Polysubstituted and ring-fused pyridazine systems from tetrafluoropyridazine

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Abstract

Tetrafluoropyridazine 1 reacts with a range of oxygen-, nitrogen-, sulfur- and carbon-centred nucleophiles to give, in general, products 2 arising from substitution of fluorine para to ring nitrogen. Subsequent reaction of the trifluoropyridazine derivatives 2 gave a range of 4,5-di- and tri-substituted products 3 and 6. Related reactions of tetrafluoropyridazine 1 with difunctional nucleophiles gave [6,6]-, [5,6]- and [6,5,6]-polycyclic ring fused pyridazine scaffolds 4 and 9. Further functionalisation of scaffolds 4 by nucleophilic aromatic substitution processes involving displacement of fluorine atoms at activated sites ortho to ring nitrogen provide an indication of the synthetic possibilities offered using tetrafluoropyridazine as a starting material for the preparation of polysubstituted pyridazine and novel polyfunctional ring fused pyridazine systems with potential applications in the drug discovery arena.

Keywords: heterocyclic scaffold, perfluoroheterocycle, multi-functional pyridazine, nucleophilic aromatic substitution.

1. Introduction
New efficient synthetic approaches to polyfunctional pyridazine derivatives and rare heterocyclic systems derived from tetrafluoropyridazine are described in this paper.

While the first identification of a pyridazine ring within a natural product structure was reported relatively recently, pyridazine heterocyclic sub-units have been incorporated into a number of successful pharmaceutical products such as Sulfamethoxypyridazine and Nifurprazine (antibacterial agents) and Minaprine (antidepressant) (Fig. 1). Consequently, new methodology that allows the rapid synthesis of libraries of novel pyridazine derivatives bearing multiple functionality for incorporation in drug discovery campaigns continues to be an important target for medicinal chemists.

**Figure 1** Pharmaceuticals containing pyridazine sub-units

In general, pyridazine systems can be constructed by either a variety of ring-forming processes or reactions of an appropriately functionalised pyridazine substrate. For example, construction of pyridazine rings can be achieved by formation of the inter-heteroatom bond involving the intramolecular oxidative coupling of two amino groups, reactions of 1,4-dicarbonyl compounds with hydrazine and Diels-Alder type [4+2] cycloaddition (Carboni-Lindsey reaction) between 1,2,4,5-tetrazine with either an alkene or alkyne substrate. Various approaches to the preparation of polysubstituted pyridazines from appropriate pyridazine substrates have been reported, including deprotonation of the parent heterocycle and subsequent trapping with an electrophile, such as reactions with LiTMP or heteroaryl Grignard derivatives, palladium-catalyzed coupling of appropriate halogenated pyridazine derivatives such as Negishi or Suzuki cross coupling processes, or reaction of appropriate halogenated pyridazines by S_NAr processes. Of course, all these approaches have their advantages and disadvantages and the choice of synthetic strategy depends on the nature of
the target pyridazine system, availability of appropriate substrates, regioselectivity of functionalisation, functional group tolerance, cost, scalability and/or applicability to parallel synthesis techniques.

Additionally, a lack of structural diversity in pharmaceutical company compound collections is often suggested to hamper the development of new drug lead candidates and, consequently, new heterocyclic scaffolds with novel, patentable molecular architectures are of growing importance for further exploration of chemical space in the search for new biologically active drug-like species. Consequently, the synthesis of structurally novel polycyclic ring-fused pyridazine systems, for example, would provide access to new areas of chemical space suitable for the assessment of novel biological activities. New synthetic approaches to ring-fused pyridazine systems require efficient access to polyheterocyclic cores which also bear suitable functional groups that would allow further transformation to libraries of novel ring-fused heterocyclic derivatives.

Tetrafluoropyridazine 1 could be a highly versatile scaffold for the synthesis of a range of both polysubstituted pyridazine systems and polyfunctional bi- and tri-cyclic fused ring systems because, in principle, all four fluorine atoms could be replaced by reaction with a nucleophilic species through sequential nucleophilic aromatic substitution processes. (Scheme 1) In this context, we demonstrated that pentafluoropyridine can, for example, be transformed to a range of polysubstituted pyridine derivatives by sequential reaction with a variety of mono- and bi-dentate nucleophilic species which has allowed the synthesis of various polysubstituted bi- and tri-cyclic ring fused systems such as pyridopyrazine\textsuperscript{4a-c} and imidopyrazine\textsuperscript{4d} derivatives bearing functionality for further structural elaboration. Tetrafluoropyridazine 1 was first prepared some time ago\textsuperscript{5} but the chemistry of this system has largely been limited to reactions in which methoxide and several amines have been reported to provide products arising from substitution of fluorine at the 4-position\textsuperscript{5,6} whereas polysubstitution processes, generally involving perfluoroalkylcarbanion nucleophiles,\textsuperscript{7} have rarely been reported. Consequently, we chose to study reactions of tetrafluoropyridazine 1 with a range of mono- and di-functional nucleophiles which could, potentially, lead to many novel multiply-substituted pyridazine and ring-fused pyridazine systems that bear wide ranging functionality following a general synthetic strategy outlined in Scheme 1.
Scheme 1. General strategy for the synthesis of highly substituted and ring fused pyridazine derivatives from tetrafluoropyridazine 1.

In this paper, we describe the synthesis of a range of polysubstituted, bi- and tri-cyclic ring fused pyridazine systems from tetrafluoropyridazine 1 which allows access to some multiply-substituted pyridazine derivatives and various very rare heterocyclic molecular frameworks by sequential S₅Ar methodology suitable for parallel synthesis techniques.
2. **Results and discussion**

A series of reactions of tetrafluoropyridazine 1 with model monodentate oxygen-, nitrogen-, carbon- and sulfur-centred nucleophiles were carried out to extend the range of systems available for further functionalisation and are collated in Table 1. In general, reactions of nucleophiles with tetrafluoropyridazine 1 occurred at 0 °C or room temperature in the presence of the strong, non-nucleophilic organic base di-isopropylethyl amine (DIPEA) and using THF as the reaction medium.
Table 1. Reactions of tetrafluoropyridazine with monofunctional nucleophiles.

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Conditions</th>
<th>Product, Yield %</th>
<th>Nucleophile</th>
<th>Conditions</th>
<th>Product, Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>OEt</td>
<td>DIPEA 0°C, 19 h</td>
<td>2a, 81</td>
<td>HO</td>
<td>DIPEA reflux, 11 h</td>
<td>2g, 73</td>
</tr>
<tr>
<td>NH</td>
<td>DIPEA 0°C, 19 h</td>
<td>2b, 82</td>
<td>OH</td>
<td>DIPEA reflux, 11 h</td>
<td>2h, 72</td>
</tr>
<tr>
<td>CHCl</td>
<td>DIPEA 0°C, 4 h</td>
<td>2c, 82</td>
<td>CHCl</td>
<td>DIPEA rt, 20 h</td>
<td>2i, 63</td>
</tr>
<tr>
<td>Br</td>
<td>DIPEA rt, 16 h</td>
<td>2d, 65</td>
<td>OH</td>
<td>DIPEA rt, 6 d</td>
<td>2j, 60</td>
</tr>
<tr>
<td>NH</td>
<td>DIPEA rt, 3 d</td>
<td>2e, 50</td>
<td>SH</td>
<td>DIPEA 0°C, 1 h</td>
<td>2k, 65</td>
</tr>
<tr>
<td>NH</td>
<td>DIPEA 0°C, 2 h</td>
<td>2f, 78</td>
<td>OH</td>
<td>DIPEA 0°C, 1 h</td>
<td>2l, 77</td>
</tr>
</tbody>
</table>

2 equiv.
In all cases, products 2a-k, obtained in high yields, were those derived from substitution of fluorine located at the 4-position as we would expect from observations reported previously.\textsuperscript{5,6} This site is the most activated position towards nucleophilic attack as it is \textit{para} to the activating ring nitrogen and has two \textit{ortho} and one \textit{meta} activating fluorine atoms, following principles for processes involving highly reactive heterocycles.\textsuperscript{5,8} The structures of the products 2a-k followed from \textsuperscript{19}F NMR analysis in which three resonances at \textit{ca.} –80, –90 and –135 ppm were observed, where resonances occurring at \textit{ca.} –90 ppm are indicative of fluorine located at sites \textit{ortho} to ring nitrogen as is the case here.\textsuperscript{9}

Whilst all nitrogen- and oxygen-centred nucleophiles gave high yields of mono-substituted products, in contrast, reaction of one equivalent of thiophenol and tetrafluoropyridazine 1 gave only the 4,5-disubstituted product 2l with no monosubstituted product observed by \textsuperscript{19}F NMR analysis of the reaction mixture. This reflects the strong \textit{ortho} activating effect of the sulfur atom which makes the monosubstituted product more reactive towards nucleophiles than 1 itself.\textsuperscript{10} Thus, a higher yield of 2l could be obtained upon reaction of 1 with two equivalents of thiophenol in similar reaction conditions. In contrast, ethanethiol gave only mono-substituted product 2k consistent with the decreasing electron withdrawing ability of the ethanethio substituent compared to the phenylthio case.

Reaction of 1 with phenylmagnesium bromide gave a mixture of two monosubstituted products 2m and 2n in a 5:1 ratio by \textsuperscript{19}F NMR analysis of the crude reaction mixture, arising from substitution of the 4- and 3-positions respectively, from which the major product 2m could be purified by repeated recrystallisation. In this reaction, some competing substitution occurs at the 3-position due to the increased reactivity of the nucleophile which allows substitution at the less activated site \textit{ortho} to ring nitrogen. In the case of reaction of 1 with methylmagnesium bromide, decomposition occurs, likely due to the highly basic reaction mixture that causes deprotonation of the pyridazyllic protons present in any product formed leading to complex reaction mixtures as observed in similar reactions of highly fluorinated pyridine derivatives.\textsuperscript{11}
Scheme 2. Reaction of 1 with phenyl magnesium bromide

Trifluoropyridazine derivatives 2 are, of course, still very electrophilic in nature and, in principle, products arising from substitution of the remaining ring fluorine atoms or the substituent itself are possible upon reaction with subsequent nucleophilic species. Consequently, our next series of reactions was aimed at exploring the behaviour of four selected representative trifluoropyridazine derivatives 2a,h,k,m with model nitrogen-, oxygen-, sulfur- and carbon-centred nucleophiles to determine how the 4-substituent affects further nucleophilic substitution processes (Table 2). All reactions were performed using similar conditions to those described above.
Table 2. Reactions of trifluoropyridazines 2a.h.k.m with nucleophiles

\[
\begin{array}{c|c|c} 
2 & \text{Conditions} & \text{Product, Yield \%} \ \\
\hline 
2m & \text{DIPEA, THF rt. 4 d} & 3a, 32\% \ \\
2h & \text{DIPEA, THF rt. 4 d} & 3b, 79\% \ \\
2k & \text{DIPEA, THF rt. 16 h} & 3c, 73\% \ \\
2m & \text{DIPEA, THF 0\degree C, 1 h} & 3d, 88\% \ \\
2h & \text{DIPEA, THF 0\degree C, 1 h} & 3e, 33\% \ \\
2a & \text{DIPEA, THF 0\degree C, 1 h} & 3f, 80\% \ \\
\end{array}
\]
Reactions of model nucleophiles with trifluoropyridazine derivatives 2a,h,k,m gave products 3a-h arising from substitution at the 5-position, para to ring nitrogen. 4,5-Disubstitution was confirmed by $^{19}$F NMR analysis which showed only resonances occurring at ca. -85 ppm for each compound 3a-h, consistent with the presence of fluorine ortho- to ring nitrogen. Reactions were noticeably slower for the trifluorinated pyridazines 2a,k,l,m than 1 as would be expected.

Having established that 1 reacts, in the majority of cases, regioselectively with two equivalents of nucleophile successively to give products 3a-h exclusively from sequential substitution of the 4- and 5-positions, we carried out a series of experiments to prepare ring-fused systems 4 arising from corresponding S$_{N}$Ar reactions of 1 with difunctional nucleophiles. Initial nucleophilic attack on 1 at the 4-position, followed by subsequent intramolecular cyclisation by substitution of fluorine attached to the most activated 5-position would be expected to occur. Consequently, reactions of tetrafluoropyridazine 1 with a small range of representative difunctional nitrogen nucleophiles were performed (Table 3). In all cases, the bi- or tri-cyclic ring fused systems 4a-g derived from reaction at the most activated 4- and 5-positions were synthesized and isolated in good yield. Symmetrical ring-fused products 4a,b,f were readily identified by the observation of only one resonance in the $^{19}$F NMR spectra and similar equivalencies in the $^1$H and $^{13}$C NMR spectra. Non-symmetric bicyclic and tricyclic products 4c,d,e,g displayed two distinct $^{19}$F NMR resonances at ca. -92.6 and -94.6 ppm which are, again, both characteristic of fluorine located ortho to ring nitrogen. Interestingly, these results show opposite regioselectivity to a cyclisation reaction previously performed between tetrafluoropyridazine and catechol, which cyclized between C4 and C3.$^{12}$
Table 3. Synthesis of polycyclic systems 4 from 1

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Conditions</th>
<th>Product, Yield %</th>
<th>Nucleophile</th>
<th>Conditions</th>
<th>Product, Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>NH₂</td>
<td>NaHCO₃, MeCN, rt, 4 h</td>
<td>4a, 92%</td>
<td>( \text{MeCN} )</td>
<td>MeCN</td>
<td>( 4d, 58% )</td>
</tr>
<tr>
<td>PhSO₂NH₂</td>
<td>1) NaHCO₃, MeCN, reflux, 3 d; 2) DIPEA, MeCN, MW, 180 °C, 15 min</td>
<td>4b, 46%</td>
<td>Br</td>
<td>MeCN</td>
<td>( 4e, 40% )</td>
</tr>
<tr>
<td>H₂NCS</td>
<td>NaHCO₃, MeCN, reflux, 16 h</td>
<td>4c, 82%</td>
<td>H₂NCS</td>
<td>MeCN</td>
<td>( 4f, 65% )</td>
</tr>
<tr>
<td>H₂NCS</td>
<td>NaHCO₃, MeCN, reflux, 16 h</td>
<td>4g, 62%</td>
<td></td>
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</table>

Reaction of 1 with benzamidine in acetonitrile at reflux temperature in the presence of four equivalents of sodium bicarbonate yielded the uncyclised amidine derivative 5. A range of bases were reacted with 5 in an attempt to effect the desired cyclisation but \( n\)-BuLi, LDA and LiHMDS gave complex product mixtures. However, cyclisation could be achieved using DIPEA and 4b was obtained in good yield after microwave irradiation at 180 °C for 15 minutes in an overall two step process. Annellation of 1 by
cyclic amino-imine and 2-aminopyridine derivatives led to the corresponding tricyclic systems 4c-e respectively in high yields.

Whilst imidazo[4,5-d]pyridazines\(^{13}\) and thiazolo[4,5-d]pyridazines\(^{14}\) are relatively common, formed by reaction of appropriate 4,5-diaminopyridazines with acid chloride derivatives\(^{13}\) and thiazole 4,5-dicarboxaldehyde with hydrazine respectively\(^{14}\), many other polycyclic systems incorporating a pyridazine ring subunit are very rarely reported in either the academic or patent literature and polyfunctional systems suitable as substrates for analogue synthesis have not been described. Only a very few examples of related pyridazino-tetrahydropyridazine,\(^{15}\) dithiino-pyridazine,\(^{16}\) pyridazino-thiazine and dioxino-pyridazine\(^{17}\) derivatives and tricyclic systems\(^{18}\) have been synthesised from reaction of appropriate chlorinated pyridazines and dinucleophiles or by reaction of appropriate dinitriles with hydrazine.

Sequential trisubstitution of 1 is also possible when a sufficiently activated difluoropyridazine 3f was further reacted with an appropriate nucleophile. Disubstituted system 3f, was reacted with morpholine upon microwave irradiation at 150 °C for 90 min (Scheme 3) and \(^{19}\)F NMR spectroscopy of the product mixture showed only a single product 6 which could be isolated in 71% yield by column chromatography and its structure was confirmed by X-ray crystallography (Figure 2). The thiophenoxy group is ortho- activating to some extent and the morpholino group is slightly deactivating, explaining the high regioselectivity of this process.

![Scheme 3. Synthesis of trisubstituted derivative 6](image-url)
Similarly, all the [5,6]- and [6,6]-ring fused scaffolds synthesised by the processes outlined in Table 3 possess fluorine atoms attached to the pyridine ring which, in principle, are also susceptible towards nucleophilic displacement. Consequently, we studied reactions of representative polycyclic products 4b-d with a small range of model nucleophiles to illustrate the potential of these novel scaffolds for the synthesis of polycyclic multi-functionalised derivatives (Scheme 4).
Scheme 4. Reactions of ring fused systems 4b-d with nucleophiles

Reaction of [6,6]-fused system 4a with nucleophiles was not successful even after prolonged heating with various reactive nucleophiles, reflecting the deactivating influence of the two amino substituents attached to the pyridazine ring. However, reaction of imidazopyridazine 4b with \( n \)-butylamine yielded the disubstituted system 7a, arising from replacement of both remaining ring fluorine atoms while reaction of tricyclic scaffold 4c with morpholine gave 7b regioselectively (Scheme 3) and the structure was confirmed by X-ray crystallography (Fig. 3).
Figure 3. Molecular structure of 7b

The regioselectivity of the reaction between 4c and morpholine can be explained by a consideration of the relative stabilities of the Meisenheimer intermediates formed by reaction at either the C-1 or C-4 sites. Attack at C-1 allows delocalisation of the negative charge formed over the pyridazine and imidazopyridazine ring system giving a more stable intermediate whilst attack at C-4 only allows delocalisation over the pyridazine ring (Scheme 5).
Scheme 5. Regioselectivity of nucleophilic substitution for reaction of 4c

Attack at C-1

Attack at C-4

Tricyclic system 4d reacted with nucleophiles under microwave irradiation in acetonitrile (Scheme 4) to give major products arising from substitution of fluorine at C-1. While small quantities of products arising from substitution of C-4 of the pyridazine ring were observed by $^{19}$F NMR analysis of the reaction mixture, major products 7c,d could be isolated by column chromatography or recrystallisation of the crude product mixture. X-ray crystallography confirmed the structure of the 1-diethylamino derivative 7e (Fig. 4) and NMR data obtained for 7a,b were comparable to those obtained for 7e. In this case, nucleophilic attack at C-1 leads to stabilisation of the Meisenheimer intermediate over the entire aromatic system whilst attack at C-4 only allows charge to be delocalised over the pyridazine ring and, consequently, reactions arising from displacement of fluorine at C-1 are preferred.
Figure 4. Molecular structure of 7e

An alternative method for the synthesis of functionalized pyridazine ring fused polycyclic derivatives is to carry out annelation reactions of monofunctionalised trifluoropyridazines 2 with appropriate difunctional nucleophiles (Table 4).
Table 4. Reaction of trifluoropyridazines 2a,k with difunctional nucleophiles

<table>
<thead>
<tr>
<th>2</th>
<th>Conditions</th>
<th>Product, Yield %</th>
<th>2</th>
<th>Conditions</th>
<th>Product, Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>DIPEA, THF, rt, 5d</td>
<td>Nuc1, 84%</td>
<td>2k</td>
<td>DIPEA, THF, 100 °C,</td>
<td>9e, 75%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>microwave, 5 min</td>
<td></td>
</tr>
<tr>
<td>2a</td>
<td>DIPEA, THF, rt, 16h</td>
<td>Nuc1, 68%</td>
<td>2k</td>
<td>DIPEA, THF, 100 °C,</td>
<td>9f, 63%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>microwave, 30 min</td>
<td></td>
</tr>
<tr>
<td>2k</td>
<td>DIPEA, THF, rt, 16h</td>
<td>Nuc1, 77%</td>
<td>2k</td>
<td>DIPEA, THF, 150 °C,</td>
<td>9g, 14%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>microwave, 30 min</td>
<td></td>
</tr>
<tr>
<td>2k</td>
<td>DIPEA, THF, rt, 16h</td>
<td>Nuc1, 74%</td>
<td>2k</td>
<td>DIPEA, THF, rt, 7d</td>
<td>9h, 50%</td>
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<td></td>
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</tr>
<tr>
<td>2k</td>
<td>DIPEA, THF, 180 °C,</td>
<td>Nuc1, 28%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>microwave, 90 min</td>
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</table>
Indeed, reaction of \( N,N' \)-dimethylethylene diamine with \( 2a \) gave the desired fused product \( 9a \) in good yield after stirring in THF at room temperature and, similarly, reaction with 2-mercaptophenol gave tricyclic product \( 9b \). 4-(Ethylthio)-3,5,6-trifluoropyridazine \( 2k \) was also used for the synthesis of ring fused systems and reaction with \( N,N' \)-dimethylethylene diamine rapidly gave fused bicyclic product \( 9c \) in good yield. 2-Mercaptophenol gave the fused bicyclic product \( 9d \) as the only product as observed by 19F NMR analysis of the crude reaction mixture and crystals that were suitable for analysis by X-ray crystallography allowed the confirmation of the structure (Fig. 5). It appears that the initial attack is performed by the sulfur atom giving initial substitution para to ring nitrogen, further activating the intermediate to nucleophilic attack by the oxygen atom at the adjacent site.

![Figure 5. Molecular structures of 9d, 9e and 9h.](image)

Reaction of \( 2k \) with 2-aminophenol using microwave irradiation at 100 °C for five minutes gave the tricyclic product \( 9e \), confirmed by X-ray crystallography (Fig. 5), which demonstrated that the product was formed via initial attack by nitrogen followed by cyclisation through oxygen. Similarly, 2-aminobenzethiol, 2-aminopyridine, 2-amino-3-picoline and ethyl acetoacetate gave the desired polycyclic products \( 9f-i \) respectively after reaction with 4-(ethylthio)-3,5,6-trifluoropyridazine \( 2k \) under microwave irradiation.

3. Conclusions

Tetrafluoropyridazine \( 1 \) may be used as a very effective scaffold for the synthesis of a range of 4,5-disubstituted pyridazine systems bearing oxygen, nitrogen, sulfur and carbon functionality. Further substitution of the difluorinated systems gave mixtures of trisubstituted pyridazine systems, processes
which were particularly regioselective in the presence of an ortho-activating sulfur substituent. Consequently, we have further extended our general strategy for using perfluorinated heteroaromatic scaffolds for analogue synthesis to pyridazine systems.

Novel bi- and tri-cyclic heterocyclic systems have been synthesised by reaction of tetrafluoropyridazine with bifunctional nitrogen centred nucleophiles providing access to tetrahydropyrazino-pyridazine, imidazopyridazine and tetraazafluorene scaffolds. The presence of fluorine atoms attached to sites activated towards nucleophilic attack allows functionalisation of these scaffolds and representative examples of nucleophilic aromatic substitution processes have been established. The developing use of highly fluorinated heteroaromatic derivatives as starting materials for heterocyclic synthesis has been further expanded to ring fused pyridazine systems.

The general strategy outlined in Scheme 1 has allowed the synthesis of a wide range of polyfunctionalised and ring-fused pyridazine derivatives from tetrafluoropyridazine and the synthetic methodology is summarised in Scheme 6, demonstrating the diverse molecular structures that can be accessed very readily after a few simple operations.

Scheme 6. Synthesis of pyridazine based systems from tetrafluoropyridazine
4. Experimental

General

Reactions were performed under an atmosphere of argon gas using dry solvents. Microwave reactions were performed on a Biotage Initiator 60 EXP. Reactions were monitored by $^{19}$F NMR or TLC on silica gel TLC plates. Column chromatography was carried out on silica gel (Merck no. 109385, particle size 0.040 – 0.063nm) or using a Biotage Horizon or Isco Companion flash chromatography system. Mass directed HPLC was performed on a Supelco LCABZ++ column using MicroMass MassLynx v4.0 software. Melting points were recorded using a Gallenkamp melting point apparatus at atmospheric pressure and are uncorrected. NMR spectra were recorded in deuteriochloroform, unless otherwise stated, using trichlorofluoromethane as an internal reference on a Varian Mercury 400 or Bruker Avance 400 operating at 400MHz ($^1$H NMR), 376MHz ($^{19}$F NMR) and 100MHz ($^{13}$C NMR), or a Varian Inova 500 operating at 500MHz ($^1$H NMR), 470MHz ($^{19}$F NMR) and 125MHz ($^{13}$C NMR), or a Varian VNMRS-700 operating at 700MHz ($^1$H NMR), 658MHz ($^{19}$F NMR) and 175MHz ($^{13}$C NMR). Chemical shifts are given in ppm and coupling constants are recorded in Hertz. Mass spectra were recorded on a Thermoquest Trace GC-MS spectrometer (in electron ionisation mode) or a Micromass LCT LC-MS spectrometer (in electrospray ES$^+$ mode). Exact mass measurements were performed on a Thermo-Finnigan LTQ-FT spectrometer. Gas chromatography was carried out on a Thermo TRACE GC. Analytical HPLC was performed on an Analytical Varian LC (5ml/min). Elemental analyses were obtained using an Exeter Analytical E-440 Elemental Analyser.

X-ray crystallography

The X-ray single crystal data have been collected on a Bruker SMART CCD 1K (compounds 7b and 9e), a Bruker SMART CCD 6000 (compounds 7e, 9d and 9h) and a Rigaku R-AXIS SPIDER IP (compound 6) diffractometers (graphite monochromators, $\lambda$MoK$\alpha$, $\lambda$ =0.71073Å) equipped with a Cryostream (Oxford Cryosystems) open-flow nitrogen cryostats at the temperatures 120(2) K. All structures were solved by direct method and refined by full-matrix least squares on F2 for all data using Olex2\textsuperscript{19} and SHELXTL\textsuperscript{20} software. All non-disordered non-hydrogen atoms were refined
anisotropically, hydrogen atoms were refined isotropically, the hydrogen atoms in the twinned structure were placed in the calculated positions and refined in riding mode. Crystallographic data for the structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC-1486844-1486849.

Reactions of Tetrafluoropyridazine 1 with nucleophiles

General procedure

A mixture of tetrafluoropyridazine 1, DIPEA, amine and THF (10 mL) was stirred for the required time under an atmosphere of nitrogen. The mixture was evaporated to dryness in vacuo, partitioned between ethyl acetate (20 mL) and water (20 mL), the phases were separated and the aqueous phase was extracted further by ethyl acetate (3 x 20 mL). The combined organic phases were dried (MgSO₄) and evaporated in vacuo. Purification by column chromatography or HPLC on silica gel using cyclohexane and ethyl acetate as eluent gave the pure product.

4-(3,5,6-Trifluoro-pyridazin-4-yl)morpholine 2a

Tetrafluoropyridazine 1 (781 mg, 5.14 mmol), DIPEA (1.35 mL, 7.73 mmol), morpholine (0.45 mL, 5.17 mmol) and THF (10 mL) after stirring at 0 °C for 2 h gave 4-(3,5,6-trifluoro-4-pyridazinyl)morpholine 2a (908 mg, 81%) as white crystals; mp 34.5 – 36.1 °C (Found: [MH]+, 220.06923; C₈H₈F₃N₃O requires: [MH]+, 220.06922; ν max(film)/cm⁻¹ 2970, 2902, 2860 and 1595; δH 3.54 (4 H, br s, CH₂N), 3.80 – 3.86 (4 H, m, CH₂O); δC 50.1 (t, 4J_CF 4.4, CH₂N), 66.7 (s, CH₂O), 129.3 (ddd, 2J_CF 24.8, 2J_CF 24.8, 3J_CF 3.2, C-4), 139.7 (ddd, 1J_CF 270.8, 2J_CF 28.8, 3J_CF 9.6, C-5), 156.8 (ddm, 1J_CF 240.5, 3J_CF 12.0, C-6), 158.0 (dd, 1J_CF 240.5, 2J_CF 3.2, C-3); δF -143.8 – -143.4 (1F, m, F-5) -98.6 (1 F, dd, 2J_FF 31.0, 4J_FF 24.1, F-3) -80.8 (1 F, dd, 3J_FF 28.7, 5J_FF 28.7, F-6); m/z (ES+)) 220 ([MH]+, 100%).

N,N-Diethyl-3,5,6-trifluoro-4-pyridazinamine 2b

Tetrafluoropyridazine 1 (774 mg, 5.09 mmol), DIPEA (1.33 mL, 7.64 mmol), diethylamine (0.53 mL, 5.09 mmol) and THF (10 mL) after stirring at 0 °C for 19 h gave N,N-diethyl-3,5,6-trifluoro-4-pyridazinamine 2b (852 mg, 82%) as a yellow oil; (Found: [MH]+, 206.08973; C₈H₁₄F₃N₂O requires: 206.08996; ν max(film)/cm⁻¹ 2983, 2940 and 1587; δH 1.28 (6 H, t, 3J_HH 7.1, CH₃), 3.47 (4 H, qt, 3J_HH
7.1, $J_{HF}$ 1.5, CH$_2$; $\delta_C$ 13.9 (s, CH$_3$), 46.8 (t, $^3J_{CF}$ 5.2, CH$_2$), 129.2 (dt, $^2J_{CF}$ 25.6, $^3J_{CF}$ 4.8, C-4), 137.9 (dd, $^1J_{CF}$ 266.8, $^2J_{CF}$ 28.8, $^3J_{CF}$ 11.2, C-5), 157.0 (dd, $^1J_{CF}$ 238.1, $^3J_{CF}$ 2.4, C-3), 171.7 (dd, $^1J_{CF}$ 238.9, $^2J_{CF}$ 4.0, C-6); $\delta_F$ -146.8 (1 F, dd, $^3J_{FF}$ 27.5, $^4J_{FF}$ 25.2, F-5), -100.7 (1 F, dd, $^4J_{FF}$ 28.7, $^5J_{FF}$ 24.1, F-3), -81.4 (1 F, dd, $^3J_{FF}$ 28.7, $^5J_{FF}$ 28.7 F-6); m/z (ES$^+$) 206 ([MH]$^+$, 100%).

**N- Allyl-3,5,6-trifluoro-N-methylpyridazin-4-amine 2c**

Tetrafluoropyridazine 1 (785 mg, 5.16 mmol), DIPEA (1.35 mL, 7.73 mmol), N-methylallylamine (0.50 mL, 5.16 mmol) and THF (10 mL) after stirring at 0 °C for 3.5 h gave *N*-allyl-3,5,6-trifluoro-N-methylpyridazin-4-amine 2c (861 mg, 82%) as a pale yellow oil; (Found: [M]$^+$, 204.07433. C$_8$H$_9$F$_3$N$_3$O requires: [M]$^+$, 204.07431); $\nu$(film)/cm$^{-1}$ 2908, 1644 and 1593; $\delta_H$ 3.14 (3 H, t, $^3J_{HF}$ 3.2, CH$_3$), 3.97 (2 H, d, $^3J_{HH}$ 5.9, CH$_2$), 5.29 (1 H, dd, $^3J_{HH}$ 16.9, $^2J_{HH}$ 1.2, HCH), 5.32 (1 H, dd, $^3J_{HH}$ 10.3, $^2J_{HH}$ 1.2, HCH), 5.82 - 5.94 (1 H, m, CH); $\delta_C$ 39.6 (t, $^1J_{CF}$ 5.6, CH$_3$), 57.3 (t, $^1J_{CF}$ 4.8, CH$_2$), 119.1 (s, =CH$_2$), 130.1 (dt, $^2J_{CF}$ 25.6, $^3J_{CF}$ 4.8, C-4), 132.2 (s, CH), 138.4 (dd, $^1J_{CF}$ 267.6, $^2J_{CF}$ 28.0, $^3J_{CF}$ 9.6, C-5), 157.0 (dd, $^1J_{CF}$ 239.7, $^3J_{CF}$ 12.8, C-3), 157.2 (dd, $^1J_{CF}$ 238.9, $^2J_{CF}$ 4.8, C-6); $\delta_F$ -145.6 (1 F, dd, $^3J_{FF}$ 27.5, $^4J_{FF}$ 27.5, F-5) -100.0 (1 F, dd, $^4J_{FF}$ 28.7, $^5J_{FF}$ 25.2, F-3) -80.9 (1 F, dd, $^2J_{FF}$ 28.7, $^3J_{FF}$ 28.7, F-6); m/z (ES$^+$) 204 ([MH]$^+$, 100%).

**N-[(4-bromophenyl)methyl]-3,5,6-trifluoro-N-methyl-4-pyridazinamine 2d**

Tetrafluoropyridazine 1 (786 mg, 5.17 mmol), DIPEA (1.3 mL, 7.46 mmol), 1-(4-bromophenyl)-N-methylethanamine (1.05 mL, 5.26 mmol) and THF (10 mL) after stirring at rt for 3 h gave N-[(4-bromophenyl)methyl]-3,5,6-trifluoro-N-methyl-4-pyridazinamine 2d (1.122 g, 65%) as white crystals, mp 77.1 – 78.5 °C (Found: C, 43.4; H, 2.70; N, 12.4. C$_{12}$H$_9$BrF$_3$N$_3$ requires: C, 43.4; H, 2.7; N, 12.6%); $\nu$(film)/cm$^{-1}$ 2940, 1601, 1573 and 1560; $\delta_H$ 3.09 (3 H, dd, $^3J_{HF}$ 3.8, $^2J_{HF}$ 2.7, CH$_3$) 4.53 (2 H, s, CH$_2$) 7.15 (2 H, d, $^3J_{HH}$ 8.5, H$_2$C-C-CH) 7.49 (2 H, d, $^3J_{HH}$ 8.5 Hz, Br-C-CH); $\delta_C$ 40.0 (t, $^1J_{CF}$ 5.2, CH$_3$), 57.6 (t, $^4J_{CF}$ 4.8, CH$_2$), 121.9 (br s, C-Br), 129.0 (s, H$_2$C-C-CH), 130.2 (ddd, $^2J_{CF}$ 24.8, $^3J_{CF}$ 4.8, $^3J_{CF}$ 3.2, C-4), 132.0 (s, Br-C-CH), 134.9 (br s, H$_2$C-C), 139.0 (ddd, $^1J_{CF}$ 270.8, $^2J_{CF}$ 29.6, $^3J_{CF}$ 10.4, C-5), 156.9 (ddd, $^1J_{CF}$ 240.5, $^3J_{CF}$ 11.9, C-6), 157.4 (ddd, $^1J_{CF}$ 239.7, $^2J_{CF}$ 3.9, C-3); $\delta_F$ -144.3 (1 F, t, $^3J_{FF}$ 26.4, F-5) -99.4 (1 F, dd, $^4J_{FF}$ 27.5, $^5J_{FF}$ 25.2, F-3) -80.6 (1 F, dd, $^3J_{FF}$ 29.8, $^5J_{FF}$ 29.8, F-6); m/z (ES$^+$) 334.1 ([MH]$^+$, 100%).

**Methyl N-methyl-N-(3,5,6-trifluoro-4-pyridazinyl)glycinate 2e**

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Tetrafluoropyridazine 1 (801 mg, 5.27 mmol), DIPEA (2.29 mL, 13.17 mmol), sarcosine methyl ester hydrochloride (735 mg, 5.27 mmol) and THF (10 mL), after stirring at reflux for 3 d gave methyl N-methyl-N-(3,5,6-trifluoro-4-pyridazinyl)glycinate 2e (616 mg, 50%) as a pale yellow oil; (Found: C, 40.5; H, 3.3; N, 17.7. C₈H₆F₃N₃O requires: C, 40.9; H, 3.4; N, 17.9%); νₓ max(film)/cm⁻¹ 2958, 1747 and 1597; δH 3.27 (3 H, dd, ⁵JHF 3.4, ⁵JHF 2.7, NCH₃), 3.81 (3 H, s, OCH₃), 4.14 (2 H, s, CH₂); δC 42.1 (t, ⁴JCF 5.6, NCH₃), 52.5 (s, OCH₃), 55.3 (dd, ⁴JCF 6.4, ⁴JCF 4.8, CH₂), 129.62 (ddd, ²JCF 25.6, ²JCF 4.8, ³JCF 3.2, C-4), 138.77 (ddd, ¹JCF 269.2, ²JCF 28.8, ³JCF 9.6, C-5), 156.9 (d, ¹JCF 240.0, C-3), 157.0 (dd, ¹JCF 238.9, ²JCF 3.9, C-6), 169.3 (s, C=O); δF -144.6 (1 F, t, ³JFF 26.4, F-5), -99.3 (1 F, dd, ⁴JFF 28.7, ⁵JFF 24.09, F-3), -81.0 (1 F, t, ³JFF 28.7, F-6); m/z (ES⁺) 236.1 ([MH⁺], 100%).

3,5,6-Trifluoro-N-phenylpyridazin-4-amine 2f

Tetrafluoropyridazine 1 (776 mg, 5.10 mmol), DIPEA (1.35 mL, 7.73 mmol) and aniline (0.46 mL, 5.10 mmol) in THF (10 mL), after stirring at 0 °C for 4 h and purification by column chromatography on silica gel using ethyl acetate:hexane as eluent, gave 3,5,6-trifluoro-N-phenylpyridazin-4-amine 2f (895 mg, 78%) as a white solid, mp 123.2 – 124.0 °C (Found: C, 53.6; H, 2.8; N, 18.7. C₁₆H₁₂F₃N₃ requires: C, 53.3; H, 2.7; N, 18.7%); δH 6.47 (1 H, br. s, NH), 7.15 – 7.40 (5 H, m, ArH); δC 122.7 (d, ⁵JCF 2.6, C-2'), 124.2 – 124.3 (m, C-4), 126.5 (s, C-4'), 129.4 (s, C-3'), 136.5 (ddd, ¹JCF 272.3, ²JCF 29.9, ³JCF 6.9, C-5), 137.1 (s, C-1'), 156.6 (dd, ¹JCF 238.2, ²JCF 3.3, C-6), 156.9 (d, ¹JCF 237.7, C-3); δF -141.5 (1 F, dd, ⁴JFF 25.4, ⁵JFF 24.5, F-5), -98.9 (1 F, dd, ⁵JFF 29.5, ³JFF 24.5, F-6), -89.0 (1 F, dd, ⁵JFF 29.5, ³JFF 25.4, F-3); m/z (ES⁺) 224.9 ([MH⁺], 100%).

3,4,6-Trifluoro-5-(2-propen-1-yl)oxy)pyridazine 2g

Tetrafluoropyridazine (780 mg, 5.13 mmol), DIPEA (1.3 mL, 7.46 mmol), allyl alcohol (0.36 mL, 5.26 mmol) and THF (10 mL) after stirring at reflux for 24 h gave 3,4,6-trifluoro-5-(2-propen-1-yl)oxy)pyridazine 2g (716 mg, 73%) as a colourless oil; (Found: [MH⁺], 191.04277. C₉H₇F₁₃N₂O requires: [MH⁺], 191.04267); νₓ max/cm⁻¹ 2898, 1648 and 1611; δH 5.03 (2 H, dd, ³JHH 5.0, ⁵JHF 0.9, O-CH₂), 5.44 (1 H, dd, ³JHH 10.5, ²JHH 1.0, CHH), 5.51 (1 H, dd, ³JHH 16.9, ²JHH 0.97, CHH), 5.96 - 6.09 (1H, m, CH); δC 74.6 (dd, ¹JCF 5.6, ³JCF 1.6, O-CH₂), 121.4 (s, CH₂), 130.5 (s, CH), 136.0 - 136.4 (m, C-5), 140.1 (dd, ¹JCF 277.2, ²JCF 28.8, ³JCF 7.9, C-4), 156.7 (dd, ¹JCF 242.0, ³JCF 11.2, ⁴JCF 1.6, C-6), 158.7 (d, ¹JCF 242.9, C-3); δF -146.6 (1 F, dd, ³JFF 25.2, ⁵JFF 25.2, F-4), -95.8 (1 F, dd, ⁴JFF 29.8, ⁵JFF 26.4, F-6), -87.6 (1 F, dd, ³JFF 27.5, ⁵JFF 27.5, F-3); m/z (ES⁺) 191.0 ([MH⁺], 100%).
3,4,6-Trifluoro-5-[(1-methylethyl)oxy]pyridazine 2h

Tetrafluoropyridazine 1 (780 mg, 5.13 mmol), DIPEA (1.3 mL, 7.46 mmol), isopropanol (0.41 mL, 5.26 mmol) and THF (10 mL) after stirring at reflux for 24 h gave 3,4,6-trifluoro-5-[(1-methylethyl)oxy]pyridazine 2h (713 mg, 72%) as a colourless oil; (Found: [MH]+, 193.05830. C_{7}H_{6}F_{3}N_{2}O requires: [MH]+, 193.05832); ν_{max}/cm⁻¹ 2990, 2941 and 1608; δ_{H} 1.47 (6 H, dd, 3_{CF} 4.0, CH), 136.0 - 136.2 (m, C-5), 140.0 (ddd, 1_{CF} 275.8, 2_{CF} 28.6, 3_{CF} 7.8, C-4), 156.7 (ddd, 1_{CF} 239.7, 2_{CF} 11.2, 4_{CF} 243.6, 3_{CF} 2.4, C-6), 159.1 (ddd, 1_{CF} 246.1, 2_{CF} 8.8, 4_{CF} 2.4, C-3); δ_{F} -147.0 (1 F, dd, 3_{FF} 25.2, 4_{FF} 25.2, F-4) -96.1 (1 F, dd, 4_{FF} 28.7, 5_{FF} 26.4, F-6) -87.9 (1 F, dd, 3_{FF} 28.7, 5_{FF} 28.7, F-3); m/z (ES⁺) 193.2 ([MH]+, 100%).

4-(Cyclohexyloxy)-3,5,6-trifluoropyridazine 2i

Tetrafluoropyridazine 1 (777 mg, 5.11 mmol), DIPEA (1.3 mL, 7.46 mmol), cyclohexanol (0.55 mL, 5.29 mmol) and THF (10 mL) after stirring at rt for 6 d gave 4-(cyclohexyloxy)-3,5,6-trifluoropyridazine 2i (752 mg, 63%) as a colourless oil; (Found: C, 51.7; H, 4.5; N, 11.8. C_{10}H_{11}F_{3}N_{2}O requires: C, 51.7; H, 4.8, N, 12.1%); ν_{max}(film)/cm⁻¹ 2940, 2863 and 1607; δ_{H} 1.02 - 2.37 (10 H, m, CH₂), 4.80 (1 H, br s, CH); δ_{C} 23.0 (s, C-3'), 24.9 (s, C-4'), 32.0 (s, C-2'), 83.3 (d, 4_{CF} 3.4, C-1'), 135.8 - 136.0 (m, C-4), 140.2 (ddd, 1_{CF} 275.6, 2_{CF} 28.6, 4_{CF} 7.9, C-5), 156.7 (ddd, 1_{CF} 242.0, 3_{CF} 11.1, 4_{CF} 1.6, C-6), 159.3 (dd, 1_{CF} 244.4, 2_{CF} 2.4, C-6); δ_{F} -146.3 (1 F, dd, 3_{FF} 26.4, 4_{FF} 26.4, F-5), -95.8 (1 F, dd, 4_{FF} 29.8, 5_{FF} 26.4, F-3), -87.5 (1 F, dd, 3_{FF} 28.7, 5_{FF} 28.7, F-6); m/z (ES⁺) 233.2 ([MH]+, 100%).

3,4,6-Trifluoro-5-[(4-methylphenyl)oxy]pyridazine 2j

Tetrafluoropyridazine 1 (768 mg, 5.05 mmol), DIPEA (1.3 mL, 7.46 mmol), p-cresol (0.53 mL, 5.07 mmol) and THF (10 mL) after stirring at rt for 26 h gave 3,4,6-trifluoro-5-[(4-methylphenyl)oxy]pyridazine 2j (740 mg, 60%) as a colourless oil (Found: C, 54.9; H, 2.9; N, 11.4. C_{11}H_{12}F_{3}N_{2}O requires: C, 55.0; H, 2.9; N, 11.7%); ν_{max}(film)/cm⁻¹ 2928, 1614, 1606 and 1571; δ_{H} 2.38 (3 H, s, CH₃), 6.97 (2 H, d, 3_{HH} 8.7, O-C-CH), 7.21 (2 H, dd, 3_{HH} 8.7, 4_{HH} 0.7, H₃C-C-CH); δ_{C} 20.7 (s, CH₃), 116.9 (s, O-C-CH), 130.5 (s, H₃C-C-CH), 134.5 - 134.7 (m, C-5), 135.7 (s, H₃C-C), 141.8 (ddd, 1_{CF} 282.8, 2_{CF} 27.9, 3_{CF} 7.1, C-4), 153.0 (s, O-C), 156.7 (ddd, 1_{CF} 243.6, 2_{CF} 9.9, 4_{CF} 2.3, C-3), 159.2 (d, 1_{CF} 246.8, C-6); δ_{F} -140.4 (1 F, dd, 3_{FF} 24.1, 4_{FF} 24.1, F-4), -94.0 (1 F, dd, 4_{FF} 31.0, 5_{FF} 24.1, F-6), -85.5 (1 F, dd, 3_{FF} 29.8, 5_{FF} 24.1, F-3); m/z (ES⁺) 241.2 ([MH]+, 100%).
4-(Ethythio)-3,5,6-trifluoropyridazine 2k

Tetrafluoropyridazine 1 (780 mg, 5.13 mmol), DIPEA (1.35 mL, 7.73 mmol), ethanethiol (0.30 mL, 4.1 mmol) and THF (10 mL) after stirring at 0 °C for 1 h gave 4-(ethylthio)-3,5,6-trifluoropyridazine 2k (514 mg, 65%) as a colourless oil; δH 3.27 (2 H, qt, 3JHH 7.4, 5JHF 1.1, CH2), 1.40 (3 H, t, 3JHH 7.4, CH3); δF -74.6 (1F, dd, 3JFF 30.2, 4JFF 21.0, F-5), -99.4 (1 F, dd, 3JFF 30.2, 5JFF 26.4, F-6), -124.8 (1 F, dd, 5JFF 26.4, 4JFF 21.0, F-3); m/z (AP+) 195.0210 (C6H6N2F3S requires 195.0204).

3,6-Difluoro-4,5-bis(phenylthio)pyridazine 2l

Tetrafluoropyridazine 1 (780 mg, 5.13 mmol), DIPEA (2.6 mL, 14.8 mmol), thiophenol (1 mL, 9.7 mmol) and THF (10 mL) after stirring at rt overnight gave 3,6-difluoro-4,5-bis(phenylthio)pyridazine 2l (1314 mg, 77%) as yellow crystals; mp 99.1 – 100.3 °C (Found: C, 57.7; H, 3.0; N, 8.3. C16H10F2N2S2 requires: C, 57.8; H, 3.0; N, 8.4%); νmax/cm⁻¹ 1578, 1500 and 1377; δH 7.34 - 7.47 (10 H, m, CH); δC 129.3 (s, C-4'), 129.6 (s, C-3'), 130.2 (s, C-1'), 132.2 (s, C-2'), 133.6 (dd, 2JCF 17.5, 3JCF 15.9, C-4), 162.6 (dd, 1JCF 249.2, 4JCF 6.3, C-3); δF -75.8 (br s); m/z (ES⁺) 333.2 (MH⁺, 100%).

3,4,6-Trifluoro-5-phenylpyridazine 2m

Tetrafluoropyridazine (780 mg, 5.13 mmol), phenylmagnesium bromide (1M solution in THF, 5.13 mL, 5.13 mmol) and THF (10 mL) under nitrogen at -78 °C and warmed to rt for 16 h and recrystallisation from cyclohexane gave 3,4,6-trifluoro-5-phenylpyridazine 2m (501 mg, 47%) as white crystals; m.p. 82.7 – 83.4 °C (Found: C, 57.1; H, 2.4; N, 13.2. C10H5F3N2 requires: C, 57.1; H, 2.4; N, 13.3%); νmax/cm⁻¹ 1580, 1558, 1458 and 1445; δH 7.56 - 7.62 (5 H, m, CH); δC 121.2 (ddd, 2JCF 31.9, 2JCF 8.7, 3JCF 4.0, C-5), 123.6 (br s, C-4'), 129.0 (s, C-2'), 129.7 (br s, C-3'), 131.1 (s, C-1'), 147.8 (ddd, 1JCF 281.2, 2JCF 27.1, 3JCF 7.9, C-4), 156.5 (ddd, 1JCF 243.6, 3JCF 12.7, 4JCF 24.3, C-6), 162.30 (d, 1JCF 245.2, C-3); δF -129.3 (1 F, dd, 3JFF 26.4, 4JFF 21.8, F-4), -97.6 (1 F, dd, 5JFF 31.0, 3JFF 26.4, F-3), -79.6 (1 F, dd, 5JFF 31.0, 4JFF 21.8, F-6); m/z (ES⁺) 211.2 (MH⁺, 100%).

Reactions of Trifluoropyridazine derivatives

General procedure
A mixture consisting of DIPEA, nucleophile, trifluorophenylpyridazine and THF was heated and stirred as appropriate. The mixture was concentrated in vacuo, partitioned between EtOAc (20 mL) and water (20 mL) and the aqueous phase was further extracted with EtOAc (2 x 20 mL). The combined organic phases were concentrated in vacuo and dried (MgSO₄). Column chromatography on silica gel gave the difunctional difluoropyridazine product.

4-(3,6-Difluoro-5-phenyl-4-pyridazinyl)morpholine 3a
DIPEA (0.18 mL, 1.03 mmol), morpholine (0.06 mL, 0.68 mmol), 3,4,6-trifluoro-5-phenylpyridazine 2m (143 mg, 0.680 mmol) and THF (10 mL) after stirring at rt for 4 d and column chromatography on silica gel using a 5-25% THF in cyclohexane gradient as eluent gave 4-(3,6-difluoro-5-phenyl-4-pyridazinyl)morpholine 3a (61 mg, 32 %) as white crystals; mp 180.6 – 182.0 °C (Found: C, 60.5; H, 4.7; N, 15.0. C₁₀H₅F₃N₂ requires: C, 60.6; H, 4.7; N, 15.1%); δH (4 H, td, 3JHH 4.7, 5JHF 1.6, NCH₂), 3.61 (4 H, dd, 3JHH 4.8, 5JHH 4.6, OCH₂), 7.31 - 7.38 (2 H, m, CH), 7.42 - 7.57 (3 H, m, CH); δC 50.5 (d, 4JCF 4.8, NCH₂), 66.5 (s, OCH₂), 120.2 (dd, 2JCF 31.2, 3JCF 6.4, C-5), 128.9 (s, C-2'), 129.4 (s, C-3'), 129.5 (br s, C-4'), 129.6 (t, 3JCF 2.4, C-1'), 139.2 (dd, 2JCF 22.4, 3JCF 6.4, C-4), 159.3 (d, 1JCF 240.5, C-3), 163.3 (d, 1JCF 239.7, C-6); δF -86.9 (1 F, d, 5JFF 31.6, F-3), -84.0 (1 F, d, 5JFF 31.6, F-6); m/z (ES⁺) 278.2 ([MH]⁺, 100%).

4-{3,6-Difluoro-5-[(1-methylethyl)oxy]-4-pyridazinyl}morpholine 3b
Method A: DIPEA (0.20 mL, 1.15 mmol), morpholine (0.07 mL, 0.80 mmol), 3,4,6-trifluoro-5-[(1-methylethyl)oxy]pyridazine 2l (153 mg, 0.80 mmol) and THF (10 mL) after stirring at rt for 4 d and column chromatography on silica gel using a 5-25% THF in cyclohexane gradient as eluent gave 4-{3,6-difluoro-5-[(1-methylethyl)oxy]-4-pyridazinyl}morpholine 3b (163 mg, 79 %) as white crystals; mp 73.9 – 75.4 °C (Found: [MH]⁺, 260.12041. C₁₁H₁₅F₂N₂O₂ requires: [MH]⁺, 260.12051); δH (6 H, d, 3JHH 6.2, CH₃), 3.39 (4 H, dd, 3JHH 4.4, 5JHF 3.3, NCH₂), 3.76 (4 H, t, 3JHH 4.4, OCH₂), 4.63 - 4.76 (1 H, m, 3JHH 6.2, 5JHF 1.4, CH); δC 22.3 (s, CH₃), 50.4 (d, 4JCF 4.8, NCH₂), 66.9 (s, OCH₂), 77.1 (d, 4JCF 5.6, CH), 133.2 (dd, 2JCF 23.2, 3JCF 8.0, C-4), 137.0 (dd, 2JCF 24.8, 3JCF 8.8, C-5), 159.5 (d, 1JCF 239.7, C-3), 160.4 (d, 1JCF 240.5, C-6); δF -93.2 (1 F, d, 5JFF 29.8, F-3), -86.2 (1 F, d, 5JFF 29.8, F-3); m/z (ES⁺) 260.3 ([MH]⁺, 100%).
Method B: Lithium isopropoxide (2 M in THF, 0.45 mL, 0.90 mmol), 4-(3,5,6-trifluoro-4-pyridazinyl)morpholine 2a (195 mg, 0.89 mmol) and THF (10 mL) at -78 °C, stirring for 16 h at rt overnight and column chromatography on silica gel using a 2-13% EtOAc in toluene gradient as eluent gave 4-(3,6-difluoro-5-[(1-methylethyl)oxy]-4-pyridazinyl)morpholine 3b (94 mg, 41%) as white crystals; physical and spectroscopic data as above.

4-(5-(Ethylthio)-3,6-difluoropyridazin-4-yl)morpholine 3c
DIPEA (0.27 mL, 1.5 mmol), morpholine (0.09 mL, 1.03 mmol), 4-(ethylthio)-3,5,6-trifluoropyridazine 2k (200 mg, 1.03 mmol) and THF (10 mL) after stirring at rt for 16 h and column chromatography on silica gel using hexane as eluent gave 4-(5-(ethylthio)-3,6-difluoropyridazin-4-yl)morpholine 3c (197 mg, 73%) as a yellow oil; (Found: C, 45.6; H, 5.1; N, 16.2. C_{10}H_{13}F_{2}N_{3}OS requires: C, 45.9; H, 5.0; N, 16.1%); ν_{max}/cm^{-1} 2965, 2853, 1638 and 1546; δ_{H} 1.29 (3 H, t, J_{HH} 7.4, J_{HF} 0.5, CH_{3}), 3.09 (2 H, qd, J_{HH} 7.4, J_{HF} 1.6, SCH_{2}), 3.41 (4 H, td, J_{HH} 4.7, J_{HF} 2.3, NCH_{2}), 3.84 (4 H, t, J_{HH} 4.7, OCH_{2}); δ_{C} 14.9 (d, J_{CF} 0.9, CH_{3}), 28.5 (d, J_{CF} 8.9, SCH_{2}), 51.0 (d, J_{CF} 4.6, NCH_{2}), 67.1 (d, J_{CF} 1.5, SCH_{2}), 121.3 (dd, J_{CF} 32.6, J_{CF} 6.8, C-4), 140.9 (dd, J_{CF} 23.4, J_{CF} 7.1, C-5), 159.5 (dd, J_{CF} 243.2, J_{CF} 1.5, C-6), 164.7 (d, J_{CF} 237.9, C-3); δ_{F} -88.4 (1 F, d, J_{FF} 31.2, F-3), -78.5 (1 F, d, J_{FF} 31.2, F-6); m/z (ES^+) 260.9 ([M]+, 100%).

3,6-Difluoro-4-phenyl-5-(phenylthio)pyridazine 3d
DIPEA (0.19 mL, 1.1 mmol), thiophenol (0.07 mL, 0.68 mmol), 3,4,6-trifluoro-5-phenylpyridazine 2m (150 mg, 0.714 mmol) and THF (10 mL) after stirring at 0 °C for 1 hour and column chromatography on silica gel using 1-7% THF in cyclohexane gradient as eluent gave 3,6-difluoro-4-phenyl-5-(phenylthio)pyridazine 3d (188 mg, 88%) as off-white crystals; mp 78.9 – 80.0 °C (Found: C, 64.0; H, 3.4; N, 9.3. C_{10}H_{10}F_{2}N_{2}S_{2} requires: C, 64.0; H, 3.4; N, 9.3%); ν_{max}/cm^{-1} 1523, 1443 and 1386; δ_{H} 7.20 - 7.31 (5 H, m, ArH), 7.33 - 7.40 (2 H, m, ArH), 7.44 - 7.55 (3 H, m, ArH); δ_{C} 128.6 (s, C-2'), 128.8 (d, J_{CF} 2.4, C-1'), 128.9 (s, C-4''), 129.3 (s, C-3''), 129.4 (s, C-3'), 130.1 (s, C-4'), 130.3 (d, J_{CF} 2.4, C-1''), 132.0 (s, C-2''''), 132.4 (dd, J_{CF} 29.6, J_{CF} 4.0, C-4), 134.5 (dd, J_{CF} 31.2, J_{CF} 3.2, C-5), 162.1 (d, J_{CF} 245.3, C-6), 163.3 (d, J_{CF} 244.5, C-3); δ_{F} -83.3 (1 F, d, J_{FF} 31.0, F-3), -75.3 (1 F, d, J_{FF} 31.0, F-6); m/z (ES^+) 301.2 ([MH]+, 100%).
3,6-Difluoro-4-[(1-methylethyl)oxy]-5-(phenylthio)pyridazine 3e
DIPEA (0.22 mL, 1.3 mmol), thiophenol (0.08 mL, 0.75 mmol), 3,4,6-trifluoro-5-[(1-methylethyl)oxy]pyridazine 2l (160 mg, 0.833 mmol) and THF (10 mL) after stirring at 0 °C for 1 h and column chromatography on silica gel using 1-7% THF in cyclohexane gradient as eluent gave 3,6-difluoro-4-[(1-methylethyl)oxy]-5-(phenylthio)pyridazine 3e (77 mg, 33%) as pale yellow crystals; mp 45.1 – 46.9 °C (Found: [MH]+, 283.07113. C_{13}H_{12}F_{2}N_{2}OS requires: [MH]+, 283.07112); ν_{max}/cm^{-1} 2985, 1581 and 1544; δ_{H} 1.26 (6 H, dd, 3^{J}HH 6.1, 6^{J}HF 0.9, CH_{3}), 4.97 - 5.08 (1 H, m, CH), 7.29 - 7.43 (5 H, m, ArH); δ_{C} 22.4 (s, CH_{3}), 78.4 (d, 5^{J}CF 8.0, CH), 121.1 (dd, 2^{J}CF 32.0, 3^{J}CF 7.2, C-5), 128.6 (s, C-4'), 129.3 (s, C-3'), 130.6 (s, C-1'), 131.8 (s, C-2'), 147.0 (dd, 2^{J}CF 24.0, 3^{J}CF 6.4, C-4), 157.8 (d, 1^{J}CF 241.3, C-6), 163.8 (d, 1^{J}CF 240.5, C-3); δ_{F} -92.1 (1 F, d, 5^{J}FF 31.6, F-3), -76.5 (1 F, d, 5^{J}FF 31.6, F-6); m/z (ES^+) 283.2 ([MH]^+, 76%).

4-(3,6-Difluoro-5-(phenylthio)-4-pyridazinyl)morpholine 3f
DIPEA (0.15 mL, 0.88 mmol), thiophenol (0.06 mL, 0.58 mmol), 4-(3,5,6-trifluoro-4-pyridazinyl)morpholine 2a (129 mg, 0.589 mmol) and THF (10 mL) after stirring at 0 °C for 1 h and column chromatography on silica gel using 5-25% EtOAc in cyclohexane gradient as eluent gave 4-(3,6-difluoro-5-(phenylthio)-4-pyridazinyl)morpholine 3f (146 mg, 80%) as pale yellow crystals; mp 109.7 – 111.2 °C (Found: C, 54.1; H, 4.2; N, 13.6. C_{14}H_{13}F_{2}N_{3}OS requires: C, 54.4; H, 4.2; N, 13.6%); ν_{max}/cm^{-1} 2982, 1581 and 1542; δ_{H} 3.40 (4 H, td, 3^{J}HH 4.7, 5^{J}HF 2.1, NCH_{2}), 3.70 (4 H, dd, 3^{J}HH 4.7, 3^{J}HH 4.5, OCH_{2}), 7.21 - 7.25 (2 H, m, ArH), 7.30 - 7.37 (3 H, m, ArH); δ_{C} 50.4 (d, 4^{J}CF 4.8, NCH_{2}), 66.8 (s, OCH_{2}), 116.3 (dd, 2^{J}CF 32.0, 3^{J}CF 5.6, C-4), 128.0 (s), 129.0 (s), 129.5 (s), 131.9 (s), 141.4 (dd, 2^{J}CF 23.2, 3^{J}CF 4.8, C-5), 159.0 (d, 1^{J}CF 243.7, C-6), 164.9 (d, 1^{J}CF 239.7, C-3); δ_{F} -86.2 (1 F, d, 5^{J}FF 31.6, F-6); m/z (ES^+) 310.2 ([MH]^+, 100%).

4-(Ethylthio)-3,6-difluoro-5-isopropoxypyridazine 3g
Lithium isopropoxide (2 M in THF, 0.58 mL, 1.16 mmol), 4-(ethylthio)-3,5,6-trifluoropyridazine 2k (227 mg, 1.17 mmol) and THF (10 mL) at -78 °C, was allowed to stir for 16 h at rt and after column chromatography on silica gel using hexane:EtOAc (9:1) as eluent gave 4-(ethylthio)-3,6-difluoro-5-isopropoxypyridazine 3g (213 mg, 78 %) as a colourless oil; (Found: C, 46.4; H, 5.3; N, 11.8.
C₉H₁₂F₂N₂OS requires: C, 46.1; H, 5.2; N, 12.0%); δ₁H 1.31 (3 H, t, ³JHH 7.4, CH₂CH₃), 4.99 (1 H, hept d, ³JHH 5.9, ⁵JHF 1.3, CH); δ₁C 15.1 (s, CH₂CH₃), 22.8 (s, CH₂CH₃), 27.3 (d, ⁴JCF 7.1, CH₂), 78.7 (d, ⁴JCF 7.2, CH), 123.3 (dd, ²JCF 32.8, ³JCF 6.6, C-4), 146.8 (dd, ²JCF 24.4, ³JCF 7.8, C-5), 158.2 (dd, ¹JCF 242.4, ⁴JCF 2.1, C-3), 164.0 (d, ¹JCF 238.4, C-6); δ₁F -93.8 (1 F, d, ⁵JFF 31.1, F-6), -78.7 (1 F, d, ⁵JFF 31.1, F-3); m/z (ES⁺) 235.1 ([MH]⁺, 100%).

3,6-Difluoro-4-isopropoxy-5-phenylpyridazine 3h
Lithium isopropoxide (2 M in THF, 0.40 mL, 0.80 mmol), 3,4,6-trifluoro-5-phenylpyridazine 2m (169 mg, 0.804 mmol) and THF (10 mL) at -78 °C, was allowed to stir for 16 h at rt and after column chromatography on silica gel using 5-13% EtOAc in cyclohexane gradient as eluent gave 3,6-difluoro-4-isopropoxy-5-phenylpyridazine 3h (138 mg, 69%) as a colourless oil; δ₁H 1.22 (6 H, dd, ³JHH 6.1, ⁶JHF 0.6, CH₃), 4.65 - 4.77 (1 H, m, CH), 7.49 - 7.52 (5 H, m, ArH); δ₁F -92.3 (1 F, d, ⁵JFF 31.1, F-6), -83.0 (1 F, d, ⁵JFF 32.1, F-6); m/z (ES⁺) 251.2 ([MH]⁺, 92%).

Reactions of tetrafluoropyridazine with difunctional nucleophiles

5,8-Difluoro-1,2,3,4-tetrahydro-1,4-dimethylpyrazino-[2,3-d]pyridazine 4a
A mixture of tetrafluoropyridazine 1 (0.60 g, 3.96 mmol), N,N’-dimethylethylene diamine (0.47 ml, 4.4 mmol), sodium hydrogen carbonate (1.33 g, 15.8 mmol) and acetonitrile (100 mL) was stirred at rt for 4 h. Water (50 mL) was added and the mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried (MgSO₄), filtered and evaporated. Column chromatography on silica gel using ethyl acetate : hexane (1:1) as eluent gave 5,8-difluoro-1,2,3,4-tetrahydro-1,4-dimethylpyrazino-[2,3-d]pyridazine 4a (0.62 g, 92 %) as white crystals; mp 169 – 171 °C (Found: C, 47.9; H, 5.0; N, 27.8, C₉H₁₀N₄F₂ requires: C, 48.0; H, 5.0; N, 28.0%); νmax / cm⁻¹ 1092, 1159, 1251, 1343, 1410, 1557, 2900 (br); δ₁H 3.05 (6H, br s, CH₃), 3.20 (4H, br s, CH₂); δ₁C 42.2 (s, CH₃), 48.4 (s, CH₂), 125.8 (dd, ²JCF 16.7, ³JCF 16.7, C-4a), 156.2 (dd, ¹JCF 235.2, ⁴JCF 3.8, C-5); δ₁F -92.1 (s); m/z (EI⁺) 200 ([M]⁺, 100%), 185 (42), 156 (20), 42 (76).

N-(3,5,6-Trifluoropyridazin-4-yl)benzamidine 5
A mixture of tetrafluoropyridazine 1 (0.60 g, 3.96 mmol), benzamidine hydrochloride (0.68 g, 4.35 mmol), sodium hydrogen carbonate (1.32 g, 15.8 mmol) and acetonitrile (100 mL) was heated at reflux for 16 h. After this period, the solvent was evaporated and the residue dissolved in ethyl acetate (50 mL). Water (25 mL) was added and the aqueous layer extracted with ethyl acetate (2 × 25 mL). The combined organic extracts were dried (MgSO₄), filtered, evaporated, recrystallised from ethyl acetate and hexane (1:1) to give \(N-(3,5,6\)-trifluoropyridazin-4-yl)benzamidine 5 (0.76 g, 75%) as a yellow solid; mp 139 – 141 °C (Found: [MH]+, 253.0695; C₁₁H₇F₃N₄ requires: [MH]+, 253.0695); \(\delta_H\) (DMSO-\(d_6\)) 7.6 – 7.9 (5H, m, Ar-H), 8.08 (1H, br s, NH); \(\delta_C\) (DMSO-\(d_6\)) 127.6 (s, C-2'), 128.4 (s, C-3'), 131.4 (dd, \(^2J_{CF}\) 31.4, \(^3J_{CF}\) 10.4, C-4), 131.6 (s, C-4'), 133.4 (s, C-1'), 141.9 (ddd, \(^1J_{CF}\) 269.1, \(^2J_{CF}\) 26.8, \(^3J_{CF}\) 9.3, C-5), 156.2 (dd, \(^1J_{CF}\) 235.8, \(^2J_{CF}\) 11.4, C-6), 159.5 (s, C=N), 160.6 (d, \(^1J_{CF}\) 239.4, C-3); \(\delta_F\) (DMSO-\(d_6\)) -86.9 (1F, t, \(^3J_{FF}\) 27.6, F-3), -101.0 (1F, t, \(^3J_{FF}\) 27.6, F-6), -140.0 (1F, t, \(^3J_{FF}\) 27.6, F-5); m/z (EI+) 252 ([M]+, 32), 104 (61), 77 (100).

4,7-Difluoro-2-phenyl-1H-imidazo[4,5-d]pyridazine 4b
A mixture of \(N-(3,5,6\)-trifluoropyridazin-4-yl)benzamidine 5 (0.25 g, 0.99 mmol), diisopropylethylamine (0.17 mL, 1.0 mmol) and acetonitrile (2.5 mL) was subjected to microwave irradiation at 150 °C for 60 min. Water (25 mL) was added and the mixture was extracted with dichloromethane (3 × 25 mL). The combined organic extracts were dried (MgSO₄), filtered, evaporated and recrystallised from toluene to give 4,7-difluoro-2-phenyl-1H-imidazo[4,5-d]pyridazine 4b (0.19 g, 62%) as a yellow solid; mp 220 °C (decomp.) (Found: [MH]+, 233.0633; C₁₁H₆F₂N₄ requires: [MH]+, 233.0633); \(\delta_H\) (DMSO-\(d_6\)) 7.5 – 7.7 (3H, m, Ar-H), 8.1 – 8.3 (2H, m, Ar-H); \(\delta_C\) (DMSO-\(d_6\)) 127.5 (s, C-2'), 129.0 (s, C-3'), 129.7 (s, C-4'), 131.0 (s, C-1'), 154.8 (d, \(^2J_{FF}\) 19.8, C-3a), 155.9 (dd, \(^1J_{CF}\) 243.4, \(^4J_{CF}\) 8.7, C-4), 159.0 (s, C=N); \(\delta_F\) (DMSO-\(d_6\)) -89.3 (s); m/z (ES+) 233 ([MH]+, 100%).

1,4-Difluoro-5,6,7,8-tetrahydro-2,3,4b,9-tetraaza-fluorene 4c
A mixture of tetrafluoropyridazine 1 (0.50 g, 3.28 mmol), 2-iminopiperidine (0.98 g, 7.22 mmol), sodium hydrogen carbonate (1.10 g, 13.1 mmol) and acetonitrile (100 mL) was stirred at rt for 3 d. The solvent was evaporated and the crude mixture partitioned between ethyl acetate (25 mL) and water (50 mL). The aqueous layer was separated and acidified with dil. HCl (10%), then extracted with ethyl acetate (2 × 25 mL) and dichloromethane (3 × 25 mL). The combined organic extracts were dried
(MgSO₄), filtered and evaporated. Column chromatography on silica gel with ethyl acetate : dichloromethane (2:1) as eluent gave 1,4-difluoro-5,6,7,8-tetrahydro-2,3,4b,9-tetraaza-fluorene 4c (0.57 g, 82%) as a yellow solid; mp 152 – 154 °C (Found: C, 51.0; H, 3.9; N, 26.7. C₉H₈N₄F₂ requires: C, 51.4; H, 3.8; N, 26.4%); δH 2.0 – 2.1 (2H, m, CH₂), 2.1 – 2.2 (2H, m, CH₂), 3.1 – 3.2 (2H, m, H-8), 4.3 – 4.4 (2H, m, H-5); δC 19.7 (s, CH₂), 22.2 (s, CH₂), 25.6 (s, CH₂), 45.9 (s, C-5), 125.1 (dd, 2JCF 28.0, 3JCF 11.7, C-4a), 133.5 (dd, 2JCF 32.9, 3JCF 6.5, C-9a), 153.4 (d, 1JCF 237.6, C-4), 157.6 (d, 1JCF 244.4, C-1), 157.7 (s, C-8a); δF -92.6 (1F, d, 5JFF 32.9), -94.6 (1F, d, 5JFF 32.9); m/z (EI⁺) 210 ([M]⁺, 100%), 209 ([M-H]⁺, 36), 182 (32), 181 (14).

1,4-Difluoro-8-methyl-2,3,4b,9-tetraaza-fluorene 4d
A mixture of tetrafluoropyridazine 1 (0.50 g, 3.28 mmol), 2-amino-3-picoline (0.83 mL, 8.22 mmol) and acetonitrile (1 mL) was subjected to microwave irradiation at 150 °C for 60 min. Water (25 mL) was added and the mixture was extracted with dichloromethane (3 × 25 mL). The combined organic extracts were dried (MgSO₄), filtered and evaporated and recrystallised. Column chromatography on silica gel with dichloromethane as eluent gave 1,4-difluoro-8-methyl-2,3,4b,9-tetraaza-fluorene 4d (0.42 g, 58%) as a white solid; mp 213 – 215 °C (Found: [MH]⁺, 221.06339. C₁₀H₆N₄F₂ requires: [MH]⁺, 221.06333); νmax / cm⁻¹ 1580, 1433, 1379, 1309, 1281, 1256, 1228, 1165, 1102, 1024, 976; δH 2.79 (3H, s, CH₃), 7.21 (1H, t, 3JHH 7.2, H-6), 7.59 (1H, d, 3JHH 7.2, H-7), 8.63 (1H, d, 3JHH 7.2, H-5); δC 17.7 (s, CH₃), 115.6 (s, C-6), 119.0 (dd, 2JCF 26.9, 3JCF 11.6, C-4a), 125.6 (d, 4JCF 4.9, C-5), 130.1 (s, C-8), 131.8 (s, C-7), 135.3 (dd, 2JCF 35.1, 3JCF 6.2, C-9a), 151.9 (s, C-8a), 154.0 (dd, 1JCF 238.6, 4JCF 2.4, C-4), 158.2 (dd, 1JCF 246.9, 4JCF 3.5, C-1); δF -89.7 (1F, d, 5JFF 34.6, F-1), -91.6 (1F, d, 5JFF 34.6, F-4); m/z (EI⁺) 220 ([M]⁺, 100%).

6-Bromo-1,4-difluoro-8-methyl-2,3,4b,9-tetraaza-fluorene 4e
A mixture of tetrafluoropyridazine 1 (0.50 g, 3.28 mmol), 2-amino-5-bromo-3-methylpyridine (1.68 g, 8.20 mmol) and acetonitrile (10 mL) was subjected to microwave irradiation at 150 °C for 60 min. Water (25 mL) was added and the mixture was extracted with dichloromethane (3 × 25 mL). The combined organic extracts were dried (MgSO₄), filtered and evaporated and recrystallised. Column chromatography on silica gel with dichloromethane as eluent gave 6-bromo-1,4-difluoro-8-methyl-2,3,4b,9-tetraaza-fluorene 4e (0.36 g, 40%) as a cream solid; mp 215 – 217 °C (Found: C, 40.2; H, 2.0; N, 18.5. C₁₀H₆N₄F₂ requires: C, 40.2; H, 1.7; N, 18.7%); νmax / cm⁻¹ 996, 1028, 1106, 1159, 1247,
1279, 1310, 1326, 1413, 1433, 1470, 1558; $\delta_H$ 2.78 (3H, s, CH$_3$), 7.66 (1H, s, H-7), 8.73 (1H, s, H-5); $\delta_C$ 17.5 (s, CH$_3$), 110.2 (s, C-6), 118.6 (dd, $^2J_{CF}$ 26.9, $^3J_{CF}$ 11.9, C-4a), 125.4 (d, $^4J_{CF}$ 4.6, C5), 131.0 (s, C-8), 135.1 (dd, $^2J_{CF}$ 36.4, $^3J_{CF}$ 6.9, C-9a), 135.3 (s, C-7), 150.1 (s, C-8a), 153.6 (dd, $^1J_{CF}$ 236.8, $^4J_{CF}$ 2.8, C-4), 158.2 (dd, $^1J_{CF}$ 246.8, $^4J_{CF}$ 3.4, C-1); $\delta_F$ -89.0 (1F, d, $^5J_{FF}$ 34.8, F-4), -90.9 (1F, d, $^5J_{FF}$ 34.8, F-1); m/z (EI$^+$) 300 ([M]+, 100%), 298 ([M]+, 93), 219 (62), 154 (26), 102 (40), 90 (30), 77 (44), 63 (57), 51 (60), 39 (34).

5,8-difluoro-2,3-dihydro-[1,4]dithiino[2,3-d]pyridazine 4f

Tetrafluoropyridazine 1 (0.25 g, 1.64 mmol) was dissolved in dry acetonitrile (20 mL) and 1,2-ethanedithiol (0.15 mL, 1.81 mmol) and sodium hydrogen carbonate (0.28 g, 3.29 mmol) were added. The mixture was allowed to stir at rt for 2 h before the solvent was evaporated, and the crude reaction mixture partitioned between dichloromethane (20 mL) and water (20 mL). The aqueous layer was separated before extraction with further portions of dichloromethane (3 × 20 mL). The combined organic extracts were then dried (MgSO$_4$), filtered and evaporated to provide a crude yellow material which after recrystallisation from acetonitrile gave 5,8-difluoro-2,3-dihydro-[1,4]dithiino[2,3-d]pyridazine 4f (0.29 g, 85%) as a white solid; mp 123 – 125°C; $\delta_H$ 3.41 (4H, s, CH$_2$); $\delta_C$ 25.5 (s, C-2), 126.0 (dd, $^2J_{CF}$ 20.0, C-4a), 160.0 (dd, $^1J_{CF}$ 242.2, $^4J_{CF}$ 5.1, C-5); $\delta_F$ -84.8 (s); m/z (EI$^+$) 206 (88%, M$^+$), 191 (100), 178 (19, [M-N$_2$]+), 132 (19), 87 (29).

4,7-difluoro-2-methylthiazolo[4,5-d]pyridazine 4g

Tetrafluoropyridazine 1 (1.00 g, 6.58 mmol) was mixed with thioacetamide (0.54 g, 7.23 mmol) and sodium hydrogen carbonate (2.21 g, 26 mmol) in acetonitrile (50 mL) under argon. The mixture was stirred at reflux for 16 h, after which the solvent was evaporated, and the crude mixture dissolved in ethyl acetate (25 mL) and water (25 mL). The aqueous layer was separated and acidified with HCl (10%), then extracted with ethyl acetate (2 × 25 mL) and dichloromethane (3 × 25 mL). The combined organic extracts were dried (MgSO$_4$), filtered and evaporated to yield a crude brown product. Column chromatography on silica gel using ethyl acetate as eluent and recrystallisation from acetonitrile gave 4,7-difluoro-2-methylthiazolo[4,5-d]pyridazine 4g (0.76 g, 62%) as a yellow solid; mp > 250°C; $\delta_H$
Reaction of 4-[3,6-difluoro-5-(phenylthio)-4-pyridazinyl]morpholine 3f

4,4’-(6-Fluoro-4-(phenylthio)pyridazine-3,5-diyl)dimorpholine 6

A mixture consisting of morpholine (56 mg, 0.626 mmol), DIPEA (84 mg, 1.20 mmol), 4-[3,6-difluoro-5-(phenylthio)-4-pyridazinyl]morpholine 3f (204 mg, 0.626 mmol) and THF (4 mL) was irradiated at 150 °C (microwave) for 80 min. The mixture was concentrated, partitioned between EtOAc (10 mL) and water (10 mL), and extracted with two further portions of EtOAc (2 x10 mL). The combined organic phases were dried (MgSO₄) and evaporated and the residue after column chromatography on silica gel using a hexane:ethyl acetate gradient as eluent gave 4,4’-(6-fluoro-4-(phenylthio)pyridazine-3,5-diyl)dimorpholine 6 (168 mg, 71%) as white crystals; mp 159.3 – 160.0 °C (Found: [MH]+, 377.1436. C₁₈H₂₁F₂N₄O₂S requires: [MH]+, 377.1448); δH 3.15 - 3.19 (4H, m, CH₂NC-5), 3.31 (4H, t, 3JHH 4.7, CH₂), 3.61 (4H, t, 3JHH 4.7, CH₂), 3.64 (4H, t, 3JHH 4.7, CH₂), 7.06 - 7.09 (2H, m, ArH), 7.22 - 7.29 (3H, m, ArH); δC 50.5 (s, CH₂), 50.6 (d, 4JCF 4.2, CH₂), 66.6 (s, CH₂), 66.9 (s, CH₂), 121.4 (d, 3JCF 6.9, C-4), 127.6 (s, C-4’), 128.4 (s, C-3’), 129.2 (s, C-2’), 133.8 (s, C-1’), 140.2 (d, 2JCF 23.4, C-5), 158.7 (d, 1JCF 241.2, C-6), 163.9 (s, C-3); δF -92.57 (s); m/z (ES+) 377.1 ([MH]+, 100%).

Crystal data for 6: C₁₈H₂₁F₂N₄O₂S, M = 376.45, monoclinic, space group P 2₁, a = 6.58813(2), b = 13.5706(4), c = 10.4143(4) Å, β = 107.70(2)°, U = 886.07(5) Å³, F(000) = 396, Z = 2, Dc = 1.416 mg m⁻³, μ = 0.214 mm⁻¹. 16499 reflections were collected yielding 5013 unique data (Rmerg = 0.0534). Final wR₂(F²) = 0.0885 for all data (319 refined parameters), conventional R₁(F) = 0.0364 for 4793 reflections with I≥2σ(I), GOF = 1.053, Flack parameter -0.01(5). CCDC-1486844.

Reactions of scaffolds 4b-d with nucleophiles

N₄,N₇-dibutyl-2-phenyl-1H-imidazo[4,5-d]pyridazine-4,7-diamine 7a
4,7-Difluoro-2-phenyl-1H-imidazo[4,5-d]pyridazine 4b (0.10g, 0.43mmol) was dissolved in acetonitrile (1mL) in a 0.5 - 2 mL microwave vial, n-butylamine (0.085 ml, 0.86 mmol) was added and the vial sealed. The mixture was heated by microwave irradiation at 150°C for 20 min before dichloromethane (10 mL) and water (10 mL) were added and the layers separated. The aqueous layer was then washed with further portions of dichloromethane (3 × 10 mL) and the organic extracts combined, dried (MgSO₄), filtered and evaporated to yield a crude yellow material. Column chromatography on silica gel using ethyl acetate as eluent gave N⁴,N⁷-dibutyl-2-phenyl-1H-imidazo[4,5-d]pyridazine-4,7-diamine 7a (51 mg, 35 %) as yellow crystals; mp 173 – 175°C; δH 0.8 – 0.9 (6H, m, CH₃), 1.33 (4H, sextet, 3JHH 7.4, CH₂CH₃), 1.61 (4H, pent, 3JHH 7.4, CH₂CH₂CH₃), 3.36 (4H, t, 3JHH 7.4, NCH₂), 7.3 – 7.5 (3H, m, ArH), 8.1 – 8.3 (1H, m, ArH); δC 13.9 (s, CH₃), 20.3 (s, CH₂CH₂), 31.3 (s, CH₂CH₂CH₃), 41.7 (s, NHCH₂), 116.2 (s), 118.9 (s), 127.3 (s), 129.0 (s), 129.7 (s), 132.7 (s), 147.1 (s); m/z (ES⁺) 339 ([MH⁺], 100%).

4-Fluoro-1-morpholin-4-yl-5,6,7,8-tetrahydro-2,3,4b,9-tetraaza-fluorene 7b
A mixture of 1,4-difluoro-5,6,7,8-tetrahydro-2,3,4b,9-tetraaza-fluorene 4c (0.10 g, 0.48 mmol), morpholine (0.083 mL, 0.95 mmol) and acetonitrile (1 mL) was heated at 150°C (microwave) for 20 min. Water (25 mL) was added and the mixture was extracted with dichloromethane (3 × 25 mL). The combined organic extracts were dried (MgSO₄), filtered and evaporated. Column chromatography on silica gel with ethyl acetate and hexane (2:1) as eluent gave 4-fluoro-1-morpholin-4-yl-5,6,7,8-tetrahydro-2,3,4b,9-tetraaza-fluorene 7b (95 mg, 72%) as a yellow solid; mp 179 – 181°C (Found: [MH⁺] 278.14106. C₁₃H₁₆N₅FO requires: [MH⁺] 278.14117); δH 2.00 - 2.10 (2H, m, CH₂), 2.12 - 2.18 (2H, m, CH₂), 3.09 (2H, t, 3JHH 6.4, CH₂), 3.87 (4H, t, 3JHH 4.8, OCH₂), 4.03 (4H, t, 3JHH 4.8, NCH₂), 4.33 (2H, t, 3JHH 6.0, NCH₂); δC 20.2 (s, CH₂), 22.6 (s, CH₂), 25.5 (s, CH₂), 45.3 (d, 4JCF 2.7, C-5), 47.3 (s, C-2'), 67.2 (s, C-3'), 121.5 (d, 4JCF 27.6, C-4a), 136.1 (d, 4JCF 5.8, C-9a), 151.5 (d, 1JCF 231.6, C-4), 152.6 (d, 4JCF 2.1, C-8a), 153.9 (d, 4JCF 2.1, C-1); δF -101.9 (s); m/z (ES⁺) 278 ([MH⁺], 100%). Crystal data for 7b: C₁₃H₁₆N₅FO, M = 277.31, orthorhombic, space group P bcn, a = 16.7598(9), b = 7.3062(4), c = 20.4845(11) Å, V = 2508.3(2) Å³, F(000) = 1168, Z = 8, Dc = 1.469 mg m⁻³, µ = 0.109 mm⁻¹. 19847 reflections were collected yielding 3035 unique data (Rmerge = 0.0807). Final wR²(F²) = 0.1179 for all data (245 refined parameters), conventional R₁(F) = 0.0472 for 2114 reflections with I≥2σ(I), GOF = 1.025. CCDC-1486846.
4-Fluoro-1-methoxy-2,3,4b,9-tetraaza-fluorene 7c
A mixture of 1,4-difluoro-8-methyl-2,3,4b,9-tetraaza-fluorene 4d (0.50 g, 2.27 mmol), sodium methoxide (0.31 g, 5.68 mmol) and methanol (3 mL) was heated at 150 °C (microwave) for 20 min. Water (25 mL) was added and the mixture was extracted with dichloromethane (3 × 25 mL). The combined organic extracts were dried (MgSO₄), filtered and evaporated. Column chromatography on silica gel using hexane : ethyl acetate (2:1) as eluent gave 4-fluoro-1-methoxy-8-methyl-2,3,4b,9-tetraaza-fluorene 7c (0.21 g, 40%) as a white solid; mp 229 – 231 °C (Found: C, 56.6; H, 3.9; N, 23.9. \(\text{C}_{11}\text{H}_{9}\text{FN}_{4}\text{O}\) requires: C, 56.9; H, 3.9; N, 24.1%); \(\nu_{\text{max}}/\text{cm}^{-1}\) 964, 980, 1030, 1102, 1132, 1168, 1236, 1286, 1320, 1372, 1424, 1466, 1579; \(\delta_{\text{H}}\) 2.76 (3H, s, CH₃), 4.38 (3H, s, OCH₃), 7.08 (1H, t, \(J_{\text{HH}}\) 6.8, H-6), 7.48 (1H, dt, \(J_{\text{HH}}\) 6.8, \(J_{\text{HCH}}\) 1.0, H-7), 8.80 (1H, d, \(J_{\text{HH}}\) 6.8, H-5); \(\delta_{\text{C}}\) 17.6 (s, CH₃), 55.6 (s, OCH₃), 114.3 (s, C-6), 120.5 (d, \(J_{\text{CF}}\) 11.4, C-9a), 126.0 (s, C-5), 129.1 (s, C-8), 130.4 (s, C-7), 133.1 (d, \(J_{\text{CF}}\) 36.4, C-4a), 150.7 (s, C-8a), 154.9 (d, \(J_{\text{CF}}\) 2.0, C-1), 156.8 (d, \(J_{\text{CF}}\) 247.6, C-4); \(\delta_{\text{F}}\) -94.5 (s); \(m/z\) (EI⁺) 232 ([M⁺], 58%), 231 (39), 217 (8), 183 (100).

Ethyl-(4-fluoro-8-methyl-2,3,4b,9-tetraaza-fluoren-1-yl)-amine 7d
A mixture of 1,4-difluoro-8-methyl-2,3,4b,9-tetraaza-fluorene 4d (0.50 g, 2.27 mmol) and ethylamine (2.83 mL, 2.0 M in THF, 5.68 mmol) was heated at 150 °C (microwave) for 20 min. Water (25 mL) was added and the mixture was extracted with dichloromethane (3 × 25 mL). The combined organic extracts were dried (MgSO₄), filtered, evaporated and recrystallised from toluene to give ethyl-(4-fluoro-8-methyl-2,3,4b,9-tetraaza-fluoren-1-yl)-amine 7d (0.36g, 65%) as a yellow solid; mp 127 – 129 °C (Found: [MH]⁺, 246.11492. \(\text{C}_{12}\text{H}_{12}\text{FN}_{5}\) requires: [MH]⁺, 246.11495); \(\nu_{\text{max}}/\text{cm}^{-1}\) 1340, 1401, 1435, 1480, 1583, 1616, 3351 (br); \(\delta_{\text{H}}\) 1.40 (3H, t, \(J_{\text{HH}}\) 6.6, CH₂CH₃), 2.71 (3H, s, CH₃), 3.77 (2H, quin, \(J_{\text{HH}}\) 6.6, NCH₂), 5.53 (1H, br s, NH), 7.03 (1H, t, \(J_{\text{HH}}\) 6.7, H-6), 7.40 (1H, dt, \(J_{\text{HH}}\) 6.7, \(J_{\text{HCH}}\) 0.9, H-7), 8.51 (1H, d, \(J_{\text{HH}}\) 6.7, H-5); \(\delta_{\text{C}}\) 14.9 (s, CH₂CH₃), 17.5 (s, CH₃), 36.5 (s, NHCH₂), 114.2 (s, C-6), 114.5 (d, \(J_{\text{CF}}\) 29.5, C-4a), 125.5 (d, \(J_{\text{CF}}\) 4.2, C-9a), 128.9 (s, C-5), 129.5 (s, C-7), 136.3 (s, C-8), 149.6 (s, C-8a), 150.2 (d, \(J_{\text{CF}}\) 230.6, C-4), 153.1 (d, \(J_{\text{CF}}\) 2.0, C-1); \(\delta_{\text{F}}\) -99.4 (s); \(m/z\) (EI⁺) 245 ([M⁺], 17%), 230 (29), 183 (67), 92 (58).

Diethyl-(4-fluoro-8-methyl-2,3,4b,9-tetraaza-fluoren-1-yl)-amine 7e
A mixture of 1,4-difluoro-8-methyl-2,3,4b,9-tetraaza-fluorene 4d (0.30 g, 1.36 mmol), diethylamine (0.35 mL, 3.41 mmol) and acetonitrile (3 mL) was heated at 150 °C (microwave) for 20 min. Water (25 mL) was added and the mixture was extracted with dichloromethane (3 x 25 mL). The combined organic extracts were dried (MgSO₄), filtered, evaporated and recrystallised from hexane / dichloromethane (4:1) to give diethyl-(4-fluoro-8-methyl-2,3,4b,9-tetraaza-fluoren-1-yl)-amine 7e (0.26 g, 70%) as yellow crystals; mp 111 – 113 °C (Found: C, 61.7; H, 5.9; N, 25.4. C₁₄H₁₆N₅F requires C, 61.5; H, 5.9; N, 25.6%); νmax / cm⁻¹ 1217, 1237, 1295, 1352, 1429, 1485, 1575, 1638, 2973; δH 1.31 (6H, t, 3JHH 7.1, CH₂CH₃), 2.66 (3H, s, CH₃), 4.09 (4H, q, 3JHH 7.1, NCH₂), 6.95 (1H, t, 3JHH 7.0, H-6), 7.31 (1H, d, 3JHH 7.0, H-7), 8.46 (1H, d, 3JHH 7.0, H-5); δC 13.8 (s, CH₂CH₃), 17.3 (s, CH₃), 44.0 (s, NCH₂), 113.9 (s, C-6), 114.4 (d, 2JCF 28.0, C-4a), 125.1 (s, C-8), 128.7 (s, C-5), 129.2 (s, C-7), 136.6 (d, 3JCF 4.6, C-8a), 148.3 (s, C-9a), 150.5 (d, 1JCF 228.4, C-4), 153.3 (d, 4JCF 1.9, C-1); δF -102.7 (s); m/z (EI⁺) 273 ([M⁺] 24%), 244 (100), 230 (74), 201 (12), 183 (56), 92 (36). Crystal data for 7e: C₁₄H₁₆FN₅, M = 273.32, monoclinic, space group C2/c, a = 15.9765(4), b = 12.4896(3), c = 14.4663(3) Å, β = 114.06(1)°, V = 2635.8(1) Å³, F(000) = 1152, Z = 8, Dc = 1.378 mg m⁻³, μ = 0.097 mm⁻¹. 19731 reflections were collected yielding 3504 unique data (Rmerge = 0.0284). Final wR₂(F²) = 0.1117 for all data (245 refined parameters), conventional R₁(F) = 0.0394 for 2913 reflections with I≥2σ(I), GOF = 1.052. CCDC-1486848.

3-Fluoro-5,8-dimethyl-4-morpholin-4-yl-5,6,7,8-tetrahydro-pyrazino[2,3-c]pyridazine 9a
DIPEA (0.25 mL, 1.5 mmol) and N,N'-dimethyl-ethane-1,2-diamine (0.05 mL, 0.5 mmol) were added to a stirred solution of 4-(3,5,6-trifluoro-pyridazin-4-yl)-morpholine 2a (100 mg, 0.46 mmol) in THF (4 mL), and the mixture was stirred at rt for 5 d. The mixture was concentrated, partitioned between DCM (10 mL) and water (10 mL), the phases were separated and the aqueous phase further extracted with DCM (2 x 10 mL). The organic phases were combined, dried and concentrated. Purification by column chromatography on silica gel using toluene:THF (1:2) as eluent gave 3-fluoro-5,8-dimethyl-4-morpholin-4-yl-5,6,7,8-tetrahydro-pyrazino[2,3-c]pyridazine 9a (103 mg, 84%) as white crystals; mp 144.2 – 147.3 °C (Found: [MH]⁺, 268.1574. C₁₂H₁₈FN₅O requires [MH]⁺, 268.1574); δH 3.08 (4H, td, 3JHH 4.7, 5JHH 1.8, NCH₂), 3.14 (3H, s, CH₃), 3.30 – 3.33 (2H, m, CH₂N), 3.31 (3H, s, CH₃), 3.38 – 3.40 (2H, m, CH₂), 3.76 (4H, t, 3JHH 4.7, CH₂O); δC 38.3 (s, CN-8), 41.4 (s, CN-5), 46.5 (s, C-7), 50.4 (d, 4JCF 4.3, CNC-4), 51.0 (s, C-6), 67.0 (d, 5JCF 0.5, CO), 119.5 (d, 2JCF 29.1, C-4), 134.9 (d, 3JCF 8.9, C-4a), 151.8 (s, C-8a), 161.2 (d, 1JCF 236.6, C-3); δF -94.5 (s); m/z (AP⁺) 267 ([M⁺]², 100%).
3-Fluoro-4-morpholin-4-yl-9-oxa-10-thia-1,2-diaza-anthracene 9b

DIPEA (1.2 mL, 6.9 mmol) and 2-mercaptophenol (0.23 mL, 2.3 mmol) were added to a stirred solution of 4-(3,5,6-trifluoro-pyridazin-4-yl)-morpholine 2a (504 mg, 2.3 mmol) in THF (4 mL), and the mixture was stirred at rt for 16 h. The mixture was concentrated, partitioned between DCM (10 mL) and water (10 mL), the phases were separated and the aqueous phase further extracted with DCM (2 x 10 mL). The organic phases were combined, dried and concentrated. Purification by column chromatography on silica gel using hexane:ethyl acetate 1-25% as gradient elution, followed by recrystallisation from ethanol gave 3-fluoro-4-morpholin-4-yl-9-oxa-10-thia-1,2-diaza-anthracene 9b (476 mg, 68%) as pale yellow crystals; mp 167.7 – 169.1 °C (Found: [MH]+, 306.0707. C14H12FN3O2S requires [MH]+, 306.0713; δH 3.24 (4H, td, 3JHH 4.7, 5JHF 2.1, CH2N), 3.85 (4H, t, 3JHH 4.7, CH2O), 7.07 – 7.10 (2H, m, H-6, H-8), 7.13 – 7.15 (1H, m, H-7), 7.20 – 7.22 (1H, m, H-5); δC 49.9 (d, 4JC 3.9, CH2N), 67.2 (d, 5JC 1.3, CH2O), 114.5 (s, C-10a), 118.9 (s, C-8), 123.5 (d, 3JC 8.0, C-4a), 125.7 (s, C-6), 126.3 (s, C-7), 129.3 (s, C-5), 134.1 (d, 2JC 26.3, C-4), 149.9 (d, 4JC 1.0, C-9a), 159.3 (s, C-8a), 160.3 (d, 1JC 243.0, C-3); δF -90.0 (s); m/z (AP+) 305 ([M]+, 100%).

4-Ethylsulfanyl-3-fluoro-5,8-dimethyl-5,6,7,8-tetrahydro-pyrazino[2,3-c]pyridazine 9c

A mixture consisting of DIPEA (0.7 mL, 4 mmol), N,N'-dimethyl-ethane-1,2-diamine (0.16 mL, 1.6 mmol), 4-ethylsulfanyl-3,5,6-trifluoro-pyridazine 2k (200 mg, 1.0 mmol) and THF (4 mL) was stirred at rt for 16 h. The mixture was concentrated, partitioned between DCM (10 mL) and water (10 mL), the phases were separated and the aqueous phase further extracted with DCM (2 x 10 mL). The organic phases were combined, dried (MgSO4) and concentrated. Purification by column chromatography on silica gel using hexane:ethyl acetate 1:9 as eluent gave 4-ethylsulfanyl-3-fluoro-5,8-dimethyl-5,6,7,8-tetrahydro-pyrazino[2,3-c]pyridazine 9c (191 mg, 77%) as a white solid; mp 78.1 – 80.0 °C (Found: C, 49.4; H, 6.2; N, 23.0. C10H15FN4S requires: C, 49.6; H, 6.2; N, 23.1%); δH 1.19 (3H, t, 3JHH 7.4, CH3CH2S), 2.78 (2H, q, 3JHH 7.4, CH2S), 3.11 (3H, s, CH3), 3.31 (3H, s, CH3), 3.30 – 3.32 (2H, m, CH2N), 3.46 – 3.49 (2H, m, CH2N); δC 14.4 (s, CH3CH2S), 29.1 (d, 4JC 4.4, CH2S), 37.8 (s, CH3N), 43.1 (s, CH3N), 46.7 (s, CH2N), 51.8 (s, CH2N), 101.9 (d, 2JC 36.1, C-4), 141.6 (d, 3JC 5.2, C-4a), 150.8 (s, C-8a), 162.3 (d, 1JC 227.0, C-3); δF -87.0 (s); m/z (EI+) 242 ([M]+, 100%).

4-Ethylsulfanyl-3-fluoro-9-oxa-10-thia-1,2-diaza-anthracene 9d
A mixture consisting of DIPEA (0.40 mL, 2.3 mmol), 2-mercaptophenol (0.08 mL, 0.8 mmol), 4-ethylsulfanyl-3,5,6-trifluoro-pyridazine 2k (150 mg, 0.77 mmol) and THF (4 mL) was stirred at rt for 16 h. The mixture was then concentrated, partitioned between DCM (10 mL) and water (10 mL), the phases were separated and the aqueous phase further extracted with DCM (2 x 10 mL). The organic phases were combined, dried and concentrated. Purification by column chromatography on silica gel using toluene:ethyl acetate (19:1) as eluent gave 4-ethylsulfanyl-3-fluoro-9-oxa-10-thia-1,2-diaza-anthracene 9d (161 mg, 74%) as yellow crystals; mp 121.4 – 123.0 °C (Found: [MH]+, 281.0220. C_{12}H_{9}FN_{2}O requires [MH]+, 281.0219); δH 1.34 (3H, t, J_{HH} 7.4, CH3), 3.14 (2H, qd, J_{HH} 7.4, J_{HF} 1.0, CH2), 7.07 – 7.09 (2H, m, H-6, H-8), 7.12 – 7.14 (1H, m, H-7), 7.19 – 7.23 (1H, m, H-5); δC 15.3 (s, CH3), 28.8 (d, J_{CF} 6.9, CH2), 114.4 (s, C-10a), 118.8 (s, C-8), 124.0 (d, J_{CF} 36.3, C-4), 125.8 (s, C-6), 126.4 (s, C-7), 129.4 (s, C-5), 133.2 (d, J_{CF} 4.9, C-4a), 149.4 (s, C-8a), 157.6 (d, J_{CF} 1.9, C-9a), 162.9 (d, J_{CF} 238.2, C-3); δF -82.2 (s); m/z (AP+1) 280 ([M]+, 100%).

Crystal data for 9d: C_{12}H_{9}FN_{2}OFS_{2}, M = 280.33, monoclinic, space group P2\textsubscript{1}/n, a = 10.6924(5), b = 9.8670(4), c = 11.0623(5) Å, β = 92.44(1)°, U = 1166.03(9) Å\textsuperscript{3}, F(000) = 576, Z = 4, Dc = 1.597 mg m\textsuperscript{-3}, µ = 0.457 mm\textsuperscript{-1}. 10747 reflections were collected yielding 3249 unique data (R\textsubscript{merg} = 0.0657). Final wR\textsubscript{2}(F\textsuperscript{2}) = 0.1129 for all data (199 refined parameters), conventional R\textsubscript{1}(F) = 0.0429 for 2369 reflections with I≥2σ(I), GOF = 1.008. CCDC-1486847.

4-Ethylsulfanyl-3-fluoro-10H-9-oxa-1,2,10-triaza-anthracene 9e
A mixture consisting of DIPEA (0.40 mL, 2.3 mmol), 2-aminophenol (84 mg, 0.77 mmol), 4-ethylsulfanyl-3,5,6-trifluoro-pyridazine 2k (150 mg, 0.77 mmol) and THF (4 mL) was heated at 100 °C (microwave) for 5 min. The mixture was concentrated, partitioned between DCM (10 mL) and water (10 mL), the phases were separated and the aqueous phase further extracted with DCM (2 x 10 mL). The organic phases were combined, dried (MgSO\textsubscript{4}) and concentrated. Purification by column chromatography on silica gel using hexane:ethyl acetate:DCM (5:2:3) as eluent gave 4-ethylsulfanyl-3-fluoro-10H-9-oxa-1,2,10-triaza-anthracene 9e (153 mg, 75%) as a yellow solid; mp 260 °C (with decomposition) (Found: [MH]+, 264.0597. C_{12}H_{10}FN_{3}OS requires [MH]+, 264.0607); δH 1.31 (3H, t, J_{HH} 7.4, CH3), 1.62 (1H, br. s, NH), 2.90 (2H, q, J_{HH} 7.4, CH2), 6.63 – 6.65 (1H, m, H-5), 6.87 – 6.94 (3H, m, ArH); δC 15.2 (s, CH3), 28.9 (d, J_{CF} 3.1, CH2), 102.2 (d, J_{CF} 40.1, C-4), 114.6 (s, C-5), 117.1 (s, C-8), 124.7 (s, C-7), 125.0 (s, C-6), 125.8 (s, C-10a), 137.6 (d, J_{CF} 7.1, C-4a), 142.8 (s, C-8a),
4-Ethylsulfanyl-3-fluoro-10H-9-thia-1,2,10-triaza-anthracene 9f

A mixture consisting of DIPEA (1.4 mL, 7.9 mmol), 2-aminophenol (0.28 mL, 1.9 mmol), 4-ethylsulfanyl-3,5,6-trifluoro-pyridazine 2k (397 mg, 2.0 mmol) and THF (4 mL) was heated at 100 °C (microwave) for 30 min. The mixture was concentrated, partitioned between DCM (10 mL) and water (10 mL), the phases were separated and the aqueous phase further extracted with DCM (2 x 10 mL). The organic phases were combined, dried (MgSO\(_4\)) and evaporated. Recrystallisation from chloroform gave 4-ethylsulfanyl-3-fluoro-10H-9-thia-1,2,10-triaza-anthracene 9f (333 mg, 63%) as yellow crystals; mp 249.2 – 251.8 °C (Found: [MH]\(^+\), 280.0378. \(\text{C}_{12}\text{H}_{10}\text{FN}_3\text{S}\) requires [MH]\(^+\), 280.0378); \(\delta_H\) 1.35 (3H, t, \(3J_{\text{HH}}\) 7.4, CH\(_3\)), 2.48 (1H, br. s, NH), 3.11 (2H, qd, \(3J_{\text{HH}}\) 7.4, \(5J_{\text{HF}}\) 0.8, CH\(_2\)), 6.83 – 6.88 (3H, m, ArH), 7.05 – 7.07 (1H, m, H-8); \(\delta_C\) 15.3 (s, CH\(_3\)), 28.8 (d, \(4J_{\text{CF}}\) 6.9, CH\(_2\)), 113.8 (s, C-8a), 117.0 (s, C-5), 122.7 (d, \(2J_{\text{CF}}\) 38.4, C-4), 124.3 (s, C-7), 126.1 (s, C-8), 129.2 (s, C-6), 135.4 (d, \(3J_{\text{CF}}\) 4.6, C-4a), 135.8 (s, C-10a), 151.7 (s, C-9a), 160.8 (d, \(1J_{\text{CF}}\) 237.5, C-3); \(\delta_F\) -85.6 (s); \(m/z\) (AP\(^+\)) 279 ([M]\(^+\), 100%).

4-Ethylsulfanyl-3-fluoro-1,2,4b,9-tetraaza-fluorene 9g

A mixture consisting of DIPEA (0.70 mL, 4.0 mmol), pyridin-2-ylamine (143 mg, 1.5 mmol), 4-ethylsulfanyl-3,5,6-trifluoro-pyridazine 2k (199 mg, 1.03 mmol) and THF (4 mL) was heated at 150 °C (microwave) for 30 min. The mixture was concentrated, partitioned between DCM (10 mL) and water (10 mL), the phases were separated and the aqueous phase further extracted with DCM (2 x 10 mL). The organic phases were combined, dried (MgSO\(_4\)) and concentrated. Purification by column chromatography on silica gel using hexane:ethyl acetate (1:9) as eluent followed by recrystallisation from ethanol gave 4-ethylsulfanyl-3-fluoro-1,2,4b,9-tetraaza-fluorene 9g (35 mg, 14%) as orange crystals; mp 197.8 – 199.5 °C (Found: [MH]\(^+\), 249.0601. \(\text{C}_{11}\text{H}_{9}\text{FN}_4\text{S}\) requires [MH]\(^+\), 249.0610); \(\delta_H\)
1.38 (3H, t, $^3J_{HH}$ 7.4, CH$_3$), 3.32 (2H, qd, $^3J_{HH}$ 7.4, $^5J_{HF}$ 0.7, CH$_2$), 6.97 (1H, td, $^3J_{HH}$ 7.2, $^3J_{HH}$ 6.8, $^4J_{HH}$ 1.1, H-6), 7.64 (1H, ddd, $^3J_{HH}$ 9.4, $^5J_{HH}$ 1.3, H-7), 7.79 (1H, dt, $^3J_{HH}$ 9.4, $^5J_{HH}$ 1.2, $^4J_{HH}$ 1.1, H-8), 9.44 (1H, dt, $^3J_{HH}$ 7.2, $^4J_{HH}$ 1.3, $^5J_{HH}$ 1.2, H-5); δ$_C$ 15.4 (s, CH$_3$), 26.9 (d, $^4J_{CF}$ 7.5, CH$_2$), 111.1 (d, $^2J_{CF}$ 38.5, C-4), 112.0 (s, C-8), 119.1 (s, C-6), 126.4 (d, $^3J_{CF}$ 8.0, C-4a), 129.5 (s, C-7), 133.7 (s, C-5), 153.3 (d, $^4J_{CF}$ 0.9, C-9a), 158.8 (s, C-8a), 160.7 (d, $^1J_{CF}$ 229.2, C-3); δ$_F$ -89.4 (s); m/z (ES$^+$) 249 ([MH]$^+$, 100%).

4-Ethylsulfanyl-3-fluoro-8-methyl-1,2,4b,9-tetraaza-fluorene 9h
A mixture consisting of DIPEA (0.70 mL, 4.0 mmol), pyridin-2-ylamine (0.15 mL, 1.29 mmol), 4-ethylsulfanyl-3,5,6-trifluoro-pyridazine 2k (200 mg, 1.03 mmol) and THF (4 mL) was stirred at rt for 7 d. The mixture was concentrated, partitioned between DCM (10 mL) and water (10 mL), the phases were separated and the aqueous phase further extracted with DCM (2 x 10 mL). The organic phases were combined, dried (MgSO$_4$) and concentrated. Purification by column chromatography on silica gel using hexane:ethyl acetate (1:9) as eluent gave 4-ethylsulfanyl-3-fluoro-8-methyl-1,2,4b,9-tetraaza-fluorene 9h (134 mg, 50%) as orange crystals; mp 160.2 – 161.1 °C (Found: [MH]$^+$, 263.0760). C$_{12}$H$_{11}$FN$_4$S requires [MH]$^+$, 263.0767; δ$_H$ 1.37 (3H, t, $^3J_{HH}$ 7.3, CH$_3$CH$_2$S), 2.72 (3H, s, CH$_3$), 3.30 (2H, qd, $^3J_{HH}$ 7.3, $^5J_{HF}$ 0.9, CH$_2$), 6.89 (1H, dd, $^3J_{HH}$ 7.0, $^3J_{HH}$ 6.9, H-6), 7.42 (1H, d, $^3J_{HH}$ 6.9, H-7), 9.31 (1H, d, $^3J_{HH}$ 7.0, H-5); δ$_C$ 15.3 (s, CH$_3$CH$_2$S), 17.6 (s, CH$_3$), 29.5 (d, $^4J_{CF}$ 7.2, CH$_2$), 110.8 (d, $^2J_{CF}$ 39.4, C-4), 112.1 (s, C-7), 126.9 (s, C-5), 126.9 (d, $^3J_{CF}$ 7.9, C-4a), 129.3 (s, C-8), 131.5 (s, C-6), 154.1 (d, $^4J_{CF}$ 1.0, C-9a), 158.7 (s, C-8a), 160.7 (d, $^1J_{CF}$ 228.9, C-3); δ$_F$ -89.6 (s); m/z (EI$^+$) 262 ([M]+, 100%).

Crystal data for 9h: C$_{12}$H$_{11}$FN$_4$S, M = 262.31, monoclinic, space group P2$_1$/c, a = 3.9174(1), b = 16.8084(2), c = 17.1269(2) Å, α = 92.58(1)°, U = 1126.58(3) Å$^3$, F(000) = 544, Z = 4, D$_c$ = 1.547 mg m$^{-3}$, μ = 0.286 mm$^{-1}$. 15223 reflections were collected yielding 3149 unique data (R$_{merge}$ = 0.0487). Final wR$_2$(F$^2$) = 0.1154 for all data (207 refined parameters), conventional R$_1$(F) = 0.0340 for 2828 reflections with I≥2σ(I), GOF = 1.069. CCDC-1486845.

4-Ethylsulfanyl-3-fluoro-6-methyl-furo[2,3-c]pyridazine-5-carboxylic acid ethyl ester 9i
A mixture consisting of DIPEA (0.82 mL, 4.7 mmol), 3-oxo-butyric acid ethyl ester (0.17 mL, 1.3 mmol), 4-ethylsulfanyl-3,5,6-trifluoro-pyridazine 2k (234 mg, 1.21 mmol) and THF (4 mL) was heated at 180 °C (microwave) for 90 min. The mixture was concentrated, partitioned between DCM (10 mL)
and water (10 mL), the phases were separated and the aqueous phase further extracted with DCM (2 x 10 mL). The organic phases were combined, dried (MgSO₄) and concentrated. Purification by column chromatography on silica gel using hexane:ethyl acetate (2:1) as eluent gave 4-ethylsulfanyl-3-fluoro-6-methyl-furo[2,3-c]pyridazine-5-carboxylic acid ethyl ester 9i (95 mg, 28%) as a colourless oil; (Found: [MH]⁺, 285.0711. C₁₂H₁₃FN₂O₃S requires [MH]⁺, 285.0709); δH 1.29 (3H, t, 3JHH 7.4, SCH₂CH₃), 1.43 (3H, t, 3JHH 7.2, OCH₂CH₃), 2.77 (3H, s, CH₃), 3.18 (2H, qd, 3JHH 7.4, 5JHF 2.3, SCH₂), 4.43 (2H, q, 3JHH 7.2, OCH₂); δC 14.3 (s, CH₃), 14.9 (d, 4JCF 11.5, SCH₂), 61.8 (s, OCH₂), 111.0 (d, 3JCF 4.7, C-4a), 122.8 (d, 2JCF 34.8, C-4), 126.6 (d, 1JCF 6.6, C-7a), 161.7 (s, C-5), 162.1 (s, C-6), 162.9 (d, 1JCF 232.4, C-3), 168.3 (s, C=O); δF -84.97 (s); m/z (ES⁺) 285 ([MH]⁺, 100%).

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