Expanding the repertoire of low-molecular-weight pentafluorosulfanyl-substituted scaffolds

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

The Covid Moonshot Consortium[m]

The pentfluorosulfanyl (-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 (DHODH). 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 pentfluorosulfanyl group is gaining popularity as a bioisostere in bioactive compounds,[6,7] and in materials[8] as it is considered to be relatively stable, electronenative 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 pentfluorosulfanyl-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

[a] Dr. A. Jose, Dr. D. Guest, Dr. B. W. Greenland, Prof. M. C. Bagley, Chemistry Department, School of Life Sciences, Falmer, Brighton, BN1 9QJ (UK)
[b] Dr. R. LeGay
Normandie Université, Laboratoire de Chimie Moléculaire et Thioorganique LCMT UMR 6507 ENSICAEN, UNICAEN, CNRS, 6 Bd. Du Marechal Juin, 14050, Caen (France)
[c] Dr. G. J. Tizzard, Prof. S. J. Coles
National Crystallography Service, School of Chemistry University of Southampton, Southampton, SO17 1BJ (UK)
[d] Dr. M. Derveni, Dr. E. Wright
Biochemistry, School of Life Sciences, Falmer, Brighton, BN1 9QG (UK)
[e] Dr. L. Morrison
eMolecules, 3430, Carmel Mountain Road, Suite 250, San Diego, CA 92121 (USA)
[f] A. A. Lee, A. Morris, M. Robinson
PostEra Inc., 2 Embarcadero Centre, San Francisco, CA 94111 (USA)
[g] Prof. F. von Delft, D. Fearon, A. Aimon
Diamond Light Source (DLS), Harwell Science and Innovation Campus, Didcot OX11 0DE (UK)
[h] Prof. F. von Delft, Dr. L. Koekemoer
Centre of Medicines Discovery (CMD), University of Oxford, Department of Biochemistry, Oxford OX1 3QX (UK)
[i] Prof. F. von Delft
Department of Biochemistry, University of Johannesburg, Auckland Park 2006 (South Africa)
[j] Dr. T. Matviuk
Enamine, Chervonatskaya St, 67, Kyiv, 02094 (Ukraine)
[k] Prof. C. J. Schofield, T. R. Malla
Chemistry Research Laboratory, The Department of Chemistry and the Ineos Oxford Institute for Antimicrobial Research, 12 Mansfield Road, OX1 3TA, Oxford (UK)
[l] Prof. N. London
Department of Chemical and Structural Biology, Weizmann Institute of Science, Rehovot, 76100 (Israel)
[m] The Covid Moonshot Consortium
Members list: https://tinyurl.com/3yr7redd
[+] Current address: Sussex Drug Discovery Centre, School of Life Sciences, Falmer, Brighton, BN1 9QG (UK)

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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 azabenziotiazole tetrachloromethane), 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.[11]

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[12] 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[14] which has been applied to Knoevenagel condensations.[15,16] We attempted the synthesis of 10a in a vibratory ball mill (VBM) in steel jars (SS7) and zirconium oxide jars (ZrO₂); with and without catalyst, and for various reaction times. Zirconia jars were best
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,

\[\text{Compounds 8a and 9a did not manifest sufficient inhibition to generate IC}_{50}\text{ 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 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 MPro (or CLPro), a vital enzyme in SARS-CoV-2 replication and transcription. MPro releases the functional polypeptides from the polyproteins by extensive proteolytic processing while digesting the polyproteins at 11 cleavage sites, starting with autolytic cleavage and exclusively cleaves polypeptides after a glutamine residue. Its functional importance and the absence of closely related homologues in humans, renders MPro an attractive target for antiviral drug design as an example of a direct acting antiviral agent. 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\textsubscript{2}H as opposed to fused aryl or methyl groups. (Figure 3 and Scheme 4).

**Table 1.** Biochemical kinase assays of semaxanib and its SF\textsubscript{5} counterparts.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>IC\textsubscript{50} [\mu M] \textsuperscript{[a]}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>semaxanib</td>
<td>1.5</td>
</tr>
<tr>
<td>2</td>
<td>8a</td>
<td>12.4</td>
</tr>
<tr>
<td>3</td>
<td>9a</td>
<td>12.4</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} n = 1; 10-dose IC\textsubscript{50} mode with twofold serial dilutions, starting at 10 \:\mu M. \textsuperscript{[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 CF₃, SF₅, 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. 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 Pro, but none had any appreciable enzyme activity (IC₅₀ > 99 μM).

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. Teriflunomide inhibits human DHODH in the low μM 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). 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 CF₃-substituted aromatic group.

We first prepared the SF₅ derivative of Leflunomide 15, which, when treated with sodium hydroxide, provided its Teriflunomide equivalent 16 in good yields (Scheme 5). The latter was further characterised in the solid state by crystallography, proving its molecular structure and regiochemistry.

Docking of SF₅-Teriflunomide 16 in DHODH 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 CF₃ and SF₅ groups, and that SF₅-Teriflunomide is slightly larger than its parent analogue.

[Following our docking studies, we tested SF₅-Teriflunomide and SF₅-Leflunomide against human HDHODH using Teriflunomide equivalent 16 in good yields (Scheme 5). The latter was further characterised in the solid state by crystallography, proving its molecular structure and regiochemistry.]

**Scheme 4.** Synthesis of a small-molecule library with CF₃/SF₅ groups.

**Scheme 5.** Synthesis of potential SF₅-containing DMARDs.
mide 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 (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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Structure</th>
<th>IC_{50} [nM]</th>
<th>pIC_{50}</th>
</tr>
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<td>6.4</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Image" /></td>
<td>982</td>
<td>6.0</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Image" /></td>
<td>27^{[a]}</td>
<td>7.6</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4.png" alt="Image" /></td>
<td>50^{[a]}</td>
<td>7.3</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5.png" alt="Image" /></td>
<td>1.8^{[b]}</td>
<td>8.7</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6.png" alt="Image" /></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[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 μM < 10%. [d] In vitro control (n = 1).

**Figure 6.** a) SF_{5}-substituted Teriflunomide in complex with HDHODH, docked using Schrödinger Maestro. b) Teriflunomide and SF_{5}-Teriflunomide located in the HDHODH binding pocket. Purple: Teriflunomide, salmon pink: SF_{5}-Teriflunomide Ligand interaction diagram, comparing c) SF_{5}-Teriflunomide and d) Teriflunomide; showing that the bulkier SF_{5} is able to fill the binding pocket better than a CF_{3} group. e) BAY-2402234, a Bayer clinical trial candidate that inhibits HDHODH with an IC_{50} value of 1.2 nM.

**Figure 7.** a) Electrostatic potential of Teriflunomide; b) Electrostatic potential of SF_{5}-Teriflunomide.
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 SF₂ analogues such as 16 to have a covalent warhead capable of potentially acting as a Michael acceptor with the Sγ atom of Cys145 of Mpro, as precedent with other Mpro inhibitors; other modes of covalent reaction are also possible including with the nitrile, as with an Mpro inhibitor in clinical trials[11] 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).[22] 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.

Figure 8. Compound 17 docked in SARS-CoV-2 Mpro.

Figure 9. HDHODH in complex with Teriflunomide (purple) and 17 (orange).

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

SF₂-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 SF₂-Teriflunomide (15) towards HDHODH compared with Teriflunomide. Molecular binding studies revealed that the bulky SF₂ group fills the binding pocket better than the CF₂ group. A singleton hit 17 with structural similarities to Teriflunomide was identified as inhibiting SARS-CoV-2 Mpro 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 SF₂ analogue of Teriflunomide, 16, might be a useful DHODH probe molecule for future investigation.

Experimental Section

4-[(Pentafluorosulfanyl)anilin]-4 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 Gemini® 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 Fisions VG Autospec instrument was used at 70 eV. All analyses were run by Dr. Alla K. Abdul Sada. Analyses are for the
aqueous layers were extracted with dichloromethane (15 mL × 3),
dried over MgSO₄, filtered and concentrated in vacuo. The crude
was purified by column of silica (dichloromethane:methanol (15 mL × 3),
and the mixture was stirred for a few minutes. HATU (787.2 mg,
addition of 3-pentafluorosulfanyl)benzoyl chloride (500.0 mg,
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 3d as a colourless solid (573.0 mg, 73 %).

H NMR (600 MHz, CDCl₃) δ 7.72 (m, 2H, ArH), 7.47 (m, 2H, ArH), 3.46 (m, 4H,
2CH₂), 1.63 (m, 4H, 2CH₂)), 1.47 (m, 2H, CH₂). ¹³C NMR (151 MHz,
CDCl₃) δ 167.9 (C=O), 153.7 (C-SCF₃), 7.52 (C=O), 73.7 (ArC), 129.8 (ArC), 128.9 (ArC), 126.5 (ArC-SCF₃), 124.6 (ArC-SCF₃), 48.6 (N-CH₂), 43.2 (N-CH₂), 26.3 (2CH₂), 25.4 (CH₂); ¹⁹F NMR (400 MHz,
CDCl₃) δ 8.60 (p, J = 150.0 Hz, 62.44 (d, J = 150.0 Hz); LCMS Purity (UV) = 96 %, tᵣ = 21.0 min; HRMS-ESI (m/z) found 439.1085, calc. for [C₁₅H₁₀F₇NO₅][Na⁺]: 439.1085; IR (neutral) νₘᵤₐₛ/cm⁻¹: 2977, 1685, 1626, 1243, 828; mp 153–155 °C.

1-[4-[3-(Pentafluoro-λ⁵-sulfanyl)benzoyl]piperazin-1-yl]ethane (3e)
Compound 3d (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, 3d (4-[3-(pentafluoro-λ⁵-sulfanyl)benzoyl)piperazinyl hydrochloride) as a colourless solid.
To crude 3d (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 3e 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), 3.88–3.82 (m, 8H, ArH), 2.11 (s, 3H, CH₃); ¹³C NMR (151 MHz, CDCl₃) δ 169.3 (C=O, MeCO), 168.4 (C=O), 154.0 (t, Jₑ₉ = 18.0 Hz, ArC), 136.0 (ArC), 130.2 (ArC), 129.3 (ArC), 127.7–127.4 (m, ArC), 125.0 (ArC), 47.4 (bs, CH₂), 45.9 (bs, CH₂), 42.4 (bs, CH₃), 41.4 (bs, CH₃), 21.3 (CH₃); ¹⁹F 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 [C₁₅H₁₀F₇NO₅][Na⁺]: 381.0667; IR (neutral) νₘᵤₐₛ/cm⁻¹: 2917 (C–H), 1633 (C=O), 1322 (S–O), 821 (S–F).
To crude 3d (75 mg, 0.21 mmol), dissolved in THF (3 mL) was added triethylamine (21 mg, 0.21 mmol) and stirred for 30 min. Methylsulfonyl chloride (24 mg, 0.21 mmol) was added to the reaction mixture and stirred overnight at room temperature. The reaction was followed by TLC. After completion of the reaction, it was separated over dichloromethane (5 mL) and water (5 mL). The biphasic layers were washed through a hydrophobic frit to obtain the organic phase which was concentrated in vacuo. The crude was then purified through a column of silica (dichloromethane:methanol, 7:3) to obtain 3f as a colourless solid (66 mg, 80%). 1H NMR (600 MHz, CDCl₃) δ 7.74 (s, 2H, ArH), 7.43 (d, J = 8.4 Hz, 2H, ArH), 7.43 (d, J = 8.4 Hz, 2H, ArH), 3.66 (m, 2H, CH₂), 3.24 (m, 2H, CH₂), 1.63 (m, 4H, (CH₂)₂), 1.47 (m, 2H, CH₃). 13C NMR (151 MHz, CDCl₃) δ 168.0 (C=O), 154.2–153.8 (m, C-SF₅), 153.7 (ArC), 130.2 (ArC), 129.4 (ArC), 127.8–127.6 (m, ArC), 125.2–125.0 (m, ArC), 47.4 (CH₂), 45.5 (2 C, (CH₂)₂), 42.0 (CH₂), 35.0 (CH₂). 19F NMR (400 MHz, CDCl₃) δ 83.32 (p, J = 150.4 Hz, 1F), 62.96 (d, J = 150.4 Hz, 4F); LCMS Purity (UV) = 98%, tᵣ 15.6 min; HRMS-ESI (m/z) found 417.0349, calc. for [C₆H₆F₅N₂OS][Na]+: 417.0342; IR (neat) ν/cm⁻¹: 3007 (C-H), 1616 (C=O), 1342 (O=C), 127.6 (m, ArC), 130.1 (ArC), 129.1 (ArC), 127.1 (m, ArC-CSF₅).

Tert-Butyl 4-(4-pentafluoro-sulfanyl)phenyl)(morpholino)methanone (4c)

To N-Boc piperezine (358.5 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 organic layer was washed with 2 M HCl (10 mL×3). The aqueous layer was extracted with dichloromethane (15 mL×3), 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, 76%). 1H NMR (600 MHz, CDCl₃) δ 7.57–7.54 (m, 2H, ArH), 4.03–3.47 (m, 4H, (CH₂)₂), 2.81 (s, 3H, CH₃). 19F NMR (400 MHz, CDCl₃) δ 42.2 (C); 13C NMR (151 MHz, CDCl₃) δ 150.4 (p, J = 150.3 Hz, 4F); LCMS Purity (UV) = 95%, tᵣ 18.3 min; HRMS-ESI (m/z) found 364.0394, calc. for [C₆H₆F₅N₂S][Na]+: 340.0401. IR (neat) ν/cm⁻¹: 3734 (CH), 1626 (s, C=O), 818 (SF₂), mp 72–73°C. Compounds 4d was used without purification in the following step.
To 4d' (80.0 mg, 0.23 mmol) was added triethylamine (20.0 mg, 0.2 mmol). The reaction mixture was stirred for 30 min. Methanesulfon 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 passed through a hydrophobic frit, to collect the organic layer. Afterwards, the crude material was purified over a column of silica (dichloromethane:methanol; 7:3) to obtain the pure product as a colourless solid (43 mg, 48%).

**To crude 4d' (82.0 mg, 0.23 mmol)** was added triethylamine (23.0 mg, 0.23 mmol) and the mixture was stirred for 30 min. Methanesulfon chloride (32 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 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%).

**HRM** (600 MHz, CDCl$_3$) $\delta$ 7.83 (d, $J = 8.2$ Hz, ArH), 7.50 (d, $J = 8.2$ Hz, ArH, 2H), 3.90 (m, CH$_2$, 2H), 3.52 (m, CH$_2$, 2H), 3.34 (m, CH$_2$, 2H), 3.18 (m, CH$_2$, 2H), 2.81 (s, CH$_3$, 3H); **$^{13}$C NMR** (151 MHz, CDCl$_3$) $\delta$ 154.8 (m, C-5F), 138.1 (ArC), 127.5 (ArC, 2C), 126.7 (ArC, 2C), 47.2 (CH), 46.0 (CH), 45.5 (CH), 41.8 (CH), 35.1 (CH); **$^{19}$F NMR** (400 MHz, CDCl$_3$) $\delta$ -82.9 (p, $J = 218.7$ Hz, 1F), 62.51 (d, $J = 10.7$ Hz, 1F), 110.0 (ArC), 106.8. (ArC), 54.1 (C-19); **HRMS - ESIMS** (m/z) found 347.0342, calc. for [C$_{10}H$_{15}F$_5$NOS]$:^{+}$ 347.0349; Analyt. calc. [%] for C$_{10}$H$_{15}$F$_5$NOS: C, 36.65; H, 3.69; N, 9.68. IR (neat) $\nu$(cm$^{-1}$) = 2187 (C-H), 1637 (C-O), 1322 (S=O), 821 (S-F); mp 163–164 °C.

**5-(Pentafluoro-1,4-sulfanyl)-1-(propan-2-ylidene)-1,2-dihydro-1H-indol-2-one (9a)**

In a 10 mL microwave vial equipped with a stirrer bar was added 5-(pentafluorosulfanyl)-1,3-dihydro-indol-2-one (0.096 g, 0.37 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 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 MgSO$_4$, filtered under gravity and concentrated in vacuo. The obtained orange solid was used without further purification (0.10 g, 90%).

**($^\text{32}$Z)-3-(3,5-Dimethyl-1H-pyrrrole-2-yl)methylene)-5-(pentafluoro-1,4-sulfanyl)-2,3-dihydro-1H-indol-2-one (8a)**

In a 10 mL microwave vial equipped with a stirrer bar was added 5-(pentafluorosulfanyl)-1,3-dihydro-indol-2-one (0.096 g, 0.37 mmol), 3,5-dimethyl-1H-pyrrrole-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 and solvent removed in vacuo. The aqueous layer was extracted using ethyl acetate (3 × 20 mL), washed with brine (3 × 20 mL), dried over MgSO$_4$, filtered under gravity and concentrated in vacuo. The crude was purified over a column of C18 silica (100% acetonitrile) (70 mg, 50%) to obtain an orange solid. **HRM** (600 MHz, CD$_3$CO) $\delta$ 13.52 (1H, s, NH), 10.02 (1H, s, NH), 7.82 (1H, d, $J = 8.5$ Hz, ArH), 7.79 (1H, s, ArH), 7.48 (1H, d, $J = 8.5$ Hz, ArH), 7.41 (1H, s, ArH), 6.08 (1H, s, C=H), 2.36 (3H, s, CH$_3$), 2.38 (3H, s, CH$_3$), 2.35 (3H, s, CH$_3$); **$^{13}$C NMR** (151 MHz, CD$_3$CO) $\delta$ 169.6 (C=O), 138.7 (ArC=), 137.3 (ArC=), 135.0 (ArC), 130.2 (ArC), 127.7 (ArC), 126.0 (ArC=), 118.6 (ArC), 117.0 (ArC), 113.6 (ArC=CSF), 110.0 (ArC), 106.8. (ArC), 54.1 (C-19), 12.9 (CH$_3$), 10.7 (CH$_3$); **$^{19}$F NMR** (400 MHz, CD$_3$CO) $\delta$ 86.32 (1F, m, 67.34 (4F, d, $J = 148.1$ Hz); LCMS Purity (UV) = 99%, $t_R$ = 18.5 min; HRMS-ESI (m/z) found 365.0742, calc. for [C$_{10}H$_{15}F$_5$NOS]$:^{+}$ 365.0737, HRMS-ESI (m/z) found 365.0737, calc. for [C$_{10}H$_{15}F$_5$NOS]$:^{+}$ 365.0737.

**5-Nitro-3-(propan-2-ylidene)-2,3-dihydro-1H-indol-2-one (10a)**

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 pipеридин. 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) was added to a round bottom flask purged with argon. Dry dimethyl formamide (15 mL) was then added to the flask followed by compound 11a (0.1 g, 0.30 mmol) and stirred for 1 hour. To this mixture was added sodium hydride (11 mg, 0.45 mmol) was added to a round bottom flask purged with argon. Dry dimethyl formamide (15 mL) was then added to the flask followed by compound 11a (0.1 g, 0.30 mmol) and stirred for 1 hour. To this mixture was added sodium hydride (11 mg, 0.45 mmol) and stirred for 1 hour. To this mixture was added sodium hydride (11 mg, 0.45 mmol) and stirred for 1 hour.
Chemical Metallurgy

(2Z)-2-Cyano-3-hydroxy-N-[4-(pentfluoro-2-sulfanyl)phenyl]phenylbut-2-enaime (16)

Compound 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%).

\[ \text{H NMR (600 MHz, CDCl}_3 \] 7.79–7.74 (m, 2H, ArH), 7.62 (d, \( J = 8.8 \text{ Hz} \), 2H, ArH), 2.38 (s, 3H, CH3); N–H and O–H not found; 13C NMR (151 MHz, CDCl3) \ deltapi = 189.2 (C–O), 167.5 (CN), 150.2 (C–F), 138.6 (ArC), 127.3 (2C, ArC), 120.2 (2C, ArC), 116.1 (C), 80.6 (C), 22.1 (CH3); 19F NMR (400 MHz, CDCl3) \ deltapi = 84.2 (p, \( J = 150.4 \text{ Hz} \), 6.34 (d, \( J = 150.4 \text{ Hz} \), HPLC Purity (UV) = 99%, tR = 17.91 min; HRMS-ESI (m/z) found 327.0427, calcd. for [C15H16F4N2O5]H+: 327.0227; IR (neat) \( \nu_{\text{max}}/\text{cm}^{-1} \) = 3312 (N–H), 2219 (CN), 1641 (C–O), 1589 (C–C), 825 (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 SF$_5$ 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 SF$_5$ bioisostere deployment led to improved inhibition of HDHODH over the parent drugs.