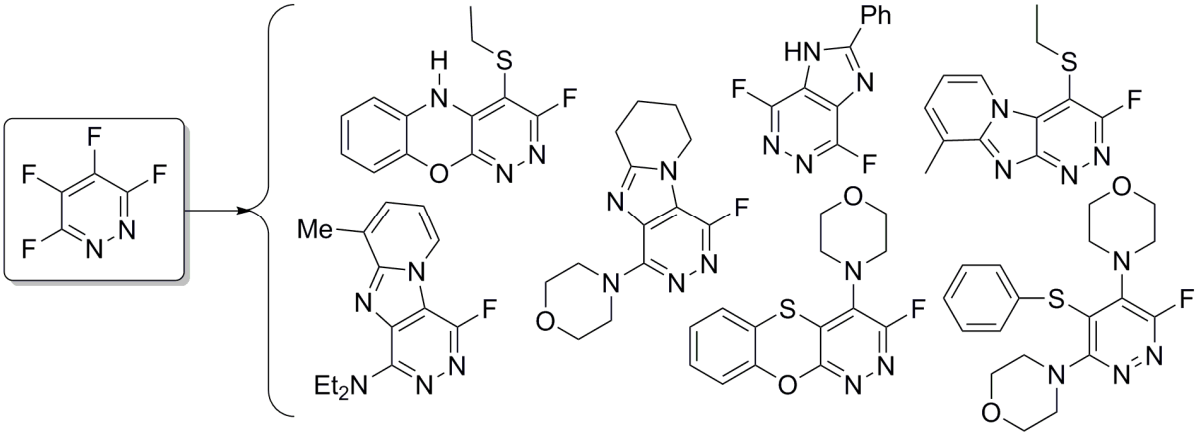

Polysubstituted and ring-fused pyridazine systems from tetrafluoropyridazine

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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 nucleophlic 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,[1] 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).[2] 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.

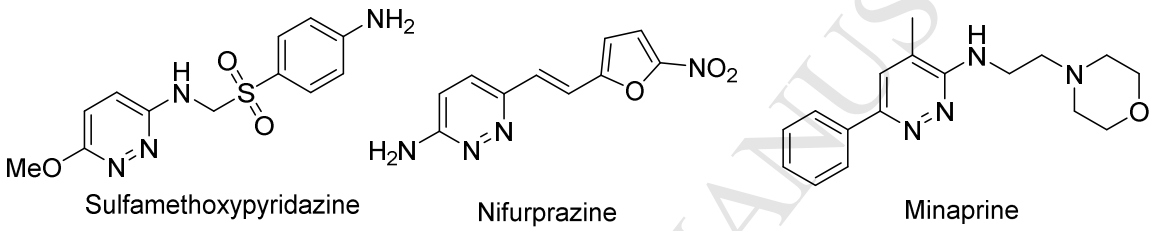


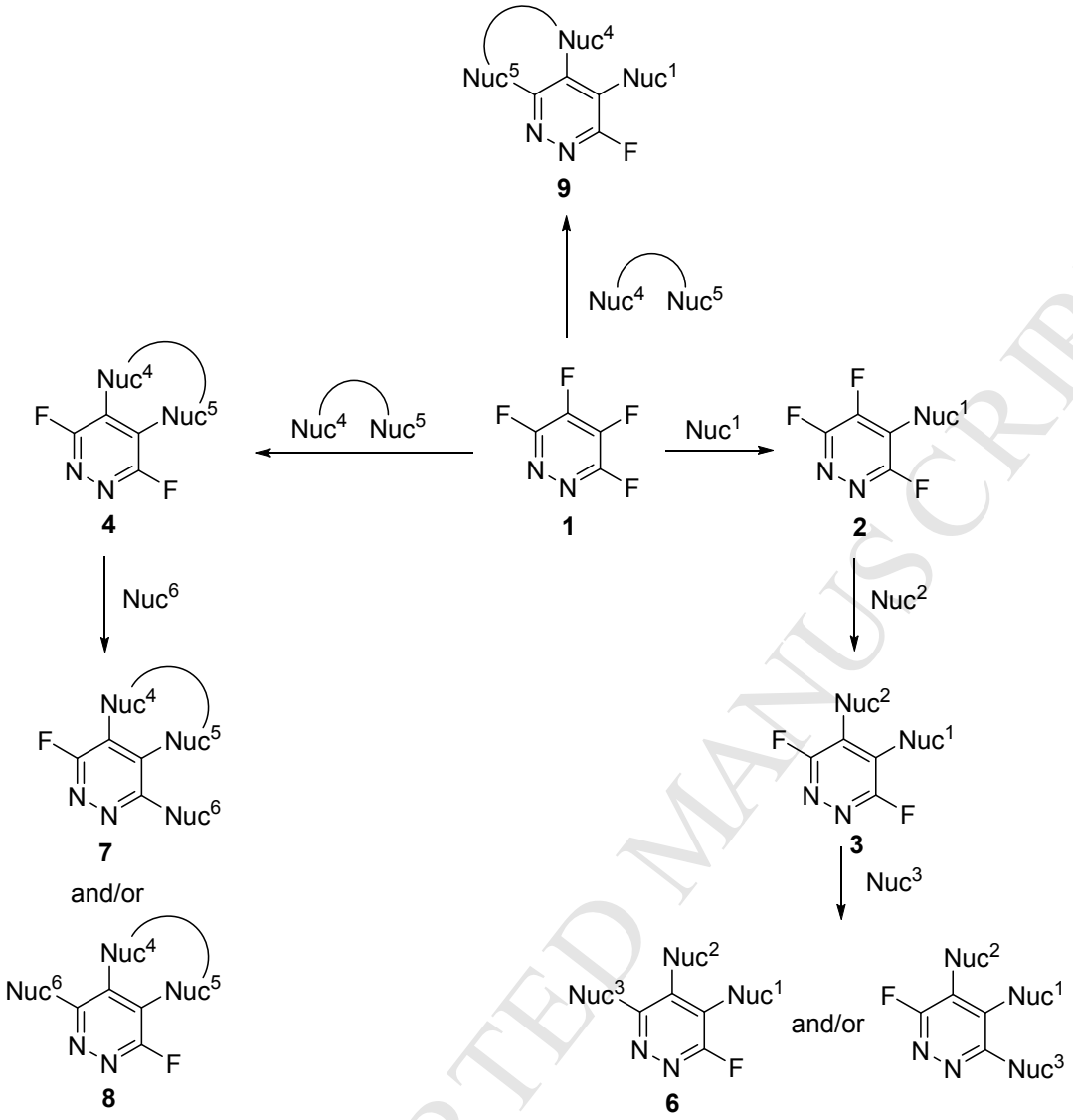
Figure 1 Pharmaceuticals containing pyridazine sub-units

In general, pyridazine systems can be constructed by either a variety of ring-forming processes or reactions of an appropriately functionalised pyridazine substrate.[3] 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[3a], reactions of 1,4-dicarbonyl compounds with hydrazine[3b-e] and Diels-Alder type [4+2] cycloaddition (Carboni-Lindsey reaction) between 1,2,4,5-tetrazine with either an alkene or alkyne substrate.[3f,g] 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[3h] or heteroaryl Grignard derivatives,[3i] palladium-catalyzed coupling of appropriate halogenated pyridazine derivatives[3j,k] such as Negishi[3l] or Suzuki cross coupling processes,[3m,n] or reaction of appropriate halogenated pyridazines by S_NAr processes.[3o-q] 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[4a-c] and imidopyrazine[4d] derivatives bearing functionality for further structural elaboration. Tetrafluoropyridazine **1** was first prepared some time ago[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[5,6] whereas polysubstitution processes, generally involving perfluoroalkylcarbanion nucleophiles,[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.



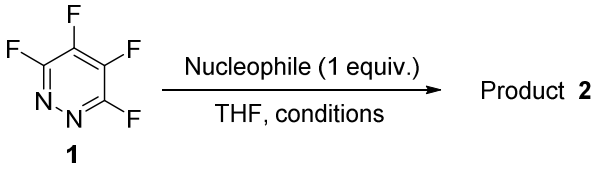
Scheme 1. General strategy for the synthesis of highly substituted and ring fused pyridazine derivatives from tetrafluoropyridazine **1**.

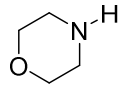
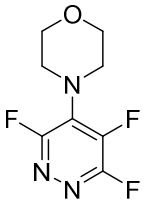
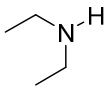
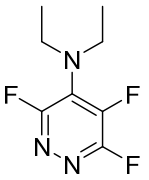
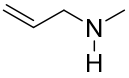
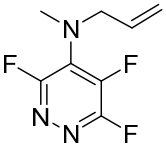
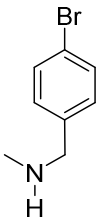
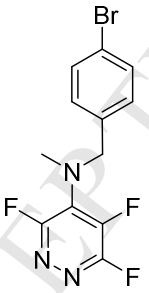
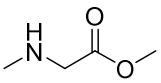
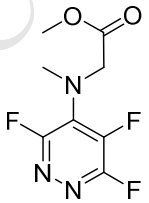
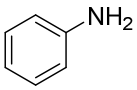
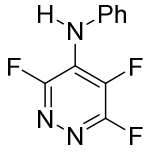
In this paper, we describe the synthesis of a range of polysubstituted, bi- and tri-cyclic ring fused pyridazine systems from tetrafluoropyridazine **1** which allows access to some multiply-substituted pyridazine derivatives and various very rare heterocyclic molecular frameworks by sequential S_NAr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

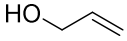
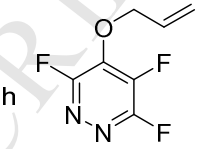
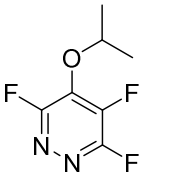
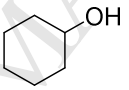
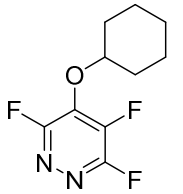
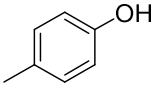
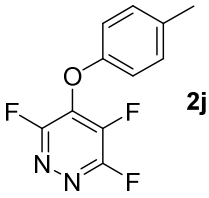
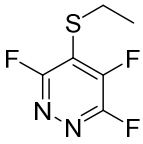
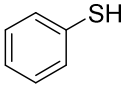
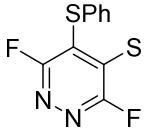
2. Results and discussion

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 ^{o}C or room temperature in the presence of the strong, non-nucleophilic organic base di-*iso*propylethyl amine (DIPEA) and using THF as the reaction medium.

Table 1. Reactions of tetrafluoropyridazine with monofunctional nucleophiles.



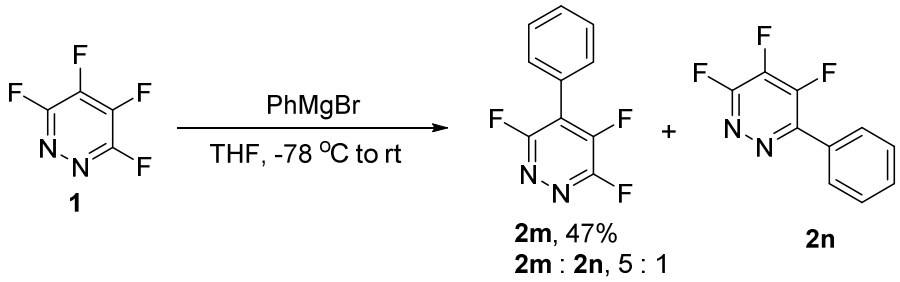
Nucleophile	Conditions	Product, Yield %
	DIPEA 0 °C,19 h	 **2a**, 81
	DIPEA 0 °C,19 h	 **2b**, 82
	DIPEA 0 °C, 4 h	 **2c**, 82
	DIPEA rt, 16 h	 **2d**, 65
	DIPEA rt, 3 d	 **2e**, 50
	DIPEA 0 °C, 2 h	 **2f**, 78

Nucleophile	Conditions	Product, Yield %
	DIPEA reflux, 11 h	 **2g**, 73
	DIPEA reflux, 11 h	 **2h**, 72
	DIPEA rt, 20 h	 **2i**, 63
	DIPEA rt, 6 d	 **2j**, 60
	DIPEA 0 °C,1 h	 **2k**, 65
 2 equiv.	DIPEA 0 °C,1 h	 **2l**, 77

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.[5,6] This site is the most activated position towards nucleophilic attack as it is *para* to the activating ring nitrogen and has two *ortho* and one *meta* activating fluorine atoms, following principles for processes involving highly reactive heterocycles.[5,8] The structures of the products **2a-k** followed from ^{19}F NMR analysis in which three resonances at *ca*. ‒80, ‒90 and ‒135 ppm were observed, where resonances occurring at *ca*. ‒90 ppm are indicative of fluorine located at sites *ortho* to ring nitrogen as is the case here.[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 ^{19}F NMR analysis of the reaction mixture. This reflects the strong *ortho* activating effect of the sulfur atom which makes the monosubstituted product more reactive towards nucleophiles than **1** itself.[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.

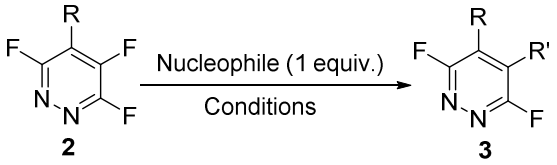
Reaction of **1** with phenylmagnesium bromide gave a mixture of two monosubstituted products **2m** and **2n** in a 5:1 ratio by ^{19}F NMR analysis of the crude reaction mixture, arising from substitution of the 4- and 3-positions respectively, from which the major product **2m** could be purified 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 *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.[11]

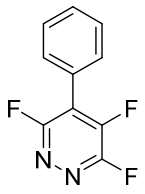
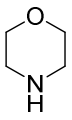
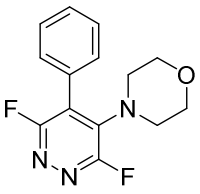
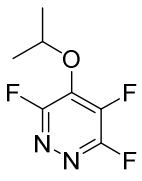
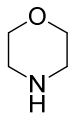
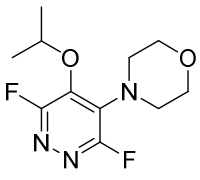
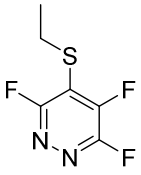
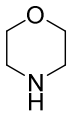
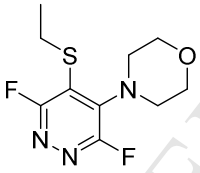
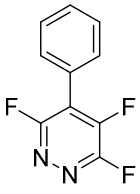
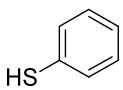
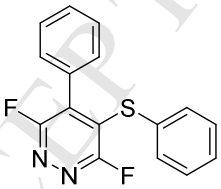
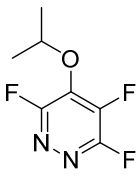
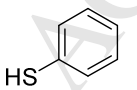
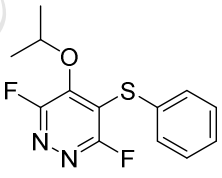


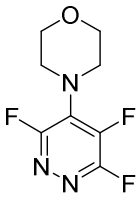
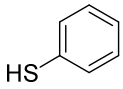
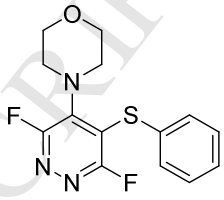
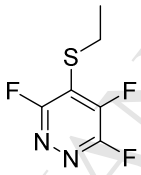
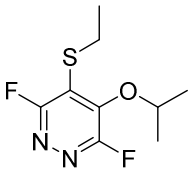
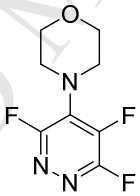
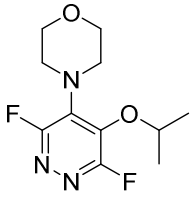
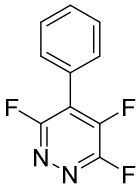
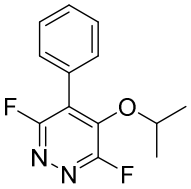
Scheme 2. Reaction of **1** with phenyl magnesium bromide

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



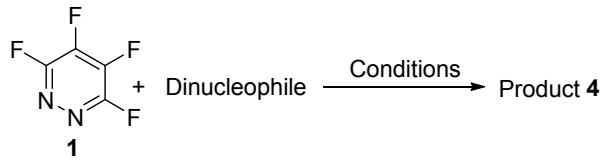
2	Conditions	Product, Yield %
 **2m**	 DIPEA, THF rt, 4 d	 **3a**, 32%
 **2h**	 DIPEA, THF rt, 4 d	 **3b**, 79%
 **2k**	 DIPEA, THF rt, 16 h	 **3c**, 73%
 **2m**	 DIPEA, THF 0 °C, 1 h	 **3d**, 88%
 **2h**	 DIPEA, THF 0 °C, 1 h	 **3e**, 33%

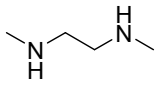
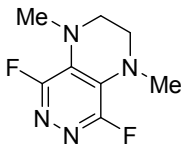
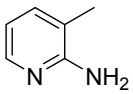
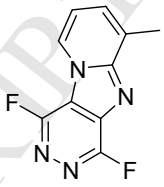
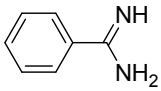
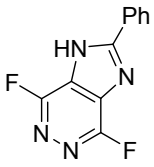
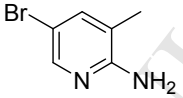
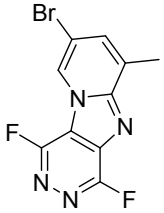
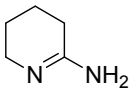
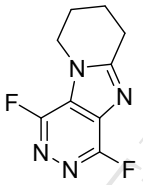
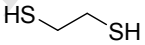
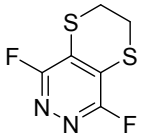
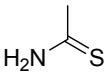
2	Conditions	Product, Yield %
 **2a**	 DIPEA, THF 0 °C, 1 h	 **3f**, 80%
 **2k**	LiO^{i}Pr, THF rt, 16 h	 **3g**, 78%
 **2a**	LiO^{i}Pr, THF rt, 16 h	 **3b**, 41%
 **2m**	LiO^{i}Pr, THF rt, 16 h	 **3h**, 69%

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 occuring 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_NAr reactions of **1** with difunctional nucleophiles. Initial nucleophilic attack on **1** at the 4-positon, 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**



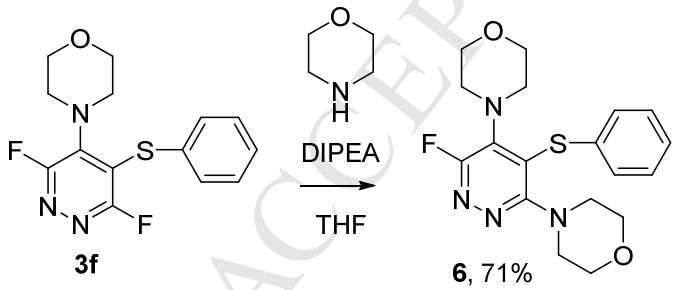
Nucleophile	Conditions	Product, Yield %	Nucleophile	Conditions	Product, Yield %
	$NaHCO_3$ MeCN rt, 4 h	 **4a,** 92%		MeCN MW, 150 °C, 10 min	 **4d**, 58%
	1) $NaHCO_3$, MeCN reflux, 3 d; 2) DIPEA, MeCN, MW, 180 °C, 15 min	 **4b**, 46%		MeCN MW, 150 °C, 10 min	 **4e**, 40%
	$NaHCO_3$ MeCN reflux, 16 h	 **4c**, 82%		$NaHCO_3$ MeCN rt, 2 h	 **4f**, 65%
				$NaHCO_3$ MeCN reflux, 16 h	 **4g**, 62%

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. Annelation 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**

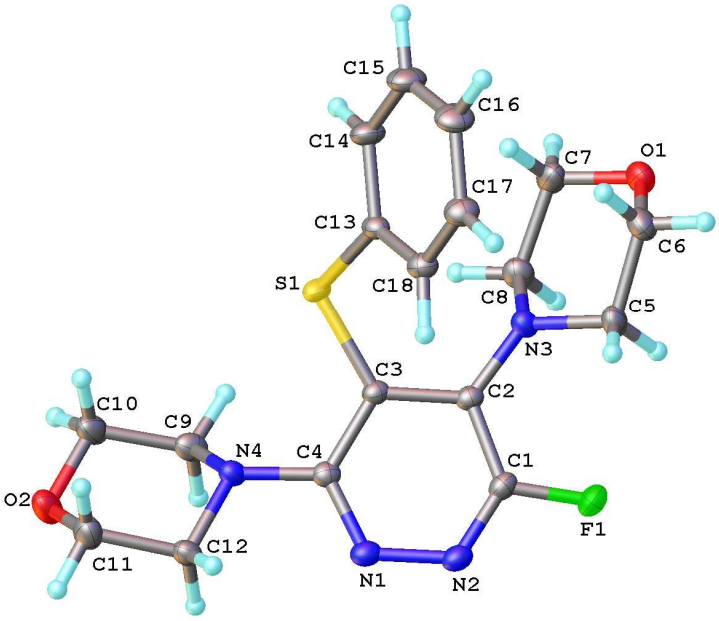
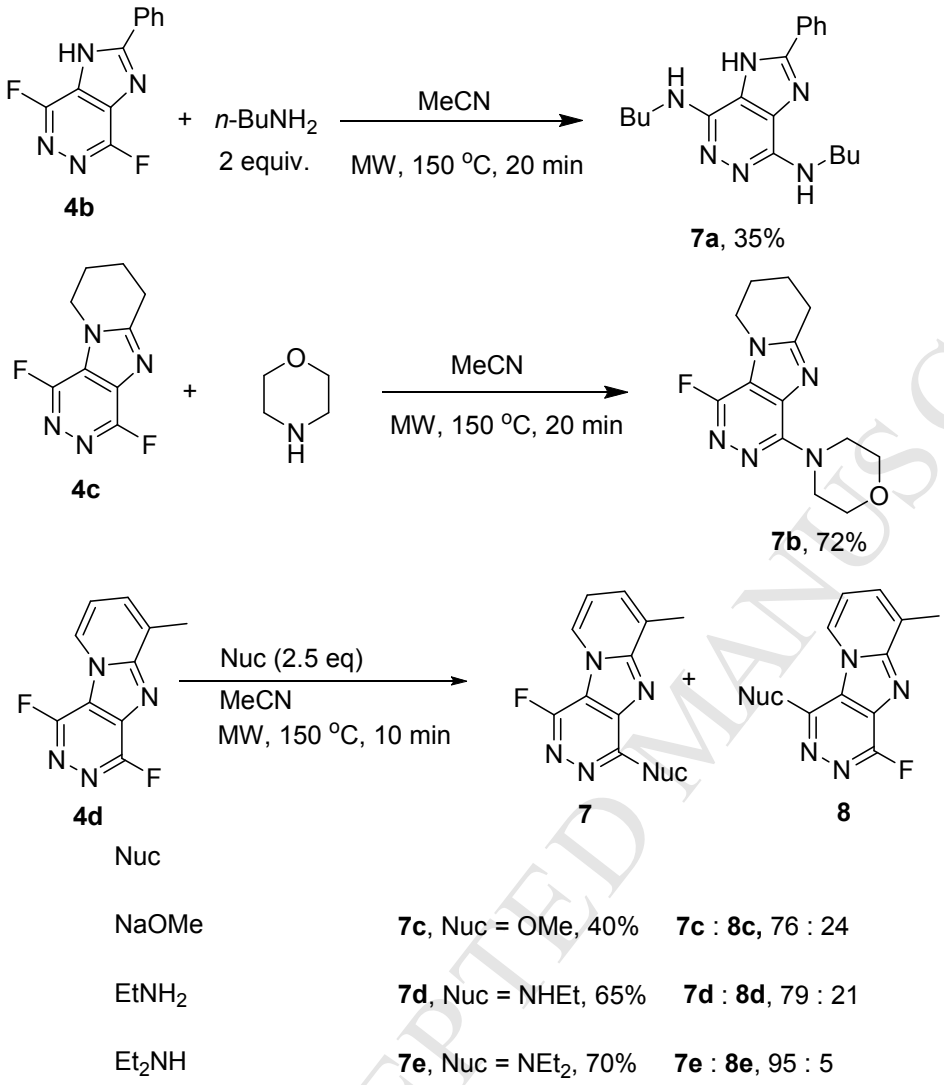


Figure 2. Molecular structure of trisubstituted derivative **6**

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



Nuc		
NaOMe	**7c**, Nuc = OMe, 40%	**7c** : **8c,** 76 : 24
$EtNH_2$	**7d**, Nuc = NHEt, 65%	**7d** : **8d**, 79 : 21
Et_2NH	**7e**, Nuc = NEt_2, 70%	**7e** : **8e**, 95 : 5

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).

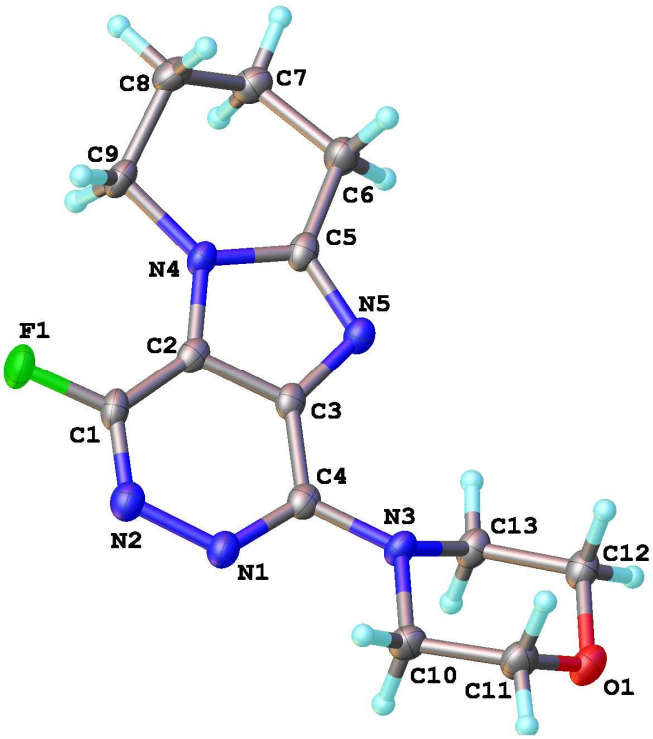
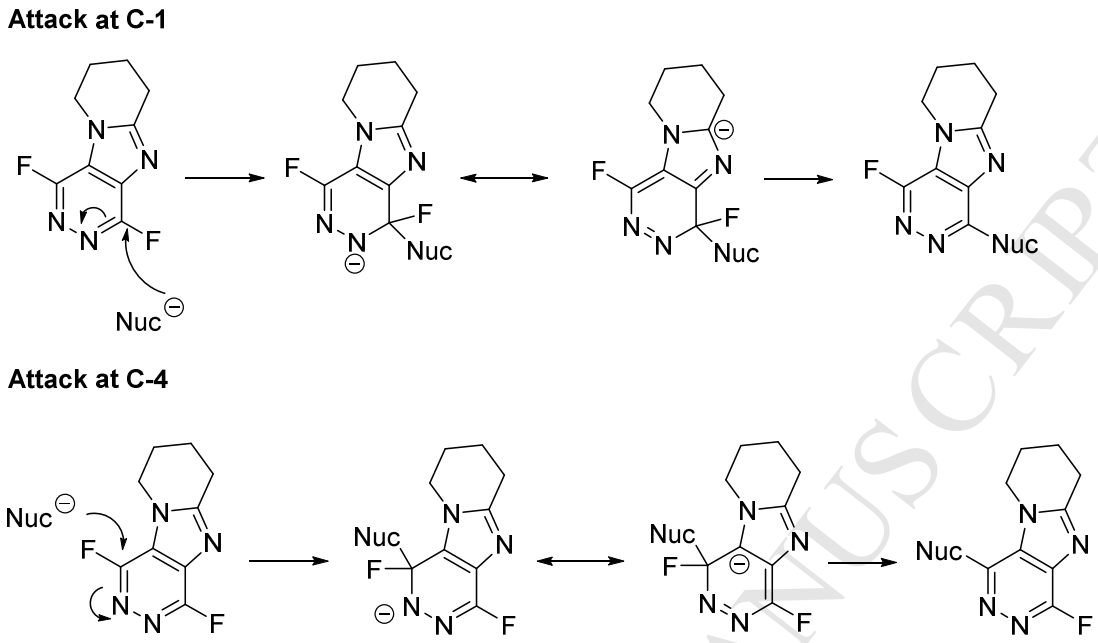


Figure 3. Molecular structure of **7b**

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**



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.

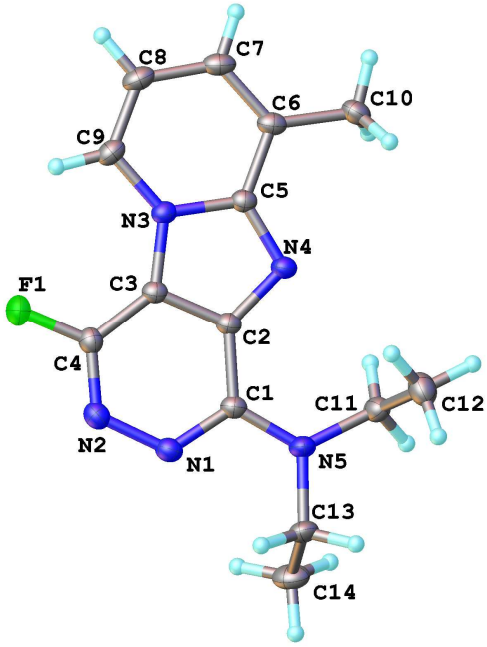
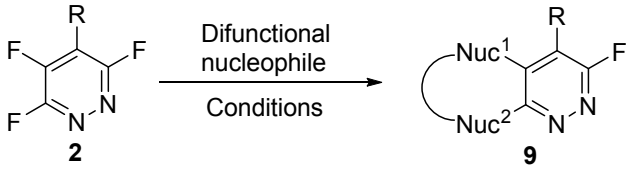
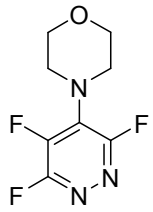
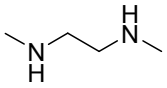
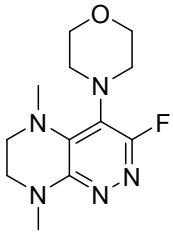
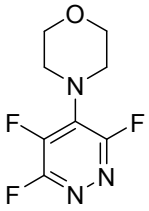
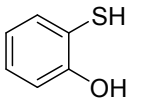
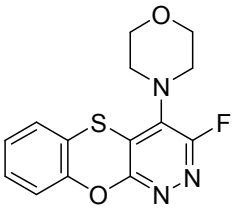
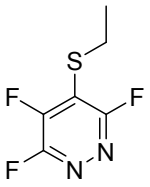
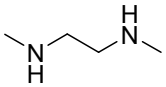
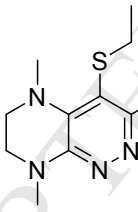
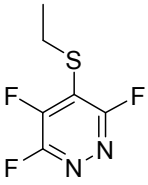
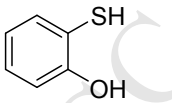
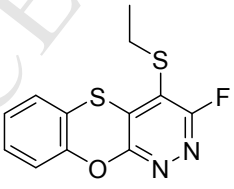


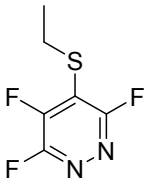
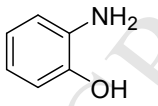
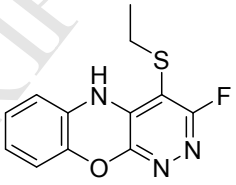
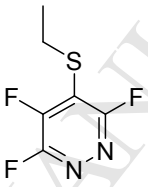
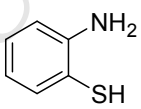
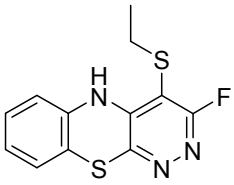
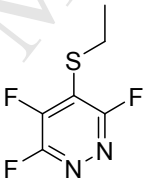
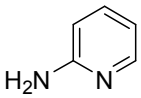
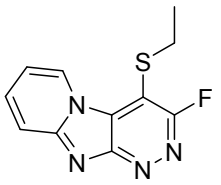
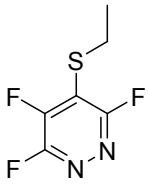
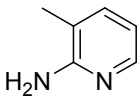
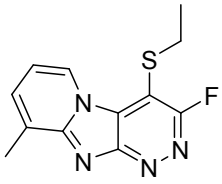
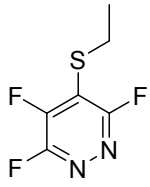
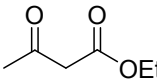
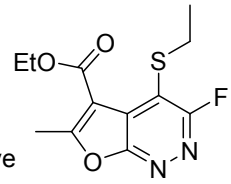
Figure 4. Molecular structure of **7e**

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



2	Conditions	Product, Yield %
 **2a**	 DIPEA, THF rt, 5 d	 **9a,** 84%
 **2a**	 DIPEA, THF rt, 16 h	 **9b,** 68%
 **2k**	 DIPEA, THF rt, 16 h	 **9c**, 77%
 **2k**	 DIPEA, THF rt, 16 h	 **9d,** 74%

2	Conditions	Product, Yield %
 **2k**	 DIPEA, THF 100 °C, microwave, 5 min	 **9e**, 75%
 **2k**	 DIPEA, THF 100 °C, microwave 30 min	 **9f**, 63%
 **2k**	 DIPEA, THF 150 °C, microwave 30 min	 **9g**, 14%
 **2k**	 DIPEA, THF rt, 7 d	 **9h**, 50%
 **2k**	 DIPEA, THF 180 °C, microwave 90 min	 **9i**, 28%

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.

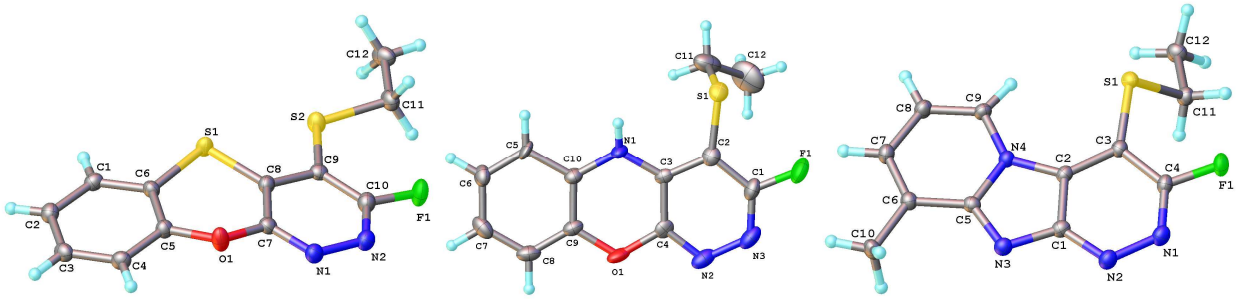


Figure 5. Molecular structures of **9d**, **9e** and **9h.**

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-aminobenzenethiol, 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

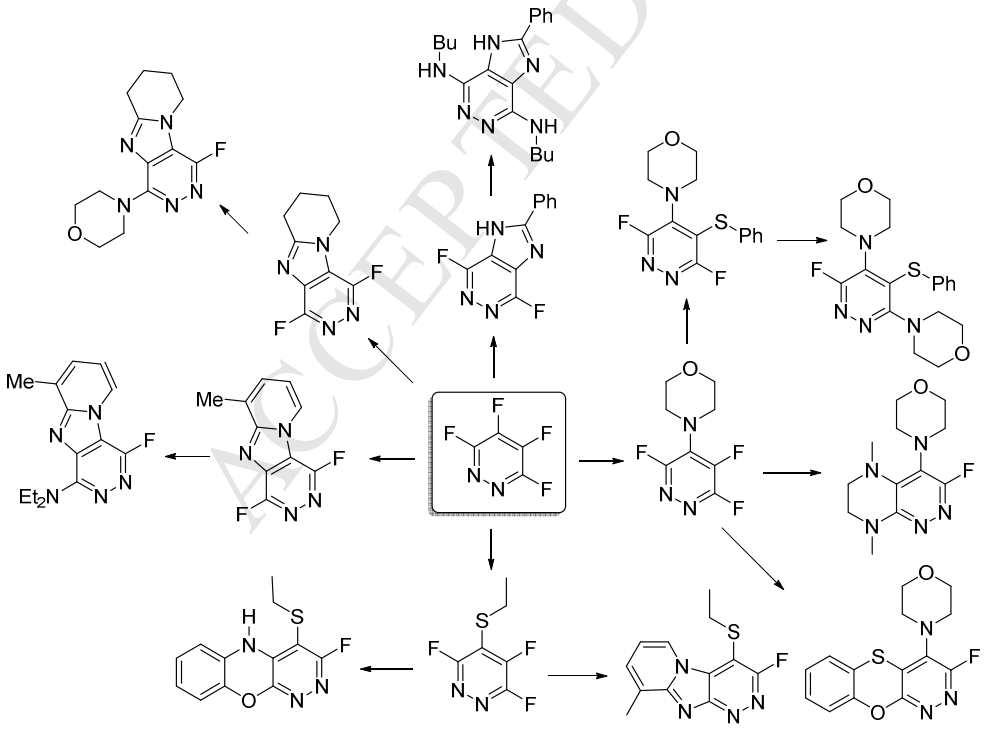
Tetrafluoropyridazine **1** may be used as a very effective scaffold for the synthesis of a range of 4,5-disubstituted pyridazine systems bearing oxygen, nitrogen, sulfur and carbon functionality. Further substitution of the difluorinated systems gave mixtures of trisubstituted pyridazine systems, processes

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, λMoKα, λ =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[19] and SHELXTL[20] software. All non-disordered non-hydrogen atoms were refined

anisotropically, hydrogen atoms were refined isotropically, the hydrogen atoms in the twinned structure 9e 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 ($MgSO_4$) 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. $C_8H_8F_3N_3O$ requires: $[MH]^+$, 220.06922); ν_{max}(film)/cm^{-1} 2970, 2902, 2860 and 1595; δ_H 3.54 (4 H, br s, CH_2N), 3.80 - 3.86 (4 H, m, CH_2O); δ_C 50.1 (t, $^4J_{CF}$ 4.4, CH_2N), 66.7 (s, CH_2O), 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); δ_F -143.8 – -143.4 (1F, m, F-5) -98.6 (1 F, dd, $^3J_{FF}$ 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. $C_8H_8F_3N_3O$ requires: 206.08996); ν_{max}(film)/cm^{-1} 2983, 2940 and 1587; δ_H 1.28 (6 H, t, $^3J_{HH}$ 7.1, CH_3), 3.47 (4 H, qt, $^3J_{HH}$

7.1, $^{5}J_{HF}$ 1.5, CH_2); δ_C 13.9 (s, CH_3), 46.8 (t, $^{4}J_{CF}$ 5.2, CH_2), 129.2 (dt, $^{2}J_{CF}$ 25.6, $^{3}J_{CF}$ 4.8, C-4), 137.9 (ddd, $^{1}J_{CF}$ 266.8, $^{2}J_{CF}$ 28.8, $^{3}J_{CF}$ 11.2, C-5), 157.0 (dd, $^{1}J_{CF}$ 238.1, $^{3}J_{CF}$ 2.4, C-3), 157.1 (dd, $^{1}J_{CF}$ 238.9, $^{2}J_{CF}$ 4.0, C-6); δ_F -146.8 (1 F, dd, $^{3}J_{FF}$ 27.5, $^{4}J_{FF}$ 25.2, F-5), -100.7 (1 F, dd, $^{4}J_{FF}$ 28.7, $^{5}J_{FF}$ 24.1, F-3), -81.4 (1 F, dd, $^{3}J_{FF}$ 28.7, $^{5}J_{FF}$ 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. $C_8H_8F_3N_3O$ requires: $[M]^+$, 204.07431); ν_{max}(film)/cm^{-1} 2908, 1644 and 1593; δ_H 3.14 (3 H, t, $^{5}J_{HF}$ 3.2, CH_3), 3.97 (2 H, d, $^{3}J_{HH}$ 5.9, CH_2), 5.29 (1 H, dd, $^{3}J_{HH}$ 16.9, $^{2}J_{HH}$ 1.2, *H*CH), 5.32 (1 H, dd, $^{3}J_{HH}$ 10.3, $^{2}J_{HH}$ 1.2, HC*H*), 5.82 - 5.94 (1 H, m, CH); δ_C 39.6 (t, $^{4}J_{CF}$ 5.6, CH_3), 57.3 (t, $^{4}J_{CF}$ 4.8, CH_2), 119.1 (s, $=CH_2$), 130.1 (dt, $^{2}J_{CF}$ 25. 6, $^{3}J_{CF}$ 4.8, C-4), 132.2 (s, CH), 138.4 (ddd, $^{1}J_{CF}$ 267.6, $^{2}J_{CF}$ 28.0, $^{3}J_{CF}$ 9.6, C-5), 157.0 (dd, $^{1}J_{CF}$ 239.7, $^{3}J_{CF}$ 12.8, C-3), 157.2 (dd, $^{1}J_{CF}$ 238.9, $^{2}J_{CF}$ 4.8, C-6); δ_F -145.6 (1 F, dd, $^{3}J_{FF}$ 27.5, $^{4}J_{FF}$ 27.5, F-5) -100.0 (1 F, dd, $^{4}J_{FF}$ 28.7, $^{5}J_{FF}$ 25.2, F-3) -80.9 (1 F, dd, $^{3}J_{FF}$ 28.7, $^{5}J_{FF}$ 28.7, F-6); *m/z* (ES^+) 204 ($[M]^+$, 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-methylmethanamine (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. $C_{12}H_9BrF_3N_3$ requires: C, 43.4; H, 2.7; N, 12.6%); ν_{max}(film)/cm^{-1} 2940, 1601, 1573 and 1560; δ_H 3.09 (3 H, dd, $^{5}J_{HF}$ 3.8, $^{5}J_{HF}$ 2.7, CH_3) 4.53 (2 H, s, CH_2) 7.15 (2 H, d, $^{3}J_{HH}$ 8.5, H_2C-C-C*H*) 7.49 (2 H, d, $^{3}J_{HH}$ 8.5 Hz, Br-C-C*H*); δ_C 40.0 (t, $^{4}J_{CF}$ 5.2, CH_3), 57.6 (t, $^{4}J_{CF}$ 4.8, CH_2), 121.9 (br s, C-Br), 129.0 (s, H_2C-C-*C*H), 130.2 (ddd, $^{2}J_{CF}$ 24.8, $^{2}J_{CF}$ 4.8, $^{3}J_{CF}$ 3.2, C-4), 132.0 (s, Br-C-*C*H), 134.9 (br s, H_2C-*C*), 139.0 (ddd, $^{1}J_{CF}$ 270.8, $^{2}J_{CF}$ 29.6, $^{3}J_{CF}$ 10.4, C-5), 156.9 (dd, $^{1}J_{CF}$ 240.5, $^{3}J_{CF}$ 11.9, C-6), 157.4 (dd, $^{1}J_{CF}$ 239.7, $^{2}J_{CF}$ 3.9, C-3); δ_F -144.3 (1 F, t, $^{3}J_{FF}$ 26.4, F-5) -99.4 (1 F, dd, $^{4}J_{FF}$ 27.5, $^{5}J_{FF}$ 25.2, F-3) -80.6 (1 F, dd, $^{3}J_{FF}$ 29.8, $^{5}J_{FF}$ 29.8, F-6); *m/z* (ES^+) 334.1 ($[MH]^+$, 100%).

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

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 rt 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. $C_8H_8F_3N_3O$ requires: C, 40.9; H, 3.4; N, 17.9%); ν_{max}(film)/cm^{-1} 2958, 1747 and 1597; δ_H 3.27 (3 H, dd, $^5J_{HF}$ 3.4, $^5J_{HF}$ 2.7, NCH_3), 3.81 (3 H, s, OCH_3), 4.14 (2 H, s, CH_2); δ_C 42.1 (t, $^4J_{CF}$ 5.6, NCH_3), 52.5 (s, OCH_3), 55.3 (dd, $^4J_{CF}$ 6.4, $^4J_{CF}$ 4.8, CH_2), 129.62 (ddd, $^2J_{CF}$ 25.6, $^2J_{CF}$ 4.8, $^3J_{CF}$ 3.2, C-4), 138.77 (ddd, $^1J_{CF}$ 269.2, $^2J_{CF}$ 28.8, $^3J_{CF}$ 9.6, C-5), 156.9 (d, $^1J_{CF}$ 240.0, C-3), 157.0 (dd, $^1J_{CF}$ 238.9, $^2J_{CF}$ 3. 9, C-6), 169.3 (s, C=O); δ_F -144.6 (1 F, t, $^3J_{FF}$ 26.4, F-5), -99.3 (1 F, dd, $^4J_{FF}$ 28.7, $^5J_{FF}$ 24.09, F-3), -81.0 (1 F, t, $^3J_{FF}$ 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. $C_{10}H_6F_3N_3$ requires: C, 53.3; H, 2.7; N, 18.7%); δ_H 6.47 (1 H, br. s, NH), 7.15 – 7.40 (5 H, m, ArH); δ_C 122.7 (d, $^5J_{CF}$ 2.6, C-2'), 124.2 – 124.3 (m, C-4), 126.5 (s, C-4'), 129.4 (s, C-3'), 136.5 (ddd, $^1J_{CF}$ 272.3, $^2J_{CF}$ 29.9, $^3J_{CF}$ 6.9, C-5), 137.1 (s, C-1'), 156.8 (dd, $^1J_{CF}$ 238.2, $^2J_{CF}$ 3.3, C-6), 156.9 (d, $^1J_{CF}$ 237.7, C-3); δ_F -141.5 (1 F, dd, $^4J_{FF}$ 25.4, $^3J_{FF}$ 24.5, F-5), -98.9 (1 F, dd, $^5J_{FF}$ 29.5, $^3J_{FF}$ 24.5, F-6), -89.0 (1 F, dd, $^5J_{FF}$ 29.5, $^3J_{FF}$ 25.4, F-3); *m/z* (ES$^+$) 224.9 ([MH]$^+$, 100%).

3,4,6-Trifluoro-5-(2-propen-1-yloxy)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-yloxy)pyridazine* **2g** (716 mg, 73%) as a colourless oil; (Found: [MH]$^+$, 191.04277. $C_7H_5F_3N_2O$ requires: [MH]$^+$, 191.04267); ν_{max}/cm^{-1} 2898, 1648 and 1611; δ_H 5.03 (2 H, dd, $^3J_{HH}$ 6.0, $^5J_{HF}$ 0.9, O-CH_2), 5.44 (1 H, dd, $^3J_{HH}$ 10.5, $^2J_{HH}$ 1.0, CH*H*), 5.51 (1 H, dd, $^3J_{HH}$ 16.9, $^2J_{HH}$ 0.97, C*H*H), 5.96 - 6.09 (1H, m, CH); δ_C 74.6 (dd, $^4J_{CF}$ 5.6, $^3J_{CF}$ 1.6, O-CH_2), 121.4 (s, CH_2), 130.5 (s, CH), 136.0 - 136.4 (m, C-5), 140.1 (ddd, $^1J_{CF}$ 277.2, $^2J_{CF}$ 28.8, $^3J_{CF}$ 7.9, C-4), 156.7 (ddd, $^1J_{CF}$ 242.0, $^3J_{CF}$ 11.2, $^4J_{CF}$ 1.6, C-6), 158.7 (d, $^1J_{CF}$ 242.9, C-3); δ_F -146.6 (1 F, dd, $^3J_{FF}$ 25.2, $^5J_{FF}$ 25.2, F-4), -95.8 (1 F, dd, $^4J_{FF}$ 29.8, $^5J_{FF}$ 26.4, F-6), -87.6 (1 F, dd, $^3J_{FF}$ 27.5, $^5J_{FF}$ 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), *iso*propanol (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. $C_7H_7F_3N_2O$ requires: $[MH]^+$, 193.05832); ν_{max}/cm^{-1} 2990, 2941 and 1608; δ_H 1.47 (6 H, dd, $^3J_{HH}$ 6.1, $^6J_{HF}$ 0.8, CH_3), 5.02 - 5.14 (1 H, m, CH); δ_C 22.5 (s, CH_3), 78.8 (d, $^4J_{CF}$ 4.0, CH), 136.0 - 136.2 (m, C-5), 140.0 (ddd, $^1J_{CF}$ 275.8, $^2J_{CF}$ 28.6, $^3J_{CF}$ 7.8, C-4), 156.7 (ddd, $^1J_{CF}$ 239.7, $^3J_{CF}$ 11.2, $^4J_{CF}$ 1.6, C-6), 159.1 (ddd, $^1J_{CF}$ 246.1, $^2J_{CF}$ 8.8, $^4J_{CF}$ 2.4, C-3); δ_F -147.0 (1 F, dd, $^3J_{FF}$ 25.2, $^4J_{FF}$ 25.2, F-4) -96.1 (1 F, dd, $^4J_{FF}$ 28.7, $^5J_{FF}$ 26.4, F-6) -87.9 (1 F, dd, $^3J_{FF}$ 28.7, $^5J_{FF}$ 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. $C_{10}H_{11}F_3N_2O$ 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, CH_2), 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, $^4J_{CF}$ 3.4, C-1'), 135.8 - 136.0 (m, C-4), 140.2 (ddd, $^1J_{CF}$ 275.6, $^2J_{CF}$ 27.9, $^4J_{CF}$ 7.9, C-5), 156.7 (ddd, $^1J_{CF}$ 242.0, $^3J_{CF}$ 11.1, $^4J_{CF}$ 1.6, C-3), 159.3 (dd, $^1J_{CF}$ 244.4, $^2J_{CF}$ 2.4, C-6); δ_F -146.3 (1 F, dd, $^3J_{FF}$ 26.4, $^4J_{FF}$ 26.4, F-5), -95.8 (1 F, dd, $^4J_{FF}$ 29.8, $^5J_{FF}$ 26.4, F-3), -87.5 (1 F, dd, $^3J_{FF}$ 28.7, $^5J_{FF}$ 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. $C_{11}H_7F_3N_2O$ 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, CH_3), 6.97 (2 H, d, $^3J_{HH}$ 8.7, O-C-C*H*), 7.21 (2 H, dd, $^3J_{HH}$ 8.7, $^4J_{HH}$ 0.7, H_3C-C-C*H*); δ_C 20.7 (s, CH_3), 116.9 (s, O-C-*C*H), 130.5 (s, H_3C-C-*C*H), 134.5 - 134.7 (m, C-5), 135.7 (s, H_3C-*C*), 141.8 (ddd, $^1J_{CF}$ 282.8, $^2J_{CF}$ 27.9, $^3J_{CF}$ 7.1, C-4), 153.0 (s, O-*C*), 156.7 (ddd, $^1J_{CF}$ 243.6, $^2J_{CF}$ 9.9, $^4J_{CF}$ 2.3, C-3), 159.2 (d, $^1J_{CF}$ 246.8, C-6); δ_F -140.4 (1 F, dd, $^3J_{FF}$ 24.1, $^4J_{FF}$ 24.1, F-4), -94.0 (1 F, dd, $^4J_{FF}$ 31.0, $^5J_{FF}$ 24.1, F-6), -85.5 (1 F, dd, $^3J_{FF}$ 29.8, $^5J_{FF}$ 24.1, F-3); *m/z* (ES^+) 241.2 ($[MH]^+$, 100%).

4-(Ethylthio)-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; δ_H 3.27 (2 H, qt, $^3J_{HH}$ 7.4, $^5J_{HF}$ 1.1, CH_2), 1.40 (3 H, t, $^3J_{HH}$ 7.4, CH_3); δ_F -74.6 (1F, dd, $^3J_{FF}$ 30.2, $^4J_{FF}$ 21.0, F-5), -99.4 (1 F, dd, $^3J_{FF}$ 30.2, $^5J_{FF}$ 26.4, F-6), -124.8 (1 F, dd, $^5J_{FF}$ 26.4, $^4J_{FF}$ 21.0, F-3); *m/z* (AP^+) 195.0210 ($C_6H_6N_2F_3S$ 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. $C_{16}H_{10}F_2N_2S_2$ requires: C, 57.8; H, 3.0; N, 8.4%); ν_{max}/cm^{-1} 1578, 1500 and 1377; δ_H 7.34 - 7.47 (10 H, m, CH); δ_C 129.3 (s, C-4'), 129.6 (s, C-3'), 130.2 (s, C-1'), 132.2 (s, C-2'), 133.6 (dd, $^2J_{CF}$ 17.5, $^3J_{CF}$ 15.9, C-4), 162.6 (dd, $^1J_{CF}$ 249.2, $^4J_{CF}$ 6.3, C-3); δ_F -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. $C_{10}H_5F_3N_2$ requires: C, 57.1; H, 2.4; N, 13.3%); ν_{max}/cm^{-1} 1580, 1558, 1458 and 1445; δ_H 7.56 - 7.62 (5 H, m, CH); δ_C 121.2 (ddd, $^2J_{CF}$ 31.9, $^2J_{CF}$ 8.7, $^3J_{CF}$ 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, $^1J_{CF}$ 281.2, $^2J_{CF}$ 27.1, $^3J_{CF}$ 7.9, C-4), 156.5 (ddd, $^1J_{CF}$ 243.6, $^3J_{CF}$ 12.7, $^4J_{CF}$ 2.4, C-6), 162.30 (d, $^1J_{CF}$ 245.2, C-3); δ_F -129.3 (1 F, dd, $^3J_{FF}$ 26.4, $^4J_{FF}$ 21.8, F-4), -97.6 (1 F, dd, $^5J_{FF}$ 31.0, $^3J_{FF}$ 26.4, F-3), -79.6 (1 F, dd, $^5J_{FF}$ 31.0, $^4J_{FF}$ 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 approprite. 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 ($MgSO_4$). 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. $C_{10}H_5F_3N_2$ requires: C, 60.6; H, 4.7; N, 15.1%); ν_{max}/cm^{-1} 2977, 2857 and 1543; δ_H 3.04 (4 H, td, $^3J_{HH}$ 4.7, $^5J_{HF}$ 1.6, NCH_2), 3.61 (4 H, dd, $^3J_{HH}$ 4.8, $^3J_{HH}$ 4.6, OCH_2), 7.31 - 7.38 (2 H, m, CH), 7.42 - 7.57 (3 H, m, CH); δ_C 50.5 (d, $^4J_{CF}$ 4.8, NCH_2), 66.5 (s, OCH_2), 120.2 (dd, $^2J_{CF}$ 31.2, $^3J_{CF}$ 6.4, C-5), 128.9 (s, C-2'), 129.4 (s, C-3'), 129.5 (br s, C-4'), 129.6 (t, $^3J_{CF}$ 2.4, C-1'), 139.2 (dd, $^2J_{CF}$ 22.4, $^3J_{CF}$ 6.4, C-4), 159.3 (d, $^1J_{CF}$ 240.5, C-3), 163.3 (d, $^1J_{CF}$ 239.7, C-6); δ_F -86.9 (1 F, d, $^5J_{FF}$ 31.6, F-3), -84.0 (1 F, d, $^5J_{FF}$ 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. $C_{11}H_{15}F_2N_3O_2$ requires: $[MH]^+$, 260.12051); ν_{max}/cm^{-1} 2980, 2861, 1566; δ_H 1.33 (6 H, d, $^3J_{HH}$ 6.2, CH_3), 3.39 (4 H, dd, $^3J_{HH}$ 4.4, $^5J_{HF}$ 3.3, NCH_2), 3.76 (4 H, t, $^3J_{HH}$ 4.4, OCH_2), 4.63 - 4.76 (1 H, m, $^3J_{HH}$ 6.2, $^5J_{HF}$ 1.4, CH); δ_C 22.3 (s, CH_3), 50.4 (d, $^4J_{CF}$ 4.8, NCH_2), 66.9 (s, OCH_2), 77.1 (d, $^4J_{CF}$ 5.6, CH), 133.2 (dd, $^2J_{CF}$ 23.2, $^3J_{CF}$ 8.0, C-4), 137.0 (dd, $^2J_{CF}$ 24.8, $^3J_{CF}$ 8.8, C-5), 159.5 (d, $^1J_{CF}$ 239.7, C-3), 160.4 (d, $^1J_{CF}$ 240.5, C-6); δ_F -93.2 (1 F, d, $^5J_{FF}$ 29.8, F-6), -86.2 (1 F, d, $^5J_{FF}$ 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. $C_{10}H_{13}F_2N_3OS$ 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, td, $^3J_{HH}$ 7.4, $^6J_{HF}$ 0.5, CH_3), 3.09 (2 H, qd, $^3J_{HH}$ 7.4, $^5J_{HF}$ 1.6, SCH_2), 3.41 (4 H, td, $^3J_{HH}$ 4.7, $^5J_{HF}$ 2.3, NCH_2), 3.84 (4 H, t, $^3J_{HH}$ 4.7, OCH_2); δ_C 14.9 (d, $^5J_{CF}$ 0.9, CH_3), 28.5 (d, $^4J_{CF}$ 8.9, SCH_2), 51.0 (d, $^4J_{CF}$ 4.6, NCH_2), 67.1 (d, $^5J_{CF}$ 1.5, OCH_2), 121.3 (dd, $^2J_{CF}$ 32.6, $^3J_{CF}$ 6.8, C-4), 140.9 (dd, $^2J_{CF}$ 23.4, $^3J_{CF}$ 7.1, C-5), 159.5 (dd, $^1J_{CF}$ 243.2, $^4J_{CF}$ 1.5, C-6), 164.7 (d, $^1J_{CF}$ 237.9, C-3); δ_F -88.4 (1 F, d, $^5J_{FF}$ 31.2, F-3), -78.5 (1 F, d, $^5J_{FF}$ 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. $C_{16}H_{10}F_2N_2S_2$ 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, $^3J_{CF}$ 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, $^4J_{CF}$ 2.4, C-1''), 132.0 (s, C-2''), 132.4 (dd, $^2J_{CF}$ 29.6, $^3J_{CF}$ 4.0, C-4), 134.5 (dd, $^2J_{CF}$ 31.2, $^3J_{CF}$ 3.2, C-5), 162.1 (d, $^1J_{CF}$ 245.3, C-6), 163.3 (d, $^1J_{CF}$ 244.5, C-3); δ_F -83.3 (1 F, d, $^5J_{FF}$ 31.0, F-3), -75.3 (1 F, d, $^5J_{FF}$ 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. $C_{13}H_{12}F_2N_2OS$ requires: $[MH]^+$, 283.07112); ν_{max}/cm^{-1} 2985, 1581 and 1544; δ_H 1.26 (6 H, dd, $^3J_{HH}$ 6.1, $^6J_{HF}$ 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, $^5J_{CF}$ 8.0, CH), 121.1 (dd, $^2J_{CF}$ 32.0, $^3J_{CF}$ 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, $^2J_{CF}$ 24.0, $^3J_{CF}$ 6.4, C-4), 157.8 (d, $^1J_{CF}$ 241.3, C-6), 163.8 (d, $^1J_{CF}$ 240.5, C-3); δ_F -92.1 (1 F, d, $^5J_{FF}$ 31.6, F-3), -76.5 (1 F, d, $^5J_{FF}$ 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. $C_{14}H_{13}F_2N_3OS$ 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, $^3J_{HH}$ 4.7, $^5J_{HF}$ 2.1, NCH_2), 3.70 (4 H, dd, $^3J_{HH}$ 4.7, $^3J_{HH}$ 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, $^4J_{CF}$ 4.8, NCH_2), 66.8 (s, OCH_2), 116.3 (dd, $^2J_{CF}$ 32.0, $^3J_{CF}$ 5.6, C-4), 128.0 (s), 129.0 (s), 129.5 (s), 131.9 (s), 141.4 (dd, $^2J_{CF}$ 23.2, $^3J_{CF}$ 4.8, C-5), 159.0 (d, $^1J_{CF}$ 243.7, C-6), 164.9 (d, $^1J_{CF}$ 239.7, C-3); δ_F -86.2 (1 F, d, $^5J_{FF}$ 31.0, F-3), -76.0 (1 F, d, $^5J_{FF}$ 31.0, 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.

$C_9H_{12}F_2N_2OS$ requires: C, 46.1; H, 5.2; N, 12.0%); δ_H 1.31 (3 H, t, $^3J_{HH}$ 7.4, CH_2CH_3), 1.42 (6 H, d, $^3J_{HH}$ 5.9, $CHCH_3$), 3.16 (2 H, qd, $^3J_{HH}$ 7.4, $^5J_{HF}$ 1.3, CH_2), 4.99 (1 H, hept d, $^3J_{HH}$ 5.9, $^5J_{HF}$ 1.3, CH); δ_C 15.1 (s, CH_2CH_3), 22.8 (s, $CHCH_3$), 27.3 (d, $^4J_{CF}$ 7.1, CH_2), 78.7 (d, $^4J_{CF}$ 7.2, CH), 123.3 (dd, $^2J_{CF}$ 32.8, $^3J_{CF}$ 6.6, C-4), 146.8 (dd, $^2J_{CF}$ 24.4, $^3J_{CF}$ 7.8, C-5), 158.2 (dd, $^1J_{CF}$ 242.4, $^4J_{CF}$ 2.1, C-3), 164.0 (d, $^1J_{CF}$ 238.4, C-6); δ_F -93.8 (1 F, d, $^5J_{FF}$ 31.1, F-6), -78.7 (1 F, d, $^5J_{FF}$ 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; δ_H 1.22 (6 H, dd, $^3J_{HH}$ 6.1, $^6J_{HF}$ 0.6, CH_3), 4.65 - 4.77 (1 H, m, CH), 7.49 - 7.52 (5 H, m, ArH); δ_F -92.3 (1 F, d, $^5J_{FF}$ 32.1, F-3), -83.0 (1 F, d, $^5J_{FF}$ 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 ($MgSO_4$), 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 ^oC (Found: C, 47.9; H, 5.0; N, 27.8. $C_8H_{10}N_4F_2$ requires: C, 48.0; H, 5.0; N, 28.0%); ν_{max} / cm^{-1} 1092, 1159, 1251, 1343, 1410, 1557, 2900 (br); δ_H 3.05 (6H, br s, CH_3), 3.20 (4H, br s, CH_2); δ_C 42.2 (s, CH_3), 48.4 (s, CH_2), 125.8 (dd, $^2J_{CF}$ 16.7, $^3J_{CF}$ 16.7, C-4a), 156.2 (dd, $^1J_{CF}$ 235.2, $^4J_{CF}$ 3.8, C-5); δ_F -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, 4.35mmol), 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 ($MgSO_4$), 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 ^oC (Found: $[MH]^+$, 253.06956. $C_{11}H_7F_3N_4$ requires: $[MH]^+$, 253.06956); δ_H (DMSO-d_6) 7.6 – 7.9 (5H, m, Ar-H), 8.08 (1H, br s, NH); δ_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); δ_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 ^oC for 60 min. Water (25 mL) was added and the mixture was extracted with dichloromethane (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$), 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 ^oC (decomp.) (Found: $[MH]^+$, 233.06326. $C_{11}H_6F_2N_4$ requires: $[MH]^+$, 233.06333); δ_H (DMSO-d_6) 7.5 – 7.7 (3H, m, ArH), 8.1 – 8.3 (2H, m, ArH); δ_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); δ_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

($MgSO_4$), 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 ^oC (Found: C, 51.0; H, 3.9; N, 26.7. $C_9H_8N_4F_2$ requires: C, 51.4; H, 3.8; N, 26.4%); δ_H 2.0 – 2.1 (2H, m, CH_2), 2.1 – 2.2 (2H, m, CH_2), 3.1 – 3.2 (2H, m, H-8), 4.3 – 4.4 (2H, m, H-5); δ_C 19.7 (s, CH_2), 22.2 (s, CH_2), 25.6 (s, CH_2), 45.9 (s, C-5), 125.1 (dd, $^2J_{CF}$ 28.0, $^3J_{CF}$ 11.7, C-4a), 133.5 (dd, $^2J_{CF}$ 32.9, $^3J_{CF}$ 6.5, C-9a), 153.4 (d, $^1J_{CF}$ 237.6, C-4), 157.6 (d, $^1J_{CF}$ 244.4, C-1), 157.7 (s, C-8a); δ_F -92.6 (1F, d, $^5J_{FF}$ 32.9), -94.6 (1F, d, $^5J_{FF}$ 32.9); *m/z* (EI^+) 210 ($[M]^+$, 100%), 209 ($[M\text{-}H]^+$, 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^{o}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 ($MgSO_4$), 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 ^oC (Found: $[MH]^+$, 221.06339. $C_{10}H_6N_4F_2$ requires: $[MH]^+$, 221.06333); ν_{max} / cm^{-1} 1580, 1433, 1379, 1309, 1281, 1256, 1228, 1165, 1102, 1024, 976; δ_H 2.79 (3H, s, CH_3), 7.21 (1H, t, $^3J_{HH}$ 7.2, H-6), 7.59 (1H, d, $^3J_{HH}$ 7.2, H-7), 8.63 (1H, d, $^3J_{HH}$ 7.2, H-5); δ_C 17.7 (s, CH_3), 115.6 (s, C-6), 119.0 (dd, $^2J_{CF}$ 26.9, $^3J_{CF}$ 11.6, C-4a), 125.6 (d, $^4J_{CF}$ 4.9, C-5), 130.1 (s, C-8), 131.8 (s, C-7), 135.3 (dd, $^2J_{CF}$ 35.1, $^3J_{CF}$ 6.2, C-9a), 151.9 (s, C-8a), 154.0 (dd, $^1J_{CF}$ 238.6, $^4J_{CF}$ 2.4, C-4), 158.2 (dd, $^1J_{CF}$ 246.9, $^4J_{CF}$ 3.5, C-1); δ_F -89.7 (1F, d, $^5J_{FF}$ 34.6, F-1), -91.6 (1F, d, $^5J_{FF}$ 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 ^{o}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 ($MgSO_4$), 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 ^{o}C (Found: C, 40.2; H, 2.0; N, 18.5. $C_{10}H_6N_4F_2$ requires: C, 40.2; H, 1.7; N, 18.7%); ν_{max} / cm^{-1} 996, 1028, 1106, 1159, 1247,

1279, 1310, 1326, 1413, 1433, 1470, 1558; δ_H 2.78 (3H, s, CH_3), 7.66 (1H, s, H-7), 8.73 (1H, s, H-5); δ_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); δ_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 o 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** (0.29g, 85%) as a white solid; mp 123 – 125^{o}C; δ_H 3.41 (4H, s, CH_2); δ_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); δ_F -84.8 (s); *m/z* (EI^+) 206 (88%, M^+), 191 (100), 178 (19, $[M\text{-}N_2]^+$), 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** (0.76g, 62%) as a yellow solid; mp > 250 ^{o}C; δ_H

(DMSO-d_6) 3.00 (3H, s, CH_3); δ_C 20.7 (s, CH_3), 129.4 (dd, $^2J_{CF}$ 38.8, $^3J_{CF}$ 16.8, C-3a), 161.0 (dd, $^1J_{CF}$ 243.0, $^4J_{CF}$ 6.0, C-4), 178.9 (s, C-2); δ_F (658MHz, DMSO-d_6) -81.4 (s); *m/z* (EI^+) 187 (M^+, 30%), 117 (24), 87 (100), 70 (92), 31 (97).

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 ($MgSO_4$) 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. $C_{18}H_{21}F_2N_4O_2S$ requires: $[MH]^+$, 377.1448); δ_H 3.15 - 3.19 (4H, m, CH_2NC-5), 3.31 (4H, t, $^3J_{HH}$ 4.7, CH_2), 3.61 (4H, t, $^3J_{HH}$ 4.7, CH_2), 3.64 (4H, t, $^3J_{HH}$ 4.7, CH_2), 7.06 - 7.09 (2H, m, ArH), 7.22 - 7.29 (3H, m, ArH); δ_C 50.5 (s, CH_2), 50.6 (d, $^4J_{CF}$ 4.2, CH_2), 66.6 (s, CH_2), 66.9 (s, CH_2), 121.4 (d, $^3J_{CF}$ 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, $^2J_{CF}$ 23.4, C-5), 158.7 (d, $^1J_{CF}$ 241.2, C-6), 163.9 (s, C-3); δ_F -92.57 (s); *m/z* (ES^+) 377.1 ($[MH]^+$, 100%). *Crystal data for* ***6***: $C_{18}H_{21}N_4O_2FS$, M = 376.45, monoclinic, space group P 2_1, a = 6.58813(2), b = 13.5706(4), c = 10.4143(4) Å, β = 107.70(2)°, U = 886.07(5) $Å^3$, F(000) = 396, Z = 2, D_c = 1.416 mg m^{-3}, μ = 0.214 mm^{-1}. 16499 reflections were collected yielding 5013 unique data (R_{merg} = 0.0534). Final $wR_2(F^2)$ = 0.0885 for all data (319 refined parameters), conventional $R_1(F)$ = 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-1*H*-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 ($MgSO_4$), 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; δ_H 0.8 – 0.9 (6H, m, CH_3), 1.33 (4H, sextet, $^3J_{HH}$ 7.4, C*H*$_2$CH$_3$), 1.61 (4H, pent, $^3J_{HH}$ 7.4, C*H*$_2$CH$_2$CH$_3$), 3.36 (4H, t, $^3J_{HH}$ 7.4, NCH_2), 7.3 – 7.5 (3H, m, ArH), 8.1 – 8.3 (1H, m, ArH); δ_C 13.9 (s, CH_3), 20.3 (s, *C*H$_2$CH$_2$), 31.3 (s, *C*H$_2$CH$_2$CH$_3$), 41.7 (s, NHCH$_2$), 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-2,3,4*b*,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 ($MgSO_4$), 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. $C_{13}H_{16}N_5FO$ requires: [MH]$^+$ 278.14117); δ_H 2.00 - 2.10 (2H, m, CH_2), 2.12 - 2.18 (2H, m, CH_2), 3.09 (2H, t, $^3J_{HH}$ 6.4, CH_2), 3.87 (4H, t, $^3J_{HH}$ 4.8, OCH_2), 4.03 (4H, t, $^3J_{HH}$ 4.8, NCH_2), 4.33 (2H, t, $^3J_{HH}$ 6.0, NCH_2); δ_C 20.2 (s, CH_2), 22.6 (s, CH_2), 25.5 (s, CH_2), 45.3 (d, $^4J_{CF}$ 2.7, C-5), 47.3 (s, C-2'), 67.2 (s, C-3'), 121.5 (d, $^2J_{CF}$ 27.6, C-4a), 136.1 (d, $^3J_{CF}$ 5.8, C-9a), 151.5 (d, $^1J_{CF}$ 231.6, C-4), 152.6 (d, $^4J_{CF}$ 2.1, C-8a), 153.9 (d, $^4J_{CF}$ 2.1, C-1); δ_F -101.9 (s); *m/z* (ES$^+$) 278 ([MH]$^+$, 100%). *Crystal data for* ***7b***: $C_{13}H_{16}N_5FO$, M = 277.31, orthorhombic, space group P bcn, a = 16.7598(9), b = 7.3062(4), c = 20.4845(11) Å, U = 2508.3(2) Å^3, F(000) = 1168, Z = 8, D_c = 1.469 mg m^{-3}, μ = 0.109 mm^{-1}. 19847 reflections were collected yielding 3035 unique data (R_{merg} = 0.0807). Final $wR_2(F^2)$ = 0.1179 for all data (245 refined parameters), conventional $R_1(F)$ = 0.0472 for 2114 reflections with I≥2σ(I), GOF = 1.025. CCDC-1486846.

4-Fluoro-1-methoxy-8-methyl-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 ^{o}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 ($MgSO_4$), 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 ^{o}C (Found: C, 56.6; H, 3.9; N, 23.9. $C_{11}H_9FN_4O$ requires: C, 56.9; H, 3.9; N, 24.1%); ν_{max} / cm^{-1} 964, 980, 1030, 1102, 1132, 1168, 1236, 1286, 1320, 1372, 1424, 1466, 1579; δ_H 2.76 (3H, s, CH_3), 4.38 (3H, s, OCH_3), 7.08 (1H, t, $^3J_{HH}$ 6.8, H-6), 7.48 (1H, dt, $^3J_{HH}$ 6.8, $^4J_{HH}$ 1.0, H-7), 8.80 (1H, d, $^3J_{HH}$ 6.8, H-5); δ_C 17.6 (s, CH_3), 55.6 (s, OCH_3), 114.3 (s, C-6), 120.5 (d, $^3J_{CF}$ 11.4, C-9a), 126.0 (s, C-5), 129.1 (s, C-8), 130.4 (s, C-7), 133.1 (d, $^2J_{CF}$ 36.4, C-4a), 150.7 (s, C-8a), 154.9 (d, $^4J_{CF}$ 2.0, C-1), 156.8 (d, $^1J_{CF}$ 247.6, C-4); δ_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 ^{o}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 ($MgSO_4$), 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 ^{o}C (Found: [MH]$^+$, 246.11492. $C_{12}H_{12}FN_5$ requires: [MH]$^+$, 246.11495); ν_{max} / cm^{-1} 1340, 1401, 1435, 1480, 1583, 1616, 3351 (br); δ_H 1.40 (3H, t, $^3J_{HH}$ 6.6, CH_2CH_3), 2.71 (3H, s, CH_3), 3.77 (2H, quin, $^3J_{HH}$ 6.6, NCH_2), 5.53 (1H, br s, NH), 7.03 (1H, t, $^3J_{HH}$ 6.7, H-6), 7.40 (1H, dt, $^3J_{HH}$ 6.7, $^4J_{HH}$ 0.9, H-7), 8.51 (1H, d, $^3J_{HH}$ 6.7, H-5); δ_C 14.9 (s, CH_2CH_3), 17.5 (s, CH_3), 36.5 (s, $NHCH_2$), 114.2 (s, C-6), 114.5 (d, $^2J_{CF}$ 29.5, C-4a), 125.5 (d, J_{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, $^1J_{CF}$ 230.6, C-4), 153.1 (d, $^4J_{CF}$ 2.0, C-1); δ_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-2,3,4*b*,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 ^{o}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 ($MgSO_4$), 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 ^{o}C (Found: C, 61.7; H, 5.9; N, 25.4. $C_{14}H_{16}N_5F$ requires C, 61.5; H, 5.9; N, 25.6%); ν_{max} / cm^{-1} 1217, 1237, 1295, 1352, 1429, 1485, 1575, 1638, 2973; δ_H 1.31 (6H, t, $^3J_{HH}$ 7.1, CH_2CH_3), 2.66 (3H, s, CH_3), 4.09 (4H, q, $^3J_{HH}$ 7.1, NCH_2), 6.95 (1H, t, $^3J_{HH}$ 7.0, H-6), 7.31 (1H, d, $^3J_{HH}$ 7.0, H-7), 8.46 (1H, d, $^3J_{HH}$ 7.0, H-5); δ_C 13.8 (s, CH_2CH_3), 17.3 (s, CH_3), 44.0 (s, NCH_2), 113.9 (s, C-6), 114.4 (d, $^2J_{CF}$ 28.0, C-4a), 125.1 (s, C-8), 128.7 (s, C-5), 129.2 (s, C-7), 136.6 (d, $^3J_{CF}$ 4.6, C-8a), 148.3 (s, C-9a), 150.5 (d, $^1J_{CF}$ 228.4, C-4), 153.3 (d, $^4J_{CF}$ 1.9, C-1); δ_F -102.7 (s); *m/z* (EI$^+$) 273 ([M]$^+$, 24%), 244 (100), 230 (74), 201 (12), 183 (56), 92 (36). *Crystal data for* ***7e***: $C_{14}H_{16}FN_5$, 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)°, U = 2635.8(1) Å^3, F(000) = 1152, Z = 8, D_c = 1.378 mg m^{-3}, μ = 0.097 mm^{-1}. 19731 reflections were collected yielding 3504 unique data (R_{merg} = 0.0284). Final $wR_2(F^2)$ = 0.1117 for all data (245 refined parameters), conventional $R_1(F)$ = 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. $C_{12}H_{18}FN_5O$ requires [MH]$^+$, 268.1574); δ_H 3.08 (4H, td, $^3J_{HH}$ 4.7, $^5J_{HF}$ 1.8, NCH_2), 3.14 (3H, s, CH_3), 3.30 – 3.33 (2H, m, CH_2N), 3.31 (3H, s, CH_3), 3.38 – 3.40 (2H, m, CH_2), 3.76 (4H, t, $^3J_{HH}$ 4.7, CH_2O); δ_C 38.3 (s, CN-8), 41.4 (s, CN-5), 46.5 (s, C-7), 50.4 (d, $^4J_{CF}$ 4.3, *C*NC-4), 51.0 (s, C-6), 67.0 (d, $^5J_{CF}$ 0.5, CO), 119.5 (d, $^2J_{CF}$ 29.1, C-4), 134.9 (d, $^3J_{CF}$ 8.9, C-4a), 151.8 (s, C-8a), 161.2 (d, $^1J_{CF}$ 236.6, C-3); δ_F -94.5 (s); *m/z* (AP$^+$) 267 ([M]$^+$, 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. $C_{14}H_{12}FN_3O_2S$ requires $[MH]^+$, 306.0713); δ_H 3.24 (4H, td, $^3J_{HH}$ 4.7, $^5J_{HF}$ 2.1, CH_2N), 3.85 (4H, t, $^3J_{HH}$ 4.7, CH_2O), 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); δ_C 49.9 (d, $^4J_{CF}$ 3.9, CH_2N), 67.2 (d, $^5J_{CF}$ 1.3, CH_2O), 114.5 (s, C-10a), 118.9 (s, C-8), 123.5 (d, $^3J_{CF}$ 8.0, C-4a), 125.7 (s, C-6), 126.3 (s, C-7), 129.3 (s, C-5), 134.1 (d, $^2J_{CF}$ 26.3, C-4), 149.9 (d, $^4J_{CF}$ 1.0, C-9a), 159.3 (s, C-8a), 160.3 (d, $^1J_{CF}$ 243.0, C-3); δ_F -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 ($MgSO_4$) 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. $C_{10}H_{15}FN_4S$ requires: C, 49.6; H, 6.2; N, 23.1%); δ_H 1.19 (3H, t, $^3J_{HH}$ 7.4, C*H*$_3$CH$_2$S), 2.78 (2H, q, $^3J_{HH}$ 7.4, CH_2S), 3.11 (3H, s, CH_3), 3.31 (3H, s, CH_3), 3.30 – 3.32 (2H, m, CH_2N), 3.46 – 3.49 (2H, m, CH_2N); δ_C 14.4 (s, *C*H$_3$CH$_2$S), 29.1 (d, $^4J_{CF}$ 4.4, CH_2S), 37.8 (s, CH_3N), 43.1 (s, CH_3N), 46.7 (s, CH_2N), 51.8 (s, CH_2N), 101.9 (d, $^2J_{CF}$ 36.1, C-4), 141.6 (d, $^3J_{CF}$ 5.2, C-4a), 150.8 (s, C-8a), 162.3 (d, $^1J_{CF}$ 227.0, C-3); δ_F -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. $C_{12}H_9FN_2OS_2$ requires $[MH]^+$, 281.0219); δ_H 1.34 (3H, t, $^3J_{HH}$ 7.4, CH_3), 3.14 (2H, qd, $^3J_{HH}$ 7.4, $^5J_{HF}$ 1.0, CH_2), 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); δ_C 15.3 (s, CH_3), 28.8 (d, $^4J_{CF}$ 6.9, CH_2), 114.4 (s, C-10a), 118.8 (s, C-8), 124.0 (d, $^2J_{CF}$ 36.3, C-4), 125.8 (s, C-6), 126.4 (s, C-7), 129.4 (s, C-5), 133.2 (d, $^3J_{CF}$ 4.9, C-4a), 149.4 (s, C-8a), 157.6 (d, $^4J_{CF}$ 1.9, C-9a), 162.9 (d, $^1J_{CF}$ 238.2, C-3); δ_F -82.2 (s); *m/z* (AP^+) 280 ($[M]^+$, 100%). *Crystal data for* ***9d***: $C_{12}H_9N_2OFS_2$, M = 280.33, monoclinic, space group $P2_1/n$, a = 10.6924(5), b = 9.8670(4), c = 11.0623(5) Å, β = 92.44(1)°, U = 1166.03(9) $Å^3$, F(000) = 576, Z = 4, D_c = 1.597 mg m^{-3}, μ = 0.457 mm^{-1}. 10747 reflections were collected yielding 3249 unique data (R_{merg} = 0.0657). Final $wR_2(F^2)$ = 0.1129 for all data (199 refined parameters), conventional $R_1(F)$ = 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 x10 mL). The organic phases were combined, dried ($MgSO_4$) 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. $C_{12}H_{10}FN_3OS$ requires $[MH]^+$, 264.0607); δ_H 1.31 (3H, t, $^3J_{HH}$ 7.4, CH_3), 1.62 (1H, br. s, NH), 2.90 (2H, q, $^3J_{HH}$ 7.4, CH_2), 6.63 – 6.65 (1H, m, H-5), 6.87 – 6.94 (3H, m, ArH); δ_C 15.2 (s, CH_3), 28.9 (d, $^4J_{CF}$ 3.1, CH_2), 102.2 (d, $^2J_{CF}$ 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, $^3J_{CF}$ 7.1, C-4a), 142.8 (s, C-8a),

153.4 (d, $^4J_{CF}$ 0.9, C-9a), 164.4 (d, $^1J_{CF}$ 235.1, C-3); δ_F -81.0 (s); *m/z* (AP^+) 263 ($[M]^+$, 100%). *Crystal data for* ***9e***: $C_{12}H_{10}N_3SFO$, M = 263.29, orthorhombic, space group P $ca2_1$, a = 12.566(9), b = 5.2062(4), c = 35.081(3) Å, U = 2295.0(17) $Å^3$, F(000) = 1088, Z = 8, D_c = 1.524 mg m^{-3}, μ = 0.286 mm^{-1}. 13348 reflections were collected yielding 4103 unique data (R_{merg} = 0.0642). Final $wR_2(F^2)$ = 0.1088 for all data (336 refined parameters), conventional $R_1(F)$ = 0.0490 for 2874 reflections with $I \geq 2\sigma(I)$, GOF = 1.014. CCDC-1486849.

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. $C_{12}H_{10}FN_3S_2$ requires $[MH]^+$, 280.0378); δ_H 1.35 (3H, t, $^3J_{HH}$ 7.4, CH_3), 2.48 (1H, br. s, NH), 3.11 (2H, qd, $^3J_{HH}$ 7.4, $^5J_{HF}$ 0.8, CH_2), 6.83 – 6.88 (3H, m, ArH), 7.05 – 7.07 (1H, m, H-8); δ_C 15.3 (s, CH_3), 28.8 (d, $^4J_{CF}$ 6.9, CH_2), 113.8 (s, C-8a), 117.0 (s, C-5), 122.7 (d, $^2J_{CF}$ 38.4, C-4), 124.3 (s, C-7), 126.1 (s, C-8), 129.2 (s, C-6), 135.4 (d, $^3J_{CF}$ 4.6, C-4a), 135.8 (s, C-10a), 151.7 (s, C-9a), 160.8 (d, $^1J_{CF}$ 237.5, C-3); δ_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. $C_{11}H_9FN_4S$ requires $[MH]^+$, 249.0610); δ_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, $^3J_{HH}$ 6.8, $^4J_{HH}$ 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. $C_{12}H_{11}FN_4S$ requires $[MH]^+$, 263.0767); δ_H 1.37 (3H, t, $^3J_{HH}$ 7.3, C*H*$_3$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, *C*H$_3$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***: $C_{12}H_{11}N_4SF$, M = 262.31, monoclinic, space group $P2_1/c$, a = 3.9174(1), b = 16.8084(2), c = 17.1269(2) Å, β = 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_{merg} = 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 $I \geq 2\sigma(I)$, 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 ($MgSO_4$) 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. $C_{12}H_{13}FN_2O_3S$ requires $[MH]^+$, 285.0709); δ_H 1.29 (3H, t, $^3J_{HH}$ 7.4, SCH_2CH_3), 1.43 (3H, t, $^3J_{HH}$ 7.2, OCH_2CH_3), 2.77 (3H, s, CH_3), 3.18 (2H, qd, $^3J_{HH}$ 7.4, $^5J_{HF}$ 2.3, SCH_2), 4.43 (2H, q, $^3J_{HH}$ 7.2, OCH_2); δ_C 14.3 (s, CH_3), 14.9 (d, $^5J_{CF}$ 1.9, SCH_2CH_3), 15.0 (s, OCH_2CH_3), 28.6 (d, $^4J_{CF}$ 11.5, SCH_2), 61.8 (s, OCH_2), 111.0 (d, $^3J_{CF}$ 4.7, C-4a), 122.8 (d, $^2J_{CF}$ 34.8, C-4), 126.6 (d, $^4J_{CF}$ 6.6, C-7a), 161.7 (s, C-5), 162.1 (s, C-6), 162.9 (d, $^1J_{CF}$ 232.4, C-3), 168.3 (s, C=O); δ_F -84.97 (s); *m/z* (ES^+) 285 ($[MH]^+$, 100%).

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