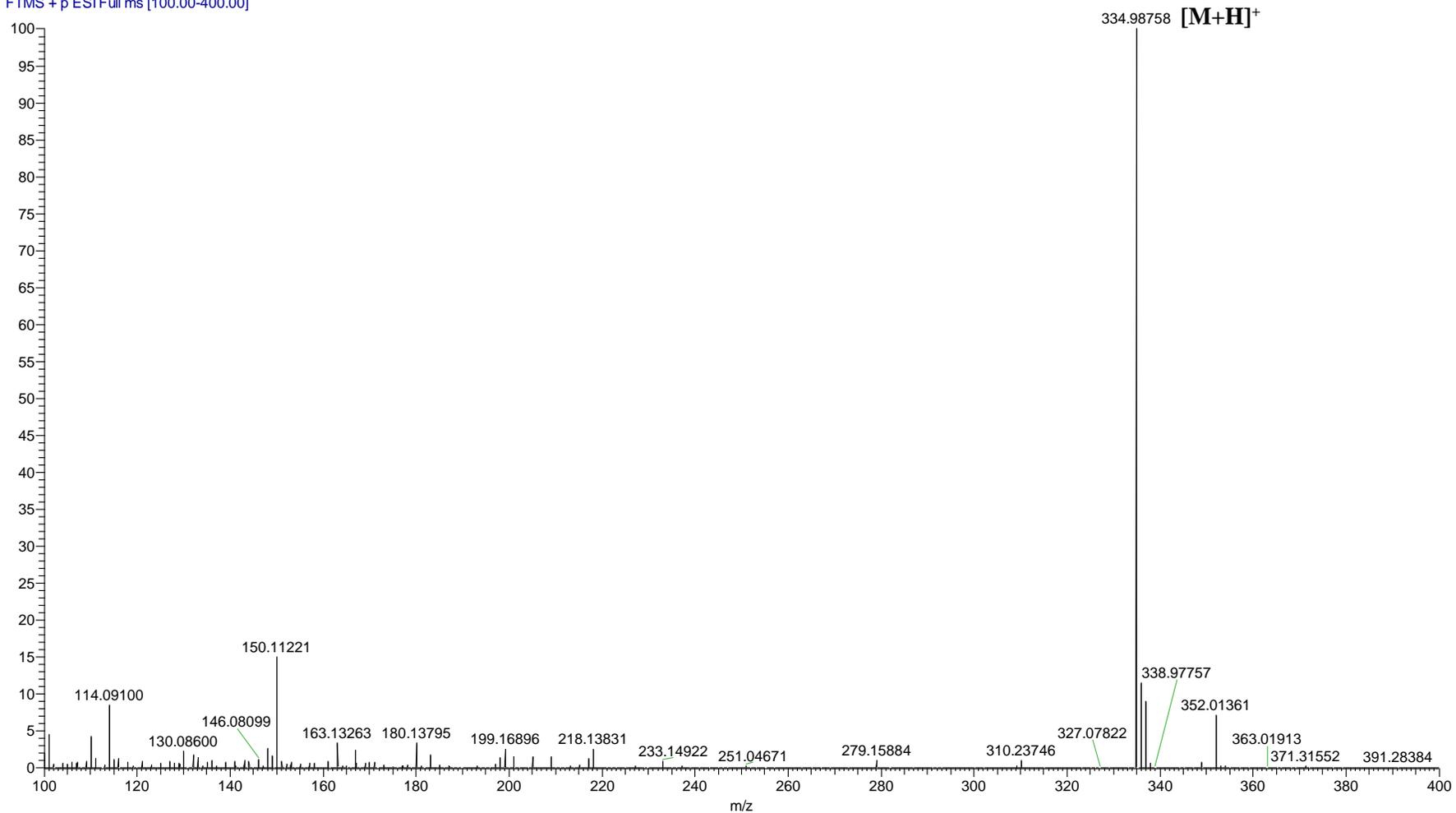
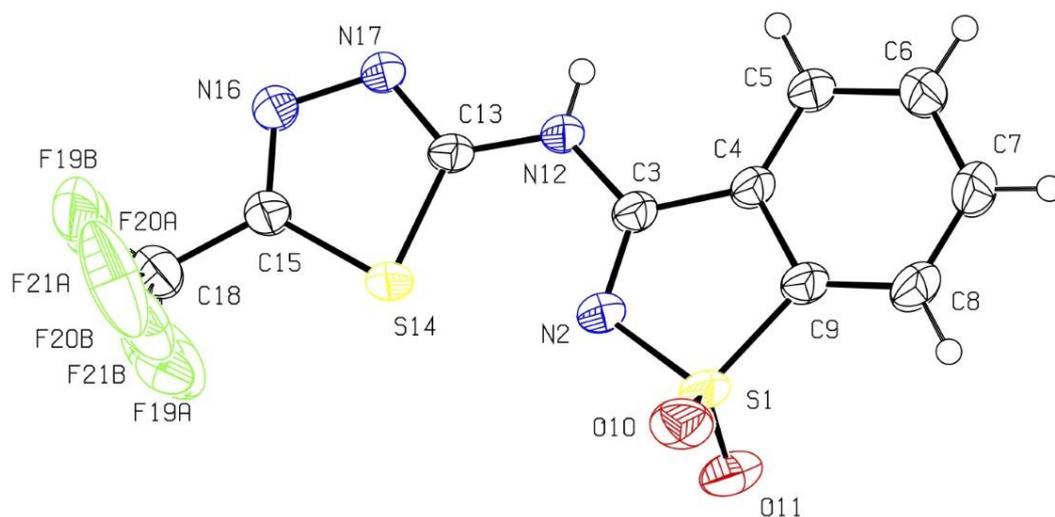


Figure S7. Electrospray ionization mass spectrum in positive-ion mode (HRMS-ESI⁺) of 3-((5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)amino)benzo[d]isothiazole 1,1-dioxide (**AL14**).

1.3. X-ray crystallography



Data were collected at room temperature on an X-ray single crystal diffractometer equipped with a kappa-geometry goniometer, a 4K CCD detector (Bruker APEXII) and a sealed, fine focus, X-ray tube, emitting MoK α radiation ($\lambda = 0.71073 \text{ \AA}$). The *bremsstrahlung* radiation and the K β component were filtered by a graphite monochromator. Data collection and data reduction were performed using the Bruker APEXIII software package [S1]. The measurements were performed on a small single crystal coated with poly-fluorinated oil, mounted on top of a thin glass fiber. Initial lattice parameters were determined from a preliminary data collection consisting of set of 36 detector frames. A subsequent data collection was performed on a full sphere, using omega and phi scans of 0.5° width. The data acquisition time was 10 s per frame. Reflections were merged and corrected for Lorentz and polarization effects, scan speed, and background using SAINT V8.38A [S2] included in the APEXIII package. Absorption corrections, including odd and even spherical harmonics up to rank 3 and 6, respectively, were performed using SADABS-2016/2 [S3].

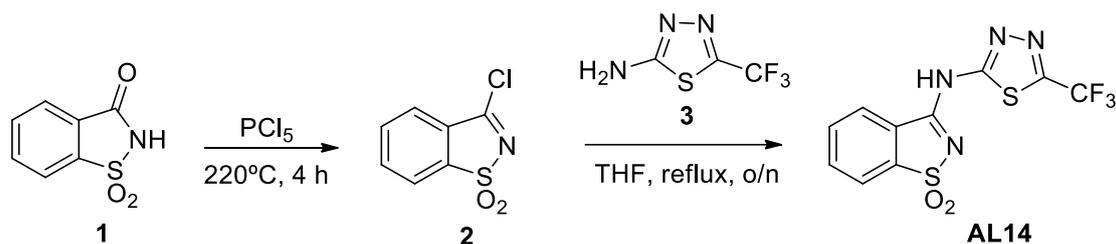
Space group assignment was based upon E statistics, and successful refinement of the structure in space group $P-1$. The structure was solved by a dual-space method using SHELXT 2014/5 [S4] and refined by full matrix least-squares (minimizing $\sum w(F_o^2 - F_c^2)^2$) using SHELXL-2018/1 [S5]. The weighting scheme was $w=1/[s^2(F_o^2)+(0.0466P)^2+0.2371]$ where $P=(F_o^2+2F_c^2)/3$, as suggested by SHELXL-2018/1. The final quality factors of the refinement were $R_1(I>2\sigma) = 0.0317$, $wR_{\text{all}} = 0.0406$ and $\text{GOF} = 1.067$ for 3097 for independent reflections and 221 refined parameters. Default SHELXL-2018/1 values for atomic scattering factors for all atoms and anomalous dispersion corrections for the non-hydrogen atoms were used. All atoms were refined anisotropically with exception for the H atoms. The H atoms attached to the C atoms were initially placed idealized positions and refined as riding using SHELXL defaults. That attached to the N12 atom had its x,y,z coordinates freely refined with an isotropic displacement parameter constrained to 1.2x of the parent atom. The F atoms of the CF3 group are disordered over two alternate positions with occupancies (0.54;0.46). The positions of the F atoms were freely refined as well as their anisotropic displacement factors without any restraints. The ORTEP plot of the molecule was generated by PLATON [S6].

CCDC 2063726 contains additional crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

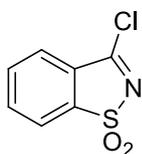
2. Experimental Methods

2.1 Synthesis

The synthesis of 3-((5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)amino)benzo[*d*]isothiazole 1,1-dioxide (**AL14**) and the preparation of pseudo-saccharyl chloride **2** were carried out by adapting the methodology described by Ismael *et al.*[S7,8], with slight modifications (Scheme S1).

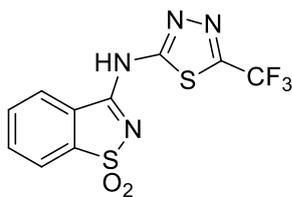


Scheme S1. Preparation of 3-((5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)amino)benzo[*d*]isothiazole 1,1-dioxide (**AL14**).



3-chloro-1,2-benzisothiazole-1,1-dioxide (2). Saccharin **1** (56 mmol) and phosphorus pentachloride (66 mmol), were heated at 220 °C for 4 hours. On cooling to room temperature, phosphorus oxychloride was then distilled off the reaction medium, under vacuum, at 180 °C. At 100 °C toluene was added, and then chloroform, below 70 °C, at 1:9 proportion. The mixture was allowed to crystallise at room temperature. The crystals obtained were washed with cold toluene and chloroform, giving the desired product as colourless needles (63% yield); m.p. 143-145 °C.

¹H NMR (400 MHz, DMSO-*d*₆): δ 8.17 (d, *J* = 7.5 Hz, 1H), 8.00 (t, *J* = 8.0 Hz, 2H), 7.93 (d, *J* = 7.3 Hz, 1H). ¹³C NMR (101 MHz, DMSO-*d*₆): δ 160.61 (s), 139.17 (s), 135.72 (s), 134.89 (s), 127.32 (s), 124.95 (s), 121.26 (s). Found: C, 41.5%; H, 2.0%; N, 6.9%; calcd for C₇H₄NO₂SCl: C, 41.7%; H, 2.0%; N, 7.0%. MS (EI, *m/z*): 201 [M]⁺.



3-((5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)amino)benzo[d]isothiazole 1,1-dioxide (AL14).

A mixture of the corresponding *pseudo*-saccharyl chloride **2** (1.00 g, 4.96 mmol) and 2-amino-5-trifluoromethyl-1,3,4-thiadiazole **3** (0.923 g, 5.46 mmol) in dry THF was stirred at 60 °C for 24 h under a nitrogen atmosphere. The solvent was then evaporated under reduced pressure and the remaining solid was washed with ethyl acetate, dried under reduced pressure at room temperature. Recrystallization with ethyl acetate gave the desired compound as light green-white crystals, yield 42% (0.69 g, 2.07 mmol). mp 320°C (dec.).

¹H NMR (500 MHz, DMSO-*d*₆): δ 8.36 – 8.30 (m, 1H), 8.08 – 8.02 (dt, *J* = 5.9, 2.4 Hz, 1H), 7.90 – 7.82 (m, 2H). ¹³C NMR (126 MHz, DMSO-*d*₆): δ 166.63, 159.67, 152.51, 152.39, 142.30, 134.60, 134.31, 129.18, 124.79, 122.29, 121.55, 119.38. HRMS (ESI⁺, *m/z*) calcd for C₁₀H₆F₃N₄O₂S₂ (M+H)⁺: 334.98760; found 334.98758.

3. REFERENCES

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