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Expanding the Repertoire of Low-Molecular-Weight Pentafluorosulfanyl-Substituted Scaffolds

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The pentafluorosulfanyl (-SF₅) functional group is of increasing interest as a bioisostere in medicinal chemistry. A library of SF₅-containing compounds, including amide, isoxazole, and oxindole derivatives, was synthesised using a range of solution-based and solventless methods, including microwave and ball-mill techniques. The library was tested against targets including human dihydroorotate dehydrogenase (HDHODH). A subsequent focused approach led to synthesis of analogues of the clinically used disease modifying anti-rheumatic drugs (DMARDs), Teriflunomide and Leflunomide, considered for potential COVID-19 use, where SF₅ bioisostere deployment led to improved inhibition of HDHODH compared with the parent drugs. The results demonstrate the utility of the SF₅ group in medicinal chemistry.

Introduction

Small-molecule organic compounds are often used as tool compounds and chemical probes for functional validation in biological systems and as therapeutics.[1] Halogen containing fragments and higher molecular weight derivatives form a large proportion of drug-like molecules.[2–5] The pentafluorosulfanyl group is gaining popularity as a bioisostere in bioactive compounds[6,7] and in materials[8] as it is considered to be relatively stable, electronaffative and lipophilic alternative to a CF₃ group. Recent years have seen a rise in SF₅-substituted compounds as direct access to aryl- and alkyl-SF₅ building blocks has been achieved.[9,10] We have recently incorporated the SF₅ group in benzodiazepine and oxindole analogues (Figure 1).[11,12] In the former example, significant activity was lost, likely due to the steric size of the SF₅ group compared to a Cl substituent.

Owing to the relative dearth of bioactive pentafluorosulfany-containing compounds, yet commercial availability of a number of attractive building blocks, we set out to synthesise libraries of SF₅-phenyl derivatives endowed with further functionality. This work was intended to serve two purposes: the synthesis of novel small libraries to show synthetic scope and possible interest for screening programmes and the

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directed synthesis of SF₅-analogues as a comparison with known, electron withdrawing, CF₃, Cl− and NO₂-substituted bioactive molecules.

Results and Discussion

Initially, SF₅-containing small molecules were constructed via a simple amide bond-forming reaction, using trimethylamine in dichloromethane (conditions “a”); in general, were satisfactory (Scheme 1). Purifications varied according to the reaction, but typically involved flash silica chromatography or the use of the nucleophilic scavenger, MP-Trisamine (macroporous polystyrene-bound nucleophilic scavenger), to remove unreacted acid or acid chloride. Attempted reactions with 1-methylpiperazine led to poor yields, e.g., 3b, and the free benzoic acid was detected in the crude reaction mixture, suggesting competing acid chloride hydrolysis and poor yields for the amide coupling. Hence, the coupling reagent, HATU (hexafluorophosphate azabenzotriazole tetramethyl uronium), was added (conditions “b”) to mitigate for any benzoic acid formed in situ; this led to mainly improved yields, e.g. 4b (83% vs 10%). The Boc-piperazine analogues 3d and 4d were successfully deprotected and further functionalised as their amide and sulphonamide derivatives 3e, 4e and 3f, 4f respectively. In total, a dozen new SF₅-containing amide analogues were made, which may have useful applications as halogen-rich screening library compounds, for example.

Next, we focussed our attention on to oxindole derivatives, having recently reported SF₅-containing analogues with kinase inhibitory properties. Microwave heating was employed as in our previous work and, for acetone-derived products, this acted both as a solvent and a reagent. In the synthesis of 8b, soon after combining the oxindole, acetone and piperidine, product formation was observed, which precipitated out of solution. Nevertheless, the reaction mixture was heated under microwave irradiation until the reaction was complete and pure product was obtained, in 90% yield. Crystallisation from acetone afforded single crystals of 8b suitable for X-ray structure determination (Scheme 2). In essence, these Knoevenagel condensations utilized a variety of solvents and nitro analogue, 10a, was prepared to demonstrate the applicability of this reaction to other electron-withdrawing systems. (Note; to avoid overpressure, ensure the microwave tube is less than half-full).

Mechanochemical synthesis is an attractive method that is an environmentally friendly alternative to traditional routes which has been applied to Knoevenagel condensations. We attempted the synthesis of 10a in a vibratory ball mill (VBM) in steel jars (SST) and zirconium oxide jars (ZrO₂); with and without catalyst, and for various reaction times. Zirconia jars were best

Figure 1. SF₅-benzodiazepine and oxindole analogues previously made in our group.

Scheme 1. Synthesis of a small SF₅-substituted amide library.

Scheme 2. Oxindole synthesis via a Knoevenagel condensation.
suited for mechanochemical condensation as opposed to steel jars. Reactions performed in the absence of catalyst did not yield any product.

We compared 8a and 9a with Semaxinib (Scheme 2), a selective inhibitor of VEGFR[19], using both molecular docking and in vitro analysis in vascular endothelial growth factor receptor-2 VEGFR2 (Figure 2). Semaxinib inhibits VEGFR2 by binding in the ATP binding site, where the pyrrole ring occupies a hydrophobic pocket and forms van der Waals interactions. The oxindole ring binds in a similar fashion to the ATP’s purine and provides a hydrogen bond donor and an acceptor to form hydrogen bond interactions. The bulk of the SF$_5$ group seemingly pushes the oxindole ring into the hydrophobic pocket and the pyrrole into the solvent region, thus the oxindole is no longer able to occupy the adenine pocket. 9a retains a key aromatic $\pi$–$\pi$ interaction, between Phe1047 (DFG motif) and the oxindole group. However, 8a does not form an interaction between the oxindole ring and the adenine pocket except for a hydrogen bond to an aromatic hydrogen. The SF$_5$ moiety is likely to form van der Waals interactions with Lys868 and Ala866 in the hydrophobic binding pocket. A biochemical assay showed Semaxinib to inhibit VEGFR2 with an IC$_{50}$ of 1.5 $\mu$M (lit. 1.04 ± 0.53 $\mu$M).[20] Compounds 8a and 9a did not manifest sufficient inhibition to generate IC$_{50}$ values. At 10 $\mu$M, the former exhibited 27% inhibition of VEGFR2 while 9a gave 23% inhibition at the same concentration (Table 1).

A spirocyclisation reaction led to the product 11a in poor yield, whose structure was determined by X-ray crystal analysis. 11a was then methylated to give 11b (Scheme 3). Such high Csp$^3$ content compounds may offer more diversity to compound libraries and improved physiochemical properties.

Biological studies

A recently initiated open source effort, termed the Covid Moonshot Consortium, has led to the design of nM-potent inhibitors of M$^{pro}$ (or CLPro), a vital enzyme in SARS-CoV-2 replication and transcription.[21] M$^{pro}$ releases the functional polypeptides from the polyproteins by extensive proteolytic processing while digesting the polyproteins at 11 cleavage sites, starting with autolytic cleavage[22] and exclusively cleaves polypeptides after a glutamine residue. Its functional importance and the absence of closely related homologues in humans, renders M$^{pro}$ an attractive target for antiviral drug design as an example of a direct acting antiviral agent.[23] Pyridine substituted 3-Cl-phenylacetamide analogues I and II were found to be moderate to active analogues and we wished to explore both alternatives to the Cl substituent and more water solubilising groups such as CO$_2$H as opposed to fused aryl or methyl groups. (Figure 3 and Scheme 4).

| Entry | Compound | IC$_{50}$ [$\mu$M] |
|-------|----------|------------------|
| 1     | semaxinib | 1.5              |
| 2     | 8a       | —                |
| 3     | 9a       | —                |

[a] $n=1$; 10-dose IC$_{50}$ mode with twofold serial dilutions, starting at 10 $\mu$M. [b] Percent inhibition at 10 $\mu$M; 8a (27%), 9a (23%).
The aminopyridine 12 was coupled with acid chlorides or an acid to yield the ester analogues 13, substituted with CF\(_3\), SF\(_5\), and Cl groups (Scheme 4). Surprisingly, reaction of the latter with ammonia led to the cyclised compounds 14, one of which, 14a, was crystallised, by a diffusion method, using hexane and dichloromethane, to obtain clear crystals which enabled confirmation of its structure by X-ray analysis.\(^{[24]}\) The reaction likely involves the formation of a carboxamide, from the methyl ester, which cyclises onto the amide carbonyl group, followed by water elimination.

Compounds 13–14 were tested for inhibition versus M\(_{\text{Pro}}\), but none had any appreciable enzyme activity (IC\(_{50}\) > 99 \(\mu\)M).

Finally, we focused our efforts on Leflunomide (Arava\(^*\)), a DMARD (disease modifying antirheumatic drug) with potential COVID-19 use\(^{[25]}\) and its active metabolite Teriflunomide (Aubagio\(^*\)), which is used for multiple sclerosis.\(^{[26]}\) Teriflunomide inhibits human DHODH in the low \(\mu\)M range and binds in the same region as ubiquinone, a redox cofactor. Both Teriflunomide and ubiquinone occupy a narrow cleft near a flavin molecule (another redox cofactor), which leads to the active site (Figure 5).\(^{[26]}\) As Teriflunomide competes with ubiquinone,\(^{[27]}\) it is regarded as a redox silent coenzyme Q antagonist of DHODH.\(^{[28]}\) Teriflunomide has a polar head consisting of one hydrogen bond donor; an enol and two hydrogen bond acceptors, a nitrile and a carbonyl group, while the tail of Teriflunomide, which occupies the entrance of the tunnel, is a hydrophobic CF\(_3\)-substituted aromatic group.

We first prepared the SF\(_5\) derivative of Leflunomide 15, which, when treated with sodium hydroxide, provided its Teriflunomide equivalent 16 in good yields (Scheme 5).\(^{[29]}\) The latter was further characterised in the solid state by crystallography, proving its molecular structure and regiochemistry.

Docking of SF\(_5\)-Teriflunomide 16 in HDHODH was performed using Schrodinger Maestro. Interactions predicted between the ligand and the binding pocket are similar to those for Teriflunomide in the same binding site (Figure 6). The hydroxyl group of 16 is hydrogen bonded to a water molecule, which, in turn is bound to Gln47 and Thr360. The hydroxyl also makes a polar interaction with Arg136. The nitrile group interacts with Tyr356 via a H-bond. Finally, the carbonyl of 16 is positioned to form a H-bond with a water molecule that H-bonds with Thr360. Several hydrophobic interactions are formed between the aromatic rings and amino acid residues lining the hydrophobic pocket. The electrostatic potential diagram (Figure 7) shows the small difference in the size of CF\(_3\) and SF\(_5\) groups, and that SF\(_5\)-Teriflunomide is slightly larger than its parent analogue.

[Following our docking studies, we tested SF\(_5\)-Teriflunomide and SF\(_5\)-Leflunomide against human HDHODH using Teriflu-
and BAY-2402234 (a DHODH inhibitor in phase I clinical trials) as positive controls. A comparison of IC\(_{50}\) and pIC\(_{50}\) values of SF\(_5\)-Teriflunomide, SF\(_5\)-Leflunomide, Leflunomide against Teriflunomide and BAY-2402234 (Table 2) was undertaken. As anticipated, SF\(_5\)-Leflunomide is more potent than Leflunomide. SF\(_5\)-Teriflunomide is approximately twice as active as Teriflunomide. The simpler analogue, 17, tested in this assay, due to its MPro affinity (\textit{vide infra}), was inactive. Compound, BAY-2402234, gave the best potency with an IC\(_{50}\) of 1.8 nM, which is comparable to its literature value (1.2 nM). From similar docking, as well as the hydrophilic interactions, BAY-2402234 makes hydrophobic interactions with a large set of non-polar residues such as Leu42, Met43, Leu46, etc. and, with its bigger

Table 2. HDHODH inhibition; comparing SF\(_5\)-Teriflunomide, SF\(_5\)-Leflunomide and Leflunomide vs. Teriflunomide and BAY-2402234.

| Entry | Structure | IC\(_{50}\) [nM] | pIC\(_{50}\) |
|-------|-----------|-----------------|------------|
| 1     | 15        | 365             | 6.4        |
| 2     | 982       | 982             | 6.0        |
| 3     | Leflunomide | 27\([a]\)     | 7.6        |
| 4     | 50\([b]\) | 50\([b]\)     | 7.3        |
| 5     | Teriflunomide | 1.8\([d]\)  | 8.7        |
| 6     | BAY-2402234 | 1.8\([d]\)  | 8.7        |

\([a]\) Mean (\(n = 2\)); 29 nM and 25 nM. \([b]\) Unless stated otherwise; in vitro fluorescence-based assays run by Reaction Biology. \([c]\) Percent inhibition at 10 \(\mu\)M < 10\%. \([d]\) In vitro control (\(n = 1\)).
size, and the combination of hydrophobic and hydrophilic groups, it is able to fill the HDHODH active site to a greater degree.

We envisioned Teriflunomide and its SF₅ analogues such as 16 to have a covalent warhead capable of potentially acting as a Michael acceptor with the Sγ atom of Cys145 of Mₚₚ, as precedent with other Mₚₚ inhibitors; other modes of covalent reaction are also possible including with the nitrile, as with an Mpro inhibitor in clinical trials, or the carbonyl of the keto form of 16. In addition to Teriflunomide and 16, fourteen other potential candidates were assayed. Out of the sixteen compounds tested, a single hit (17, Table 2) was identified which gave a promising IC₅₀ of 0.23 µM using the fluorescence-based turnover assay (ESI, Table S1). Docking studies imply ligand 17, (Figure 8, shown in orange) could covalently react with Sγ of the nucleophilic Cys145 residue (Sγ in yellow, Figure 8), resulting in Michael addition. Besides the covalent bond, the modelling suggests formation of two hydrogen bonds (yellow dashes) are formed between the O-H of 17 and Cys145, as well as the amide carbonyl of 17 and Ser144. In addition, several hydrophobic interactions are predicted.

Although 17 has structural similarities to Teriflunomide, it was found to be inactive versus HDHODH (Table 2). Docking in HDHODH suggests that 17 occupies the binding pocket differently to Teriflunomide (Figure 9). Evidently, the hydrogen bond donors and acceptors on 17 lie in a hydrophobic tunnel of HDHODH.

The outer surface of coronaviruses has a spike (S) protein which enables its entry into host cells. The S1 subunit of S protein attaches to ACE2 receptor, which is found on the surface of target cells. In addition to this, the transmembrane protease, serine 2 (TMPRSS2) processes S protein into its constituent subunits, S1 and S2, thus allowing the virus to fuse into the plasma membrane of the host cell. As HDHODH is a druggable target against SARS-CoV-2, we were interested in probing the inhibitory effect of Teriflunomide and compounds 16 and 17 against SARS-CoV-2. Teriflunomide was the most cytostatic with effects at concentrations above 0.78 µM. 16 had cytostatic effects at concentrations > 3.1 µM and DMSO had no measurable effect. An infection inhibition assay showed that none of the compounds had an inhibitory effect against SARS-CoV-2 infection in the infected cells. The normalised data show that Teriflunomide and 16 have no effect on the efficiency of infection (Fig S2).

**Conclusion**

SF₅-analogues of Leflunomide and Teriflunomide, 15 and 16 respectively, have been synthesised and tested for affinity towards HDHODH. Biophysical assays revealed an approximately two-fold greater affinity for SF₅-Teriflunomide (15) towards HDHODH compared with Teriflunomide. Molecular binding studies revealed that the bulky SF₅ group fills the binding pocket better than the CF₅ group. A singleton hit 17 with structural similarities to Teriflunomide was identified as inhibiting SARS-CoV-2 Mₚₚ the low micromolar IC₅₀ range whereas a commercial library of similar analogues as well as an in-house library showed no affinity. Testing 17 against HDHODH, however, revealed no affinity. Neither Teriflunomide nor compounds 15 and 16 gave satisfactory inhibition of SARS-CoV-2 infection. Indeed, they were found to be cytostatic in HEK293T/17 cells. Nevertheless, the SF₅ analogue of Teriflunomide, 16, might be a useful DHODH probe molecule for future investigation.

**Experimental Section**

4-[(Pentafluorosulfanyl)amino]iline was obtained from Fluorochem and 5-methyl-4-isoxazolecarbonyl chloride was purchased from Apollo Scientific. Magnesium sulphate and sodium bicarbonate were obtained from Fisher Scientific. Preparative TLC plates were obtained from Analtech. Solvents and reagents were purchased from commercial suppliers and were used without purification. All reactions were performed in a fume hood. NMR spectra were recorded on Varian 500 MHz or 400 MHz spectrometers and chemical shifts are reported in ppm, usually referenced to TMS as an internal standard. LCMS measurements were performed on a Shimadzu LCMS-2020 equipped with a Gemin® 5 µm C18 110 Å column and percentage purity measurements were run over 30 minutes in water/acetonitrile with 0.1% formic acid (5 min at 5%, 5%-95% over 20 min, 5 min at 95%) with the UV detector at 254 nm. Mass spectrometry: ESI mass spectra were obtained using a Bruker Daltonics Apex III, using Apollo ESI as the ESI source. For EI mass spectra, a Fisons VG Autospec instrument was used at 70 eV. All analyses were run by Dr. Alla K. Abdul Sada. Analyses are for the...
molecular ion peak [M]⁺ and are given in m/z, mass to charge ratio. Melting points were determined using a Stanford Research Systems Optimelt and are uncorrected.

[3-(Pentafluoro-λ⁵-sulfanyl)phenyl](piperidin-1-yl)methanone (3a)

Triethylamine (247.0 mg, 2.44 mmol), was added dropwise to piperidine (175.8 mg, 2.07 mmol) dissolved in dichloromethane (2 mL) followed by the dropwise addition of 3-(pentafluorosulfanyl)benzoyl chloride (500.0 mg, 1.88 mmol). The reaction mixture was stirred at rt overnight. It was then diluted with dichloromethane (5 mL) and the addition of 3-(pentafluorosulfanyl)benzoyl chloride (500.0 mg, 2.07 mmol) was added to this solution followed by dropwise addition of 3-(pentafluorosulfanyl)benzoyl chloride (500.0 mg, 1.88 mmol) and the mixture was stirred for a few minutes. HATU (787.2 mg, 2.07 mmol) was added to this solution followed by dropwise addition of 3-(pentafluorosulfanyl)benzoyl chloride (500.0 mg, 1.88 mmol) and the mixture was stirred at room temperature overnight. After completion of the reaction, it was diluted with dichloromethane (10 mL) and the precipitate formed was removed by filtration. MP Trisamine (520 mg, 3 mmol) was added to the filtrate then removed by gravity filtration after 3 hours of stirring. The crude material was purified over a column of silica (dichloromethane:methanol, 9:1) to obtain 3 d as a colourless solid (573.0 mg, 73 %).

4 H NMR (600 MHz, CDCl₃) δ 7.81 (m, 2H, ArH), 7.53 (m, 2H, ArH), 3.51 (m, 4H, (CH₂)₂), 3.39 (m, 4H, (CH₂)₂), 1.45 (s, 9H, (CH₂)₂); 13 C NMR (151 MHz, CDCl₃) δ 168.4 (C-O), 154.5 (C-O), 154.0 (Ar-SCF₃), 136.3 (Ar-C), 130.1 (Ar-C), 129.2 (Ar-C), 127.4 (Ar-SCF₃), 125.0 (Ar-SCF₃), 80.5 (C), 47.5 (C), 42.9 (C, m), 28.3 (C, 3F); 19 F NMR (400 MHz, CDCl₃) δ 83.20 (m, F), 62.67 (d, J = 150.1 Hz, 4F); LCMS Purity (UV) = 99%, tᵣ = 20.4 min. HRMS-ESI (m/z) found: 393.0785, calc. for [C₁₁H₁₅F₅N₂OS⁺][Na⁺]: 393.0785; IR (neat) νmax/cm⁻¹: 2977, 1685, 1626, 1243, 828; mp 153–155°C.

1-[(3-(Pentafluoro-λ⁵-sulfanyl)benzoyl)piperazinyl hydrochloride) as a colourless solid (317.0 mg, 53 %). 1 H NMR (600 MHz, CDCl₃) δ 7.75–7.71 (m, 2H, ArH), 7.50–7.43 (m, 4H, (CH₂)₂), 3.57–3.26 (m, 4H, (CH₂)₂); 13 C NMR (151 MHz, CDCl₃) δ 168.0 (C-O), 153.8 (p, J = 17.7 Hz, Ar-SCF₃), 136.2 (Ar-C), 130.1 (Ar-C), 129.1 (Ar-C), 127.2 (Ar-C), 124.9 (p, J = 4.5 Hz, Ar-SCF₃), 124.9 (p, J = 4.5 Hz, Ar-SCF₃), 66.6 (4 F); 19 F NMR (400 MHz, CDCl₃) δ 84.29–82.81 (m, 62.66 (d, J = 150.4 Hz); LCMS Purity (UV) = 97%, tᵣ = 18.3 min; HRMS-ESI (m/z) found: 340.3824, calc. for [C₁₁H₁₅F₅N₂OS⁺][Na⁺]: 340.3804; IR (neat) νmax/cm⁻¹: 2858, 1644, 821; mp 63–64°C.

tert-Butyl 4-(3-(pentafluoro-λ⁵-sulfanyl benzoyl)piperazin-1-yl)carboxylate (3 d)

To N-Boc piperazine (385.5 mg, 2.07 mmol), dissolved in dichloromethane (3 mL) was added triethylamine (247.0 mg, 2.44 mmol) and the mixture was stirred for a few minutes. HATU (787.2 mg, 2.07 mmol) was added to this solution followed by dropwise addition of 3-(pentafluorosulfanyl)benzoyl chloride (500.0 mg, 1.88 mmol) and the reaction mixture was stirred at room temperature overnight. After completion of the reaction, it was diluted with dichloromethane (10 mL) and the precipitate formed was removed by filtration. MP Trisamine (520 mg, 3 mmol) was added to the filtrate then removed by gravity filtration after 3 hours of stirring. The crude material was purified over a column of silica (dichloromethane:methanol, 9:1) to obtain 3 d as a colourless solid (573.0 mg, 73 %).

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1-[(3-(Pentafluoro-λ⁵-sulfanyl)benzoyl)piperazin-1-yl)ethanone (3 e)

Compound 3 d (573 mg, 1.38 mmol) in dichloromethane (2 mL) was treated with HCl in dioxane (4 M, 5.0 equiv.) overnight. The reaction mixture was concentrated in vacuo to afford the HCl salt, 3 d (4-[(3-(pentafluoro-λ⁵-sulfanyl)benzoyl)piperazinyl hydrochloride) as a colourless solid. To crude 3 d (0.100 g, 0.28 mmol), dissolved in THF (3 mL) was added triethylamine (0.028 g, 0.28 mmol) and stirred for 30 minutes. Acetic anhydride (0.020 g, 0.28 mmol) was added to the mixture and stirred overnight at room temperature. The reaction mixture was concentrated in vacuo and purified by flash chromatography (dichloromethane:methanol, 9:1) to obtain the purified 3 e as a colourless oil (47.0 mg, 47 %). 1 H NMR (600 MHz, CDCl₃) δ 7.84–7.81 (m, 1H, ArH), 7.80–7.79 (m, 1H, ArH), 7.57–7.51 (m, 2H, ArH), 3.88–3.28 (m, 8H, ArH), 2.11 (s, 3H, CH₃); 13 C NMR (151 MHz, CDCl₃) δ 169.3 (C=O, MeCO), 168.4 (C-O), 154.0 (t, J = 18.0 Hz, Ar-C), 136.0 (Ar-C), 130.2 (Ar-C), 129.3 (Ar-C), 127.7–127.4 (m, Ar-C), 125.0 (Ar-C), 47.4 (bs, CH₃), 45.9 (bs, CH₃), 42.4 (bs, CH₃), 41.4 (bs, CH₃), 21.3 (CH₃); 19 F NMR (400 MHz, CDCl₃) δ 83.19 (p, J = 150.3 Hz, F), 62.78 (d, J = 150.3 Hz, 4F); LCMS Purity (UV) = 96%, tᵣ = 13.5 min; HRMS-ESI (m/z) found: 381.0662, calc. for [C₁₁H₁₅F₅N₂OS⁺][Na⁺]: 381.0667; IR (neat) νmax/cm⁻¹: 2917 (C-H), 1633 (C-O), 1322 (S=O), 821 (S=O).
chloromethane (2 mL) was added triethylamine (190.3 mg, 2.07 mmol), dissolved in dichloromethane (2 mL) and triethylamine (2 mL) was stirred at room temperature overnight. The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane (5 mL) and the organic layer was washed with 2 M HCl (10 mL × 3). The combined aqueous layers were extracted with dichloromethane (15 mL × 3). The organic layers were dried over MgSO₄, filtered and concentrated in vacuo. The crude material was purified over a column of silica (dichloromethane:methanol, 9 : 1) to afford a colourless solid as the title compound (556.0 mg, 93 %). ¹H NMR (600 MHz, CDCl₃) δ 7.58 (d, J = 8.1 Hz, 2H, ArH), 7.30 (d, J = 8.1 Hz, 2H, ArH), 3.33 (m, 8H, (CH₂)₂); ¹³C NMR (151 MHz, CDCl₃) δ 161.8 (C–O), 154.2 (p, J = 17.7 Hz, Ar-CSF), 138.7 (ArC), 127.4 (2ArC), 126.3 (m, 2ArC), 66.5 (2 C, (CH₂)₂), 47.9 (CH₂), 42.4 (CH₂); ¹⁹F NMR (400 MHz, CDCl₃) δ 83.40 (p, J = 150.3 F), 62.39 (d, J = 150.3 Hz F); LCMS Purity (UV) = 95 %, tᵣ 18.3 min; HRMS-ESI (m/z) found: 439.0394, calc. for [C₅H₇F₃NO₅[S][Na]+]: 439.0401. IR (neat) νmax/cm⁻¹: 3374 (CH₃), 1626 (s, C=O), 818 (S=O); mp 72 ± 13 °C.

tert-Butyl 4-(pentafluoro-2-sulfanyl) benzoyl piperazin-1-ylcarbonyl (4d)

To N-Boc piperazine (385.5 mg, 2.07 mmol), dissolved in dichloromethane (3 mL) was added triethylamine (247.0 mg, 2.44 mmol), followed by dropwise addition of 4-(pentafluorosulfanyl) benzoyl chloride (500.0 mg, 1.88 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane (5 mL) and the precipitate formed was discarded after gravity filtration. MP-Trisamine scavenger resin (520.0 mg, 3 mmol) was added to the filtrate and after 3 hours, the scavenger was removed by gravity filtration. The crude material was purified over a column of silica (dichloromethane:methanol, 9 : 1) to obtain 4d as a white solid (352.0 mg, 76 %). ¹H NMR (600 MHz, CDCl₃) δ 7.67 (m, 2H, ArH), 7.37 (m, 2H, ArH), 3.78–3.49 (m, 4H, (CH₂)₂), 1.36 (s, 9H, (CH₂)₃); ¹³C NMR (151 MHz, CDCl₃) δ 161.4 (C–O), 154.6–153.9 (m, 2 C, C=O, Ar-CSF), 138.8 (ArC), 127.4 (2ArC), 126.5 (2ArC), 80.5 (C), 47.4 (2 C, 42.1 (2 C, 28.3 (3 C); ¹⁹F NMR (400 MHz, CDCl₃) δ 83.32 (p, J = 150.2 Hz F), 62.47 (d, J = 150.2 Hz F); LCMS Purity (UV) = 92 %, tᵣ 19.5 min; HRMS-ESI (m/z) found: 417.0394, calc. for [C₅H₇F₃NO₅[S][Na]+]: 417.0401. IR (neat) νmax/cm⁻¹: 3374 (CH₃), 1626 (s, C=O), 818 (S=O); mp 72 ± 13 °C.

(4-Pentafluoro-2-sulfanylphenyl)(4-methylpiperazin-1-yl)ethanone (4e)

Compound 4d was dissolved in dichloromethane (2 mL) and treated with HCl in dioxiane (4 M, 6.0 equiv.) overnight to remove the Boc group. The reaction was monitored by TLC. Following the completion of the reaction, it was concentrated in vacuo to obtain the HCl salt (4-(pentafluoro-2-sulfanyl)benzoyl)piperazinyl hydrochloride, 4d', as a colourless solid. Compound 4d’ was used without purification in the following step.
To 4d’ (80.0 mg, 0.2 mmol), dissolved in THF (1.0 mL), was added triethylamine (0.096 g, 0.37 mmol). The reaction mixture was stirred for 30 minutes, followed by which, acetic anhydride (20 mg, 0.2 mmol) was added to the mixture and this was stirred at room temperature overnight. The crude was dissolved in dichloromethane (5 mL) and passed through a hydrophobic frit, to collect the organic layer. Afterwards, the crude material was purified over a column of silica (dichloromethanemethanol; 7:3) to obtain the pure product as a colourless solid (59 mg, 82%). §H NMR (600 MHz, CDCl3) δ 7.81 (d, J = 8.4 Hz, 2ArH), 7.49 (d, J = 8.4 Hz, 2ArH), 3.89–3.64 (m, 4H, piperazine), 3.56 (s, 3H, CH3), 3.47–3.30 (m, 4H, piperazine); 13C NMR (151 MHz, CDCl3) δ 169.2 (Ar–C=O), 168.5 (C–O), 154.6 (m, Ar–C=O), 138.4 (Ar), 127.5 (2ArC), 47.3 (bs, C), 46.1 (bs, C), 42.1 (bs, C), 41.3 (bs, C), 21.4 (CH3) 19F NMR (400 MHz, CDCl3) δ 83.32 (p, J = 150.4 Hz, 1F), 62.96 (d, J = 150.4 Hz, 4F); HPLC Purity (UV) = 95%, tR 13.4 min; HRMS-ESI (m/z) found 381.0667, calc. for [C19H19F3N2O][Na]+ : 381.0667; IR (neat) νmax/cm–1 = 2917 (C–H), 1633 (C–O), 1625 (C–O), 820 (S–F); mp 158–160°C.

(4-Pentafluoro-1-sulfanyl phenyl)-(4-(methylsulfonyl)piperazin-1-yl)methane (4f)

To crude 4d’ (82.0 mg, 0.23 mmol) dissolved in THF (3.0 mL) was added triethylamine (23.0 mg, 0.23 mmol) and the mixture was stirred for 30 minutes. Methanesulfonyl chloride (32.0 mg, 0.28 mmol) was added to the reaction mixture, which was stirred overnight at room temperature. The reaction mixture was quenched with dichloromethane (5 mL) and water (5 mL) then passed through a hydrophobic frit. The crude was purified over a column of silica (dichloromethane:methanol; 7:3) to get the pure product as a colourless solid (43 mg, 48%). §H NMR (600 MHz, CDCl3) δ 7.83 (d, J = 8.2 Hz, ArH, 2H), 7.50 (d, J = 8.2 Hz, ArH, 2H), 3.90 (m, CH3, 2H), 3.52 (m, CH2, 3H), 3.34 (m, CH2, 3H), 3.18 (m, CH2, 2H), 2.81 (s, CH3, 3H); 13C NMR (151 MHz, CDCl3) δ 168.4 (C–O), 154.8 (m, C–SF3), 138.1 (Ar), 127.5 (Ar, C–C), 126.7 (Ar, C–C), 47.2 (CH3), 46.0 (CH3), 45.5 (CH3), 41.8 (CH3), 35.1 (CH3); 19F NMR (400 MHz, CDCl3) δ 82.99 (p, J = 150.3 Hz, 1F), 62.51 (d, J = 150.3 Hz, 4F); HRMS-ESI (m/z) found 417.0342, calc. for [C19H19F3N2O][Na]+ : 417.0349; Anal. calc. (%) for C19H19F3N2O2C5: 36.55; H: 3.68; N: 7.10; found (%): C: 36.65; H: 3.69; N: 6.98. IR (neat) νmax/cm–1 = 2117 (C–H), 1637 (C–O), 1322 (S–O), 821 (S–F); mp 163–164°C.

(3Z)-3-{[(3,5-Dimethyl-1H-pyrrol-2-yl)methylidene]-5-(pentafluorosulfonyl)-1,3-dihydro-indol-2-one (9a)

In a 10 mL microwave vial equipped with a stirrer bar was added 5-(pentafluorosulfonyl)-1,3-dihydro-indol-2-one (0.100 g, 0.4 mmol), 3,5-dimethyl-1H-pyrrole-2-carbaldehyde (0.062 g, 0.5 mmol), ethanol (2.5 mL) and 3 drops of piperidine. The vessel was then sealed using a rubber microwave septum and placed into the microwave cavity. The reaction mixture was irradiated with 200 W of power. It was maintained at 150°C by modulation of power for 30 min. The vessel was then cooled to room temperature. The reaction mixture was extracted with ethyl acetate (3×20 mL), washed with water (20 mL), dried over MgSO4 filtered under gravity and concentrated in vacuo. The obtained orange solid was used without further purification (0.100 g, 90%). Crystallization by mixed solvents, dichloromethane and hexane, provided orange crystals of 9b.

§H NMR (600 MHz, CD2OD) δ N–H not observed, 7.87 (1H, s, ArH), 6.75 (1H, d, J = 8.5 Hz, ArH), 6.94 (1H, d, J = 8.5 Hz, ArH), 2.59 (3H, s, CH3), 2.39 (3H, s, CH3); 13C NMR (600 MHz, CD2OD) δ 169.6 (C–O), 159.0 (C–C), 147.6 (Ar–C=O), 142.5 (ArC–SF3), 126.3 (ArC–SF3), 121.8 (ArC–SF3), 108.2 (C–C), 24.0 (CH3); 19F NMR (400 MHz, CD2OD) δ 6.29 (4F, d, J = 147.8 Hz, equatorial), 85.3 (F, p, J = 147.8, axial); LCMS Purity (UV) = 99%, tR 18.5 min; HRMS-ESI (m/z) found 322.0285, calc. for [C19H19F3N2O][Na]+ : 322.0295;IR (neat) νmax/cm–1 = 3062 (N–H), 2925 (C–C), 1694 (C–C), 1618 (C–C), 813 (S–F); mp 191–194°C.

5-(Pentafluoro-1-sulfanyl)-3-(propan-2-ylidene)-2,3-dihydro-1H-indol-2-one (8b)

In a 10 mL microwave vial equipped with a stirrer bar was added 5-(pentafluorosulfonyl)-1,3-dihydro-indol-2-one (0.096 g, 0.37 mmol) in acetone (2 mL) followed by 3 drops of piperidine. The vessel was then sealed using a rubber microwave septum and placed into the microwave cavity. The reaction mixture was irradiated with 200 W of power. It was maintained at 100°C by modulation of power for 20 min. The vessel was then cooled to room temperature. The reaction mixture was extracted with ethyl acetate (3×20 mL), washed with water (20 mL), dried over MgSO4 filtered under gravity and concentrated in vacuo. The obtained orange solid was used without further purification (0.100 g, 90%). Crystallization by mixed solvents, dichloromethane and hexane, provided orange crystals of 8b.

§H NMR (600 MHz, CD2OD) δ N–H not observed, 7.87 (1H, s, ArH), 6.75 (1H, d, J = 8.5 Hz, ArH), 6.94 (1H, d, J = 8.5 Hz, ArH), 2.59 (3H, s, CH3), 2.39 (3H, s, CH3); 13C NMR (600 MHz, CD2OD) δ 169.6 (C–O), 159.0 (C–C), 147.6 (Ar–C=O), 142.5 (ArC–SF3), 126.3 (ArC–SF3), 121.8 (ArC–SF3), 108.2 (C–C), 240.0 (CH3); 19F NMR (400 MHz, CD2OD) δ 6.29 (4F, d, J = 147.8 Hz, equatorial), 85.3 (F, p, J = 147.8, axial); LCMS Purity (UV) = 99%, tR 18.5 min; HRMS-ESI (m/z) found 322.0285, calc. for [C19H19F3N2O][Na]+ : 322.0295; IR (neat) νmax/cm–1 = 3062 (N–H), 2925 (C–C), 1694 (C–C), 1618 (C–C), 813 (S–F); mp 191–194°C.

Microwave reaction procedure

In a 10 mL microwave vial equipped with a stirrer bar was added 5-nitro-2-oxindole (0.50 g, 2.85 mmol), acetone (0.25 mL, 3.42 mmol),
acetonitrile (5 mL) and 3 drops of piperidine. The vessel was then sealed using a rubber microwave septum and placed into the microwave cavity. The reaction mixture was irradiated with 200 W of power and heated to 100 °C in a CEM Explorer. It was maintained at 100 °C by moderation of power for 20 min. The vessel was then cooled to ambient temperature and the reaction mixture was concentrated in vacuo. The crude material was recrystallized in acetonitrile to obtain a brown solid as pure product (0.411 g, 66%).

**Solventless reaction procedure**

5-Nitro-2-oxindole (242.0 mg, 1.36 mmol), acetonitrile (200.0 mL, 2.71 mmol) and piperidine (40.2 mL, 0.41 mmol) were mechanically activated in a Retsch MM400 vibratory ball-mill for 90 minutes at 30 Hz in 25 mL zirconia jar with one, 1.2 cm dia. ball. The product was suspended in acetonitrile (10 mL) and filtered, and the crude mixture was then added to LiHMDS (1 M) in dry dimethyl formamide (10 mL), extracted with ethyl acetate (10 mL × 3), washed with brine (3×10 mL), 1-Methyl-5-(pentafluoroacetonitrile (5 mL) and 3 drops of piperidine. The vessel was then dissolved in tetrahydrofuran (10 mL) was added to LiHMDS (1 M) in 2022 Hz in 25 mL zirconia jar with one, 1.2 cm dia. ball. The product was then triturated with argon. Dry dimethyl formamide (20 mL), extracted with ethyl acetate (10 mL × 3), washed with brine (3×10 mL), and concentrated in vacuo.

The crude material was purified over a column of silica (hexane:ethyl acetate;4:1) to give a brown solid as pure product (0.411 g, 66%).

**Methyl 3-[2-(3-trifluoromethyl)phenyl]acetamido pyridine-4-carboxylate (13 a)**

To methyl 3-aminopyridine-4-carboxylate (100.0 mg, 0.66 mmol) in dichloromethane (5 mL) was added triethylamine (14.0 mg, 0.12 mmol) followed by di-2-(trifluoromethyl)phenyl acetyl chloride (220.0 mg, 0.99 mmol). The reaction mixture was stirred at room temperature for 4 h and monitored by TLC. After 4 h, it was diluted with dichloromethane (10 mL) washed with 2 M HCl (10 mL × 3) and the aqueous layer was extracted with dichloromethane (25 mL). The combined organic layers were washed with sodium bicarbonate (25 mL, brine (15 mL × 3), dried over MgSO4, filtered and concentrated in vacuo. The crude material was purified over a column of silica (dichloromethane:methanol; 19:1) to give 13 a, as a colourless solid (144 mg, 65%), which was used as such for the next step. 4H NMR (600 MHz, CDCl3) δ 10.96 (1H, s, NH), 8.21 (1H, s, ArH), 8.11 (1H, dd, J = 8.6, 1.9 Hz, 1H), 7.68 (2H, m, ArH), 4.22 (2H, m, OCH2), 3.88 (2H, m, OCH2). The crude material was purified by flash chromatography on silica gel (19:1). The target compound (0.66 g, 66%) was obtained as a white solid, which was recrystallized from dichloromethane:methanol (1:2) to yield a colourless solid (0.37 g, 39%).

**Methyl 3-[2-(3-chlorophenyl)acetamido]pyridine-4-carboxylate (13 c)**

N-N-Diisopropylethylamine (1.28 g, 9.92 mmol) was added to a stirred solution of 2-(3-chlorophenyl)acetic acid (0.56 g, 3.29 mmol) and hexafluorophosphate azabenzotrizole tetramethyl uronium hexafluorophosphate (0.99 g, 2.97 mmol). The reaction mixture was stirred at room temperature overnight. Once the reaction was complete, water (20 mL) was added to the mixture and the product extracted with ethyl acetate (3×10 mL). The crude material was purified over a column of silica (dichloromethane:methanol; 19:1) to give 13 c, as a colourless solid (144 mg, 65%), which was used as such for the next step. 4H NMR (600 MHz, CDCl3) δ 10.96 (1H, s, NH), 8.21 (1H, s, ArH), 8.11 (1H, dd, J = 8.6, 1.9 Hz, 1H), 7.68 (2H, m, ArH), 4.22 (2H, m, OCH2), 3.88 (2H, m, OCH2) as a yellow solid (68 mg, 66%).

**2-[3-(Trifluoromethyl)phenyl]phenyl-3H,4H-pyrido[3,4-d]pyrimidin-4-one (14 a)**

Product 13 a (144 mg, from above) was refluxed with 7 M ammonia in methanol (10 mL) for 48 hours. After cooling, the crude product was diluted with dichloromethane (15 mL) and washed with 2 M HCl (10 mL × 2). The combined organic layers were dried over MgSO4, filtered and concentrated in vacuo. The crude mixture was purified over a column of silica (dichloromethane:methanol; 97:3) to obtain the title compound as a colourless solid (30 mg, 23%). Crystallization of 14 a was achieved by dissolving it in minimum amount of dichloromethane. 1H NMR (600 MHz, CDCl3) δ 12.79 (s, 1H, NH), 8.94 (s, 1H, ArH), 8.59 (d, J = 5.1 Hz, 1H, ArH), 7.89 (d, J = 5.1 Hz, 1H, ArH), 7.77 (s, 1H, ArH), 7.67 (d, J = 7.8 Hz, 1H, ArH), 7.62 (dd, J = 13.4, 9.5, 4.3 Hz, 2H), 1.82 (dt, J = 13.4, 2.0 Hz, 2H). 13C NMR (151 MHz, CDCl3) δ 179.5 (C–O), 148.8 (Ar, p, Jd,c = 17.7, 1.7 Hz), 145.1 (Ar), 134.0 (Ar), 126.7 (Ar–H, p, Jd,c = 4.7 Hz), 120.9 (Ar–H, p, Jd,c = 4.7 Hz), 107.3 (Ar–H), 62.6 (2 C, (CH3)2), 44.4 (C), 32.7 (2 C, (CH3)2), 26.3 (C). 19F NMR (400 MHz, CDCl3) δ 86.61–84.84 (p, J = 150.1 Hz), 64.2 (d, J = 150.1 Hz). HRMS-ESI (m/z) found 344.0743, calc. for [C14H10F4NO,S]H+: 344.0744; IR ( neat) v/cm–1 2947 (C–H, st), 1727 (C=O), 1258 (N–C, methyl), 828 (C–F); LCMS Purity (UV) = 95%, tR = 18.7 min; mp: 158–158 °C.
To 2-[3-(pentfluoro-λ²-sulfanyl)phenyl]acetic acid (120.0 mg, 0.46 mmol) was added triethylamine (50.0 mg, 0.54 mmol) followed by dropwise addition of 2-[3-(pentfluoro-λ²-sulfanyl)phenyl]acetyl chloride (made as above) 115.0 mg, 0.40 mmol). The reaction mixture was stirred at room temperature for 48 h and monitored by TLC. After 48 h, it was diluted with dichloromethane (10 mL), washed with 2 M HCl (10 mL × 3) and aqueous layer extracted with dichloromethane (25 mL). The combined organic layers were washed with sodium bicarbonate (25 mL), brine (15 mL × 3), and dried over MgSO₄ and concentrated in vacuo. The crude material was purified using a column of silica (dichloromethane:methanol; 19 : 1) to obtain crude 2-[3-(pentfluoro-λ²-sulfanyl)phenyl]acetyl chloride. The crude was taken through to the following steps without purification (115 mg).

To methyl 3-aminopyridine-4-carboxylate (530 mg, 70 %). The reaction mixture was stirred at room temperature for 48 h and monitored by TLC. After 48 h, it was diluted with dichloromethane (25 mL), brine (15 mL × 3), and dried over MgSO₄ and concentrated in vacuo. The white precipitate formed was filtered under vacuum and washed with water and toluene, then dried to give the product (330 mg, 70 %). ¹H NMR (600 MHz, CDCl₃) δ 7.95–7.90 (m, 2H, ArH), 7.60 (d, J = 8.0 Hz, 1H, ArH), 7.11–7.07 (m, 1H, ArH), 6.06 (d, J = 7.7 Hz, 1H, ArH), 4.19 (s, 2H, CH₂); ¹³C NMR (151 MHz, CDCl₃) δ 168.2 (C=O), 139.3 (ArC), 135.3 (ArC), 126.6 (ArC), 124.1 (ArC), 78.7 (C=O). Purity 99 %, mp 167–170 °C.

2-(3-[Pentfluoro-λ²-sulfanyl]phenyl)methyl-3H,4H-pyrrolo[3,4-d]-pyrimidin-4-one (14b)

Compounds 15 (304 mg, 0.93 mmol) was suspended in a mixture of IPA (2 mL) and water (2 mL). To the stirred mixture was added dropwise an aqueous solution of NaOH (39 % in water) until the solution reached a pH of ca. 12, at which point, all of the starting material dissolved. The solution was then filtered and concentrated. Concentrated HCl was added to the filtrate until pH 3. The resultant precipitate was filtered, washed with water and dried under vacuum to obtain the product as a colourless powder (283 mg, 93 %). ¹H NMR (600 MHz, CDCl₃) δ 7.79–7.74 (m, 2H, ArH), 7.62 (d, J = 8.8 Hz, 2H, ArH), 2.38 (s, 3H, CH₃); H and O–H not found; ¹³C NMR (151 MHz, CDCl₃) δ 189.2 (C=O), 167.5 (CN), 150.2 (C-F), 138.6 (ArC), 127.3 (2 C, ArC, m), 120.2 (2 C, ArC), 116.1 (C), 80.6 (C), 22.1 (CH₃); ¹⁹F NMR (400 MHz, CDCl₃) δ 84.82 (p, J = 150.4 Hz), 63.43 (d, J = 150.4 Hz). HPLC Purity (UV) = 99 %, t₁ 17.91 min; HRMS-EI (m/z) found 327.0427, calc. for [C₅H₄F₆N₄O₅S][H]⁺: 327.0427; IR (neat) νmax/cm⁻¹: 3366 (N–H), 1663 (C=O), 824 (S–F); mp = 167–170 °C.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: SF · group · DMARDs · COVID-19 · SARS-COV-2 main protease (Mpro)
A range of molecules containing a pentafluorosulfanyl group have been made and tested versus known drug-like entities. The SF₅ functional group is of increasing interest as a bioisostere in medicinal chemistry. This library was tested against targets including human dihydroorotate dehydrogenase (HDHODH). A subsequent focused approach led to analogues of Teriflunomide and Leflunomide, considered for potential COVID-19 treatment, where SF₅ bioisostere deployment led to improved inhibition of HDHODH over the parent drugs.