Accepted Manuscript

Structure-activity relationships (SAR) and structure-kinetic relationships (SKR) of sulphone-based CRTh2 antagonists

Maria Antonia Buil, Marta Calbet, Marcos Castillo, Jordi Castro, Cristina Esteve, Manel Ferrer, Pilar Forns, Jacob González, Sara López, Richard. S. Roberts, Sara Sevilla, Bernat Vidal, Laura Vidal, Pere Vilaseca

PII: S0223-5234(16)30093-9

DOI: 10.1016/j.ejmech.2016.02.023

Reference: EJMECH 8374

To appear in: *European Journal of Medicinal Chemistry*

Received Date: 3 December 2015

Revised Date: 5 February 2016

Accepted Date: 7 February 2016

Please cite this article as: M.A. Buil, M. Calbet, M. Castillo, J. Castro, C. Esteve, M. Ferrer, P. Forns, J. González, S. López, R.S. Roberts, S. Sevilla, B. Vidal, L. Vidal, P. Vilaseca, Structure-activity relationships (SAR) and structure-kinetic relationships (SKR) of sulphone-based CRTh2 antagonists, *European Journal of Medicinal Chemistry* (2016), doi: 10.1016/j.ejmech.2016.02.023.

Title

2 Structure-activity relationships (SAR) and structure-kinetic relationships (SKR) of sulphone-based CRTh2 antagonists

Corresponding author (address until 24 feb 2016)

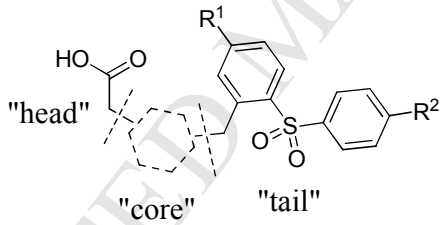
* Richard S. Roberts, Drug Discovery Division, Almirall R&D Centre, Laureano Miró, 408-410, 08980 Sant Feliu de Llobregat, Barcelona, Spain. Tel: +34 93 291 7540. Fax: +34 93 291 3420. e-mail: rick.roberts@almirall.com

(address from 26 feb 2016)

* Richard S. Roberts, Minoryx Therapeutics S.L., TecnoCampus Mataró-Maresme, Av. Ernest Lluch 32, TCM3, 08302 Mataró (Barcelona), Spain.

Tel: +34 93 544 14 66. e-mail: rroberts@minoryx.com

Graphical abstract



monocyclic or bicyclic

low nanomolar CRTh2 antagonists
Receptor dissociation half-lives up to 21 h

Structure-activity relationships (SAR) and structure-kinetic relationships (SKR) of sulphone-based CRTh2 antagonists

Maria Antonia Buil,[a] Marta Calbet,[a] Marcos Castillo,[b] Jordi Castro,[a] Cristina Esteve,[a] Manel Ferrer,[a] Pilar Forns,[b] Jacob González,[a] Sara López,[a] Richard. S. Roberts,[a,c]* Sara Sevilla,[a] Bernat Vidal,[a] Laura Vidal,[a] Pere Vilaseca,[a]

[a] Almirall R&D Centre, Laureano Miró, 408-410, 08980 Sant Feliu de Llobregat, Barcelona, Spain.

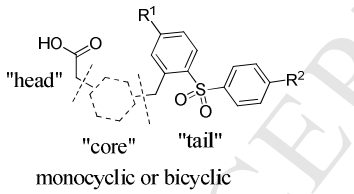
[b] Almirall-Barcelona Science Park Unit, Barcelona Science Park, Josep Samitier 1-5, 08028 Barcelona, Spain

[c] Present address: Minoryx Therapeutics S.L. TecnoCampus Mataró-Maresme, Av. Ernest Lluch 32, TCM3, 08302 Mataró (Barcelona), Spain. Tel: +34 93 544 14 66. e-mail: rroberts@minoryx.com

Corresponding author
* Richard S. Roberts, Drug Discovery Division, Almirall R&D Centre, Laureano Miró, 408-410, 08980 Sant Feliu de Llobregat, Barcelona, Spain. Tel: +34 93 291 7540. Fax: +34 93 291 3420.
e-mail: rick.roberts@almirall.com

Highlights
- Synthesis of sulphone-containing heteraromatic acetic acids as CRTh2 antagonists
- A multitude of synthetic routes are given
- Structure-activity relationships (SAR) are discussed
- Structure-kinetic relationships (SKR) are discussed
- Potent and long resident compounds were identified

Graphical abstract



Abstract
Monocyclic and bicyclic ring systems were investigated as the "core" section of a series of diphenylsulphone-containing acetic acid CRTh2 receptor antagonists. A range of potencies were observed and single-digit nanomolar potencies were obtained in both the monocyclic and bicyclic cores. Residence times for the monocyclic compounds were very short. Some of the bicyclic cores displayed better residence times. A methyl group in the northern part of the core, between the head and tail was a necessary requirement for the beginnings of long residence times. Variations of the tail substitution maximised potencies and residence times.

Keywords
CRTh2 Antagonist
Receptor residence time
Structure-Activity Relationship (SAR)
Structure-Kinetic Relationship (SKR)

1. Introduction

CRTh2 (chemoattractant receptor homologous molecule expressed on Th2 lymphocytes) is a GPCR involved in the chemotaxis of Th2 lymphocytes, eosinophils and basophils.[1,2] CRTh2 also inhibits the apoptosis of Th2 lymphocytes[3] and stimulates the production of IL4, IL5, and IL13,[4] cytokines involved in pro-inflammatory biological responses. CRTh2 antagonists are therefore under active development as potential treatments in pathologies related to allergic inflammation. Several recent reviews have highlighted the progress and most advanced series of CRTh2 antagonists, both in pre-clinical[5,6] and clinical development.[7,8]

As a continuation of our drug discovery program into potent, oral CRTh2 antagonists with long receptor residence times, we were keen to expand the Structure-Activity Relationship (SAR) and more importantly the Structure-Kinetic Relationship (SKR) around a series of diphenylsulphone-containing acetic acid CRTh2 receptor antagonists. The compounds could be split into three conceptual areas; the acetic acid "head" group, a mono- or bicyclic aromatic "core" ring system and a "tail" group. We, and others had previously had success in finding potent antagonists when the tail groups was a 2-(phenylsulphonyl)benzyl group. In this case, different cores such as pyrazole **1**,[9] reverse pyrazole **2**,[10] indole **3**[11] or pyrrolopiperidinones (PPAs) **4**[12] could all be successfully introduced (Figure 1). Potency and dissociation time data for compounds **1**-**4** are shown in Table 1. In a parallel line of research, we had shown that the bicyclic core or a series of biaryl CRTh2 antagonists was open to wide variation.[13,14] Good potencies were generally accessible through modification of the core. The core also had a profound effect on the receptor residence half-life as demonstrated between compounds **1** and **4**. Clearly, there was scope to investigate further structural modifications to the core. In a first approximation, any core giving rise to a residence half-life ≥1h was of interest. Only those most promising cores would then be taken forward with a view of finding compounds displaying long receptor residence time, if possible ≥12h.

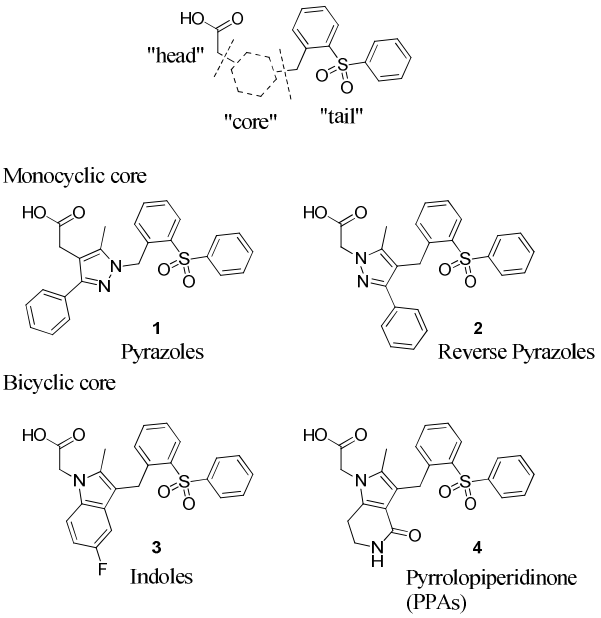


Fig. 1. Sulphone-containing CRTh2 antagonists.

Table 1
Monocyclic and bicyclic core SAR and SKR

Compound	Series	GTPγS IC_{50} (nM)	Dissociation half-life (h)
1	Pyrazole	7	0.1
2	Rev Pyr	85	0.02
3	Indole	14	1.3
4	PPA	5	2.3

2. Chemistry

In almost all cases, each different central core required a separate synthetic route. In general, the acetic acid head group was added from one of three synthons (Figure 2): when the core contained an NH suitable for alkylation, a bromoacetate was sufficient. When the head-to-core linkage was a carbon-carbon bond, we used either Friedel-Crafts reaction with a monooxalyl chloride followed by reduction, or an organometallic coupling with an acetate zincate reagent. The tails were added via a bromide, if alkylation was an option, or in many case from an aldehyde by reductive alkylation. Other methods were also used where appropriate.

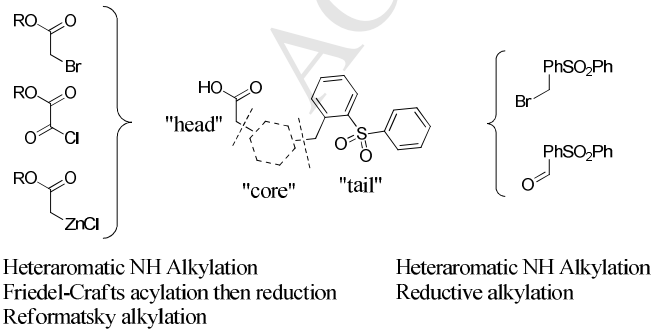
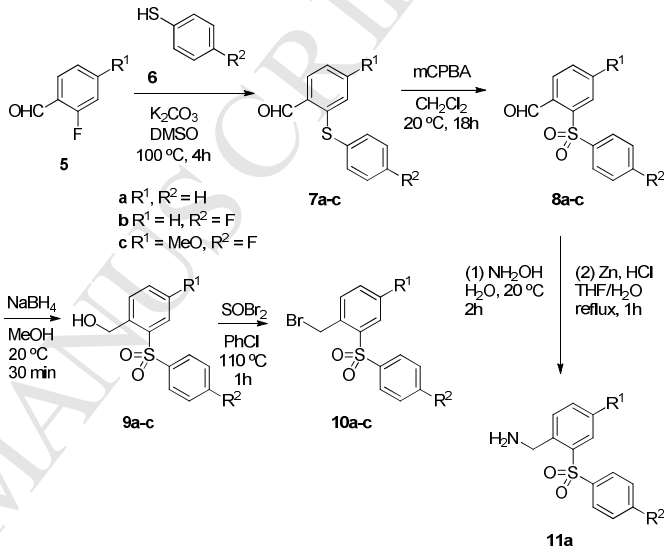


Fig. 2. Typical synthetic strategies.

Here we describe the various synthetic routes used to obtain the various aromatic cores. Due to the wide variation of structures, in many cases yields were not optimized, as obtaining a sample for biological testing was the priority.

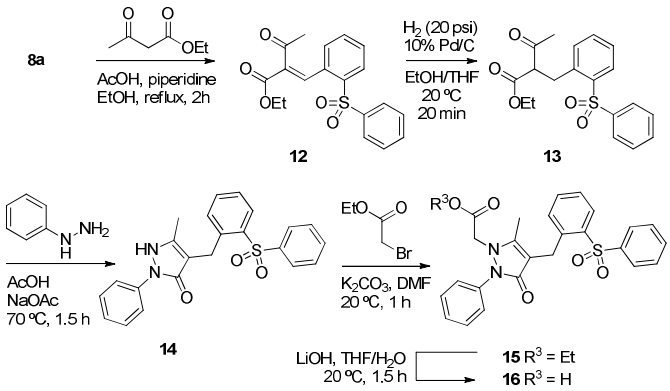
The general tail synthons were synthesized according to Scheme 1. We limited ourselves to just three tails: (a) unsubstituted, (b) para-fluoro in the terminal phenyl ring and (c) a methoxy-fluoro disubstituted tail. Smooth addition of sulphides **6** to ortho-fluoro aldehydes **5** gave sulphides **7** which were then oxidized to sulfones **8**. Bromides **10** were obtained by reduction of the aldehyde and bromination. Amine **11a** was obtained by a two-step reductive amination.



Scheme 1. Synthetic route to tail synthons **8**, **10** and **11** (0.2-1.9 g scale).

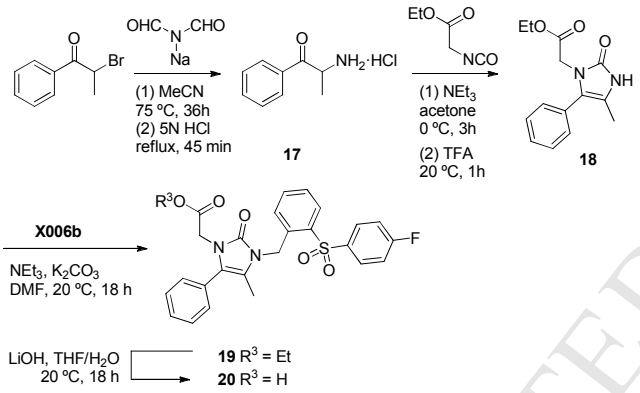
The monocyclic cores were synthesized as follows:

Pyrazolone **16**, a close analogue of our original pyrazole **1**, was synthesized as shown in Scheme 2. Knoevenagel condensation of tail aldehyde **8a** with ethyl acetoacetate[15] gave a mixture of regioisomers **12**, and the double bond was then reduced with hydrogen over palladium on carbon. This process was generally higher yielding than direct alkylation of ethyl acetoacetate with bromide **10a**. Acetoacetate **13** was condensed with phenyl hydrazine,[16] again giving a mixture of regioisomers and a low yield after a tricky separation. **14** was alkylated with ethyl bromoacetate and ester hydrolysis gave **16**.



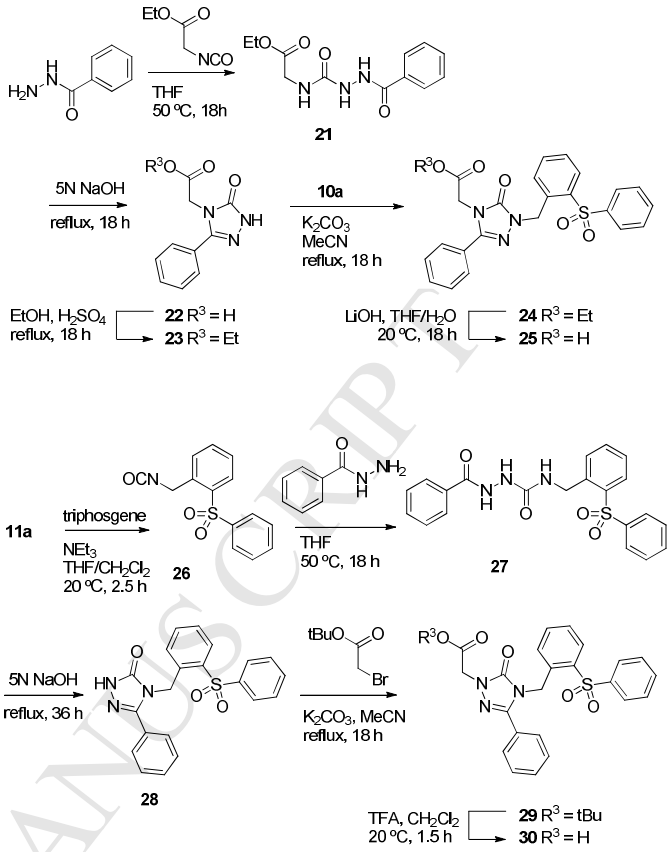
Scheme 2. Synthesis of pyrazolone **16** (7 mg scale).

Imidazolone **20**, a regioisomeric core of **16**, was synthesized according to Scheme 3. 2-Bromo-1-phenylpropan-1-one was aminated with sodium diformylamide[17] and resulting aminoketone **17** was cyclized with ethyl 2-isocyanatoacetate.[18] The completed core **18** was then alkylated with tail bromide **10b** and ester hydrolysis gave the imidazolone **20**.



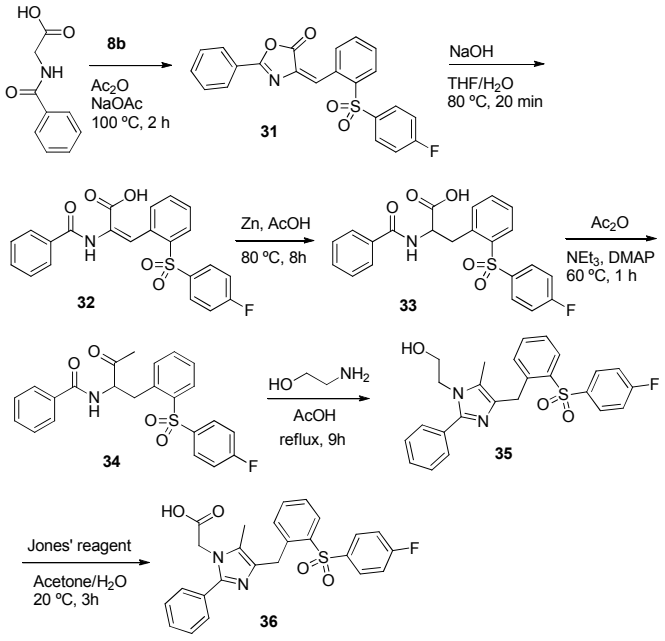
Scheme 3. Synthesis of imidazolone **20** (34 mg scale).

Regioisomeric triazolones **25** and **30** were synthesized according to Scheme 4. Benzohydrazide was condensed with ethyl 2-isocyanatoacetate to give urea **21**. This was cyclized under highly basic conditions,[19] also resulting in ester hydrolysis. Carboxylic acid **22** was re-esterified prior to tail alkylation. A second ester hydrolysis of **24** gave the desired product. Regioisomer **30** was synthesized along similar lines, but reversing the reactivity of the reagents. Here, tail amine **11a** was converted to the isocyanate **26** and this was used for condensation with benzohydrazide. After base-catalyzed cyclization, the core of **23** was alkylated with ethyl bromoacetate and hydrolysed as before to the desired product **30**. In both cases, the base-catalyzed cyclization (**21** → **22** and **28** → **29**) was a dirty reaction with many sub-products. The products of these reactions were not purified at this stage, but used crude in the subsequent alkylations and purified at that point.



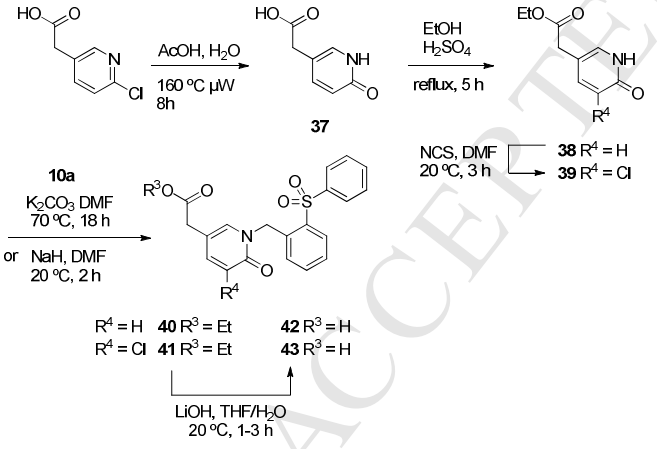
Scheme 4. Synthesis of triazolones **24** and **30** (85-100 mg scale).

Imidazole **36** was synthesized according to Scheme 5. Hippuric acid (N-benzoyl glycine) was condensed with tail aldehyde **8b** in an Erlenmeyer-Plöchi azlactone synthesis.[20] Hydrolysis of the azlactone (oxazolinone) of **31** gave **32** and reduction of the double bond gave functionalized phenylalanine **33**. Methyl ketone **34** was synthesized through an acylation-decarboxylation sequence using acetic anhydride. We tried to synthesize **36** directly by condensation of **34** with glycine, or glycine esters, however no reaction or decomposition was observed. Finally we achieved cyclization of **34** to the imidazole core by condensation with 2-aminoethanol,[21] albeit in a very poor 7% yield. However this gave us sufficient material to obtain **36** via a Jones oxidation.[22]



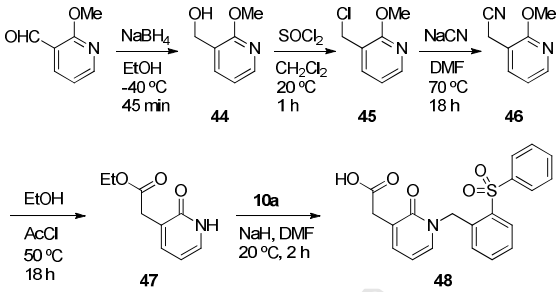
Scheme 5. Synthesis of imidazole **36** (4 mg scale).

We also synthesized some 6-membered monocyclic cores. Pyridones **42** and **43** were synthesized according to Scheme 6. Common intermediate **37** was obtained by hydrolysis of commercial (6-chloropyridin-3-yl)acetic acid and then esterified to give **38**. Here we also chlorinated the core to at least generate 2 final products from the same synthetic route. Both pyridine cores were taken through to their final products by alkylation with the tail and ester hydrolysis (**38** → **40** → **42** and **39** → **41** → **43** respectively).



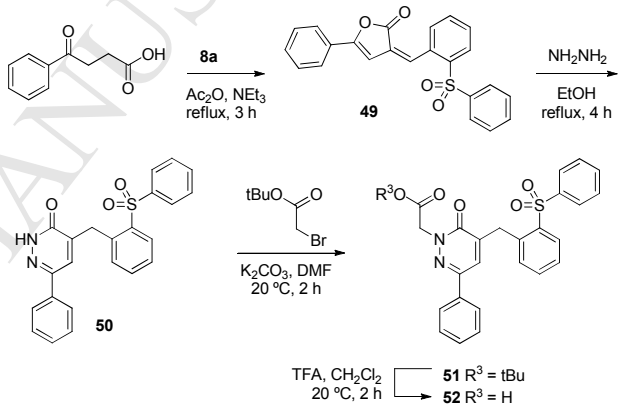
Scheme 6. Synthesis of pyridones **42** and **43** (23-83 mg scale).

Regioisomeric pyridone **48** was synthesized according to Scheme 7. A classical carbon-chain homologation route was used to obtain the acetate-substituted core, namely aldehyde reduction to alcohol **44**, chlorination (**45**), cyanide substitution (**46**) and nitrile hydrolysis (**47**). The core was then alkylated with tail bromide **10a** and in situ ester hydrolysis have the product **48**.



Scheme 7. Synthesis of pyridones **48** (130 mg scale).

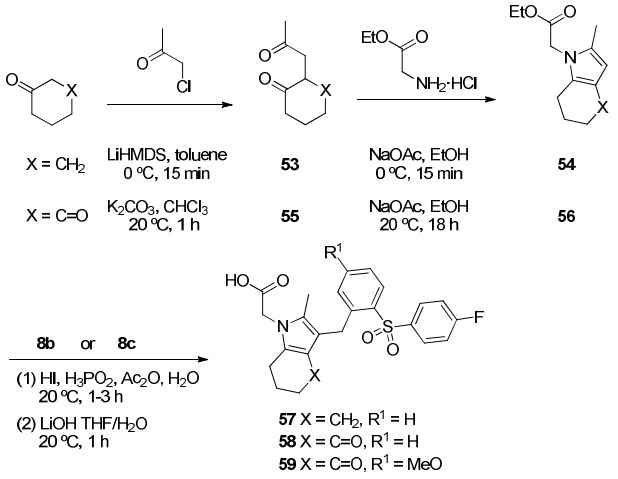
The final monocycle, pyridazinone **52** was synthesized according to Scheme 8. Tail aldehyde **8a** was condensed with 4-oxo-4-phenylbutanoic acid under dehydrating conditions.[23] Treatment of furanone **49** with hydrazine gave the pyridazinone core **50**.[24] Alkylation with *tert*-butyl bromoacetate and ester hydrolysis gave the final compound **52**.



Scheme 8. Synthesis of pyridazinone **52** (54 mg scale).

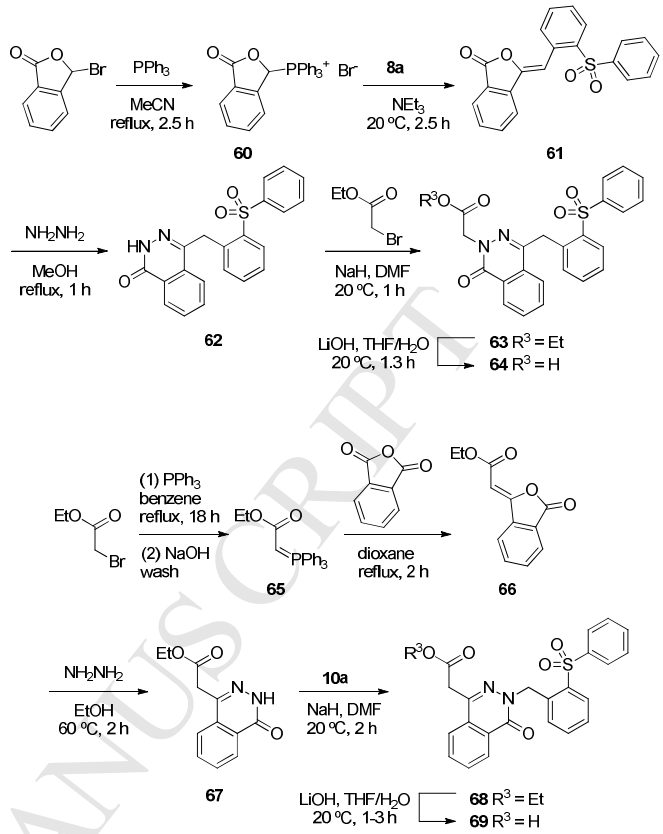
The bicyclic cores we chose to study were also synthesized following a range of synthetic routes. The first cores selected were a crossover between the the monocycles and the bicycles: pyrrole-based compounds **57**, **58** and **59** all possessed an aromatic monocycle fused to an aliphatic ring. These compounds were also close analogues of our pyrrolopiperidinones (PPAs, e.g. **4**) and could be obtained by similar synthetic routes, simply by varying the starting cyclohexanone (Scheme 9).[12] The route to **57** was fraught with impurities, degradations and low yields (see Experimental Section) but was short enough to rapidly obtain the final product. Cyclohexanone was alkylated with chloroacetone to give diketone **53** but in a highly crude mixture. Condensation with ethyl glycinate gave pyrrole **54**, also in a highly crude form. In the final step, reductive alkylation with tail aldehyde **8a** gave a tiny amount of the desired product, sufficient to characterize biologically, but only after repeated purifications. The same route starting from Meldrum's acid (1,3-cyclohexadione) gave far fewer problems. Alkylation proceeded under milder basic conditions to give tricarbonyl **55**. Condensation with ethyl glycinate proceeded smoothly to **56** and reductive alkylation gave the desired products **58** and

59. The extra carbonyl group (X = CO in Scheme 9) clearly reduced the electron density of the pyrrole ring of the core to make it a more stable and less prone to decompositions.



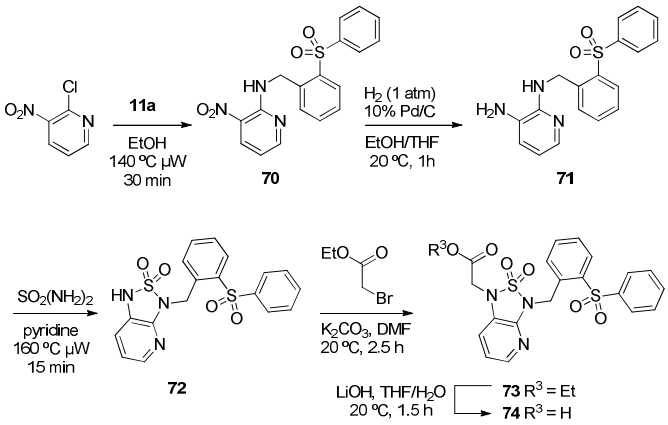
Scheme 9. Synthesis of pyrrole-derived cores **57, 58** and **59** (2-180 mg scale).

Moving to wholly aromatic bicyclic cores, two regioisomeric phthalazinones **64** and **69** were synthesized according to Scheme 10. As seen previously, the synthetic routes were just variations of each other, swapping the reactivities of the head, the core and tail portions accordingly. In the first case, Wittig reagent of the core **60** was reacted with tail aldehyde **8a** to give the alkylidene **61**.[25] Condensation with hydrazine gave the phthalazinone core **62**.[26] Alkylation with ethyl bromoacetate and hydrolysis gave the product **64**. In the case of the reversed core, Wittig reagent of the head **65** was reacted with phthalic anhydride to give alkylidene **66**. As before, condensation with hydrazine gave the reversed phthalazinone core **67** and alkylation with tail bromide **10a** and ester hydrolysis gave the final product **69**.



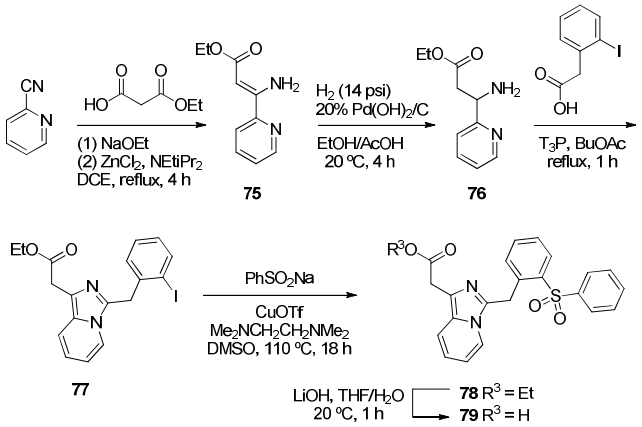
Scheme 10. Synthesis of phthalazinones **64** and **69** (28-33 mg scale).

For the 5,6-bicyclic cores, we started with sulfamide **74** (Scheme 11). 3-Nitro-2-chloropyridine was substituted with tail amine **11a**. Reduction of the nitro group of **70** gave diamine **71** which was cyclized with sulfamide under microwave irradiation to give the thiadiazolopyridine dioxide core **72**.[27] NH Alkylation and ester hydrolysis as before completed the synthesis of **74**.



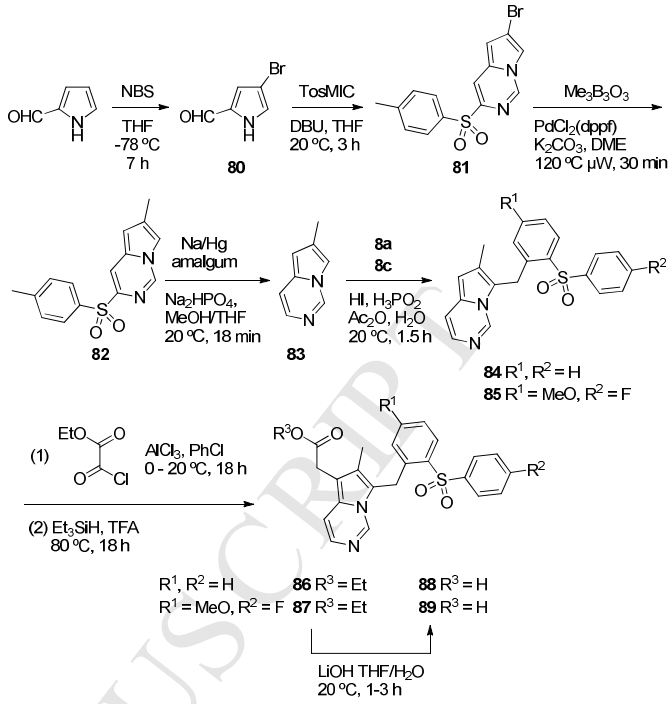
Scheme 11. Synthesis of thiadiazolopyridine dioxide **74** (3 mg scale).

The remaining cores were all based on the same 5,6-bicyclic structure and containing 2 nitrogen atoms, but altering the position of the nitrogens around the 2 rings. The first core of this type was imidazopyridine **79** (Scheme 12). Monoethyl malonate was condensed with 2-cyanopyrine in a Blaise reaction followed by Lewis acid-mediated decarboxylation.[28] Reduction of the double bond double bond (**75** → **76**) gave the acetate-substituted aminomethylpyridine, ready for cyclization. This was carried out with (2-iodophenyl)acetic acid to form the imidazopyridine core of **77**.[29] The iodo group then served as a handle and was displaced with sodium phenylsulfinate, albeit in a low 15% yield. Ester hydrolysis gave the final product **79**.



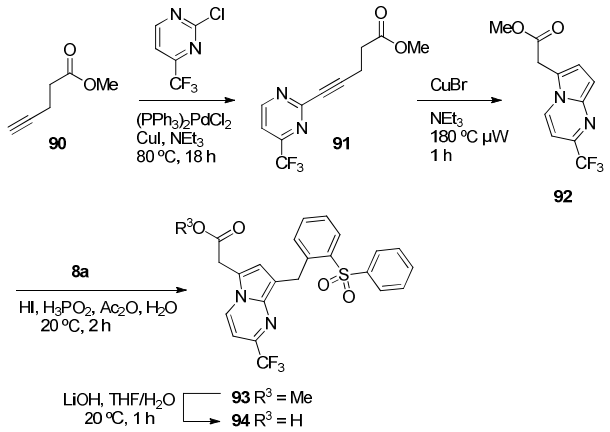
Scheme 12. Synthesis of imidazopyridine **79** (6 mg scale).

Pyrrolo[1,2-c]pyrimidines **88** and **89** first required the synthesis of the naked core fragment **83** (Scheme 13). This was achieved in 4 steps: pyrrole-2-carbaldehyde was brominated selectively in the 4-position. Compound **80** was unstable to light and so was rapidly converted to the pyrrolopyrimidine core **81** with TosMIC.[30] Suzuki reaction installed the methyl group in the 6-position of the core. We settled on this bromine → methyl route as there were no better options to source the 4-methyl-pyrrole-2-carbaldehyde. Finally, we obtained the unsubstituted core **83** via a sodium amalgam reductive desulfonylation,[31] optimized to a decent 63% yield. With the core fragment **83** in hand, we could install the tails from the corresponding aldehydes **8** via reductive alkylation.[32] The head group was then installed in 2 steps: Friedel-Crafts acylation with ethyl 2-chloro-2-oxoacetate installed the 2-carbon chain. These compounds were not isolated, but directly reduced with trimethylsilane under acidic conditions to give the acetates (**86** and **87**). Basic ester hydrolysis completed the synthesis.



Scheme 13. Synthesis of pyrrolo[1,2-c]pyrimidines **88** and **89** (20-50 mg scale).

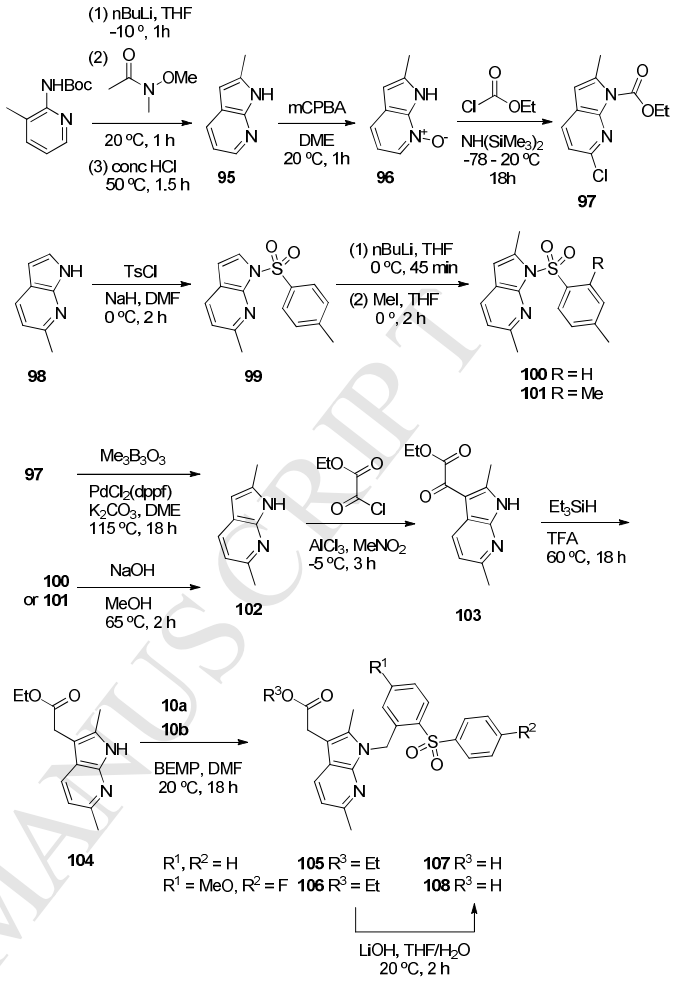
Pyrrolo[1,2-a]pyrimidine **94** was synthesized in just 4 steps according to Scheme 14. We used a Sonogashira coupling to install all of the necessary carbon atoms for the head and core, but in an open form (**91**). Copper-catalyzed isomerization of the alkynopiperidine then gave the desired core.[33] Again, we used reductive alkylation to install the tail (**92** → **93**) and basic ester hydrolysis to complete the synthesis.



Scheme 14. Synthesis of pyrrolo[1,2-a]pyrimidine **94** (15 mg scale).

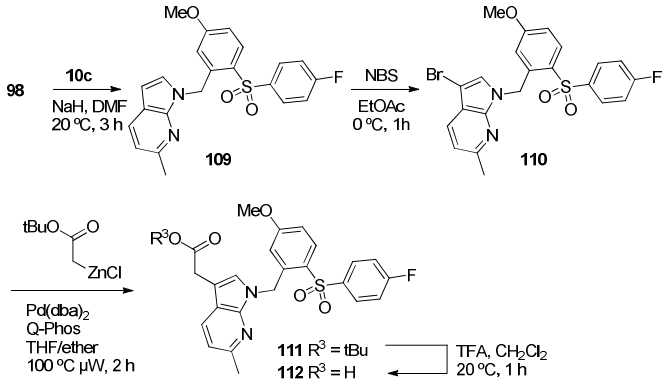
For the synthesis of the dimethyl 7-azindole core, we developed two different routes according to the availability of starting materials (Scheme 15). 2-Methyl-7-azaindole **95** was readily prepared from 3-methyl-2-(Boc)aminopyridine. The methyl group was lithiated, the neighbouring Boc group directing the lithiation and the anion was added to the Weinreb

acetamide. In situ acidic workup quenched the Weinreb intermediate, de-protected the Boc group and condensed the newly formed amine and ketone to give the azaindole **95**.[34] 6-Methyl-7-azaindole **98** was commercially available.[35] From the respective mono-methyl azaindoles, the dimethyl azaindole core **102** was synthesized. 2-Methylazaindole **95** was N-oxidized and rearranged to the protected 6-chloroazaindole **97** with ethyl chloroacetate. Suzuki coupling introduced the 6-methyl substituent to give dimethyl fragment **102**. In the other approach, 6-methyl azaindole **98** was tosylated. We then used a directed ortho metalation (DOM) to lithiate the 2-position of the azaindole and trap with methyl iodide (**100**).[36] Surprisingly, we also detected significant amounts of **101**, a product of double methylation, arising from a second DOM at the ortho position of the tosyl protecting group. Ultimately, we used an excess of butyllithium to force the conversion of **99** to a mixture of **100** and **101** as subsequent hydrolysis of the sulphonamides gave **102** from both compounds. With core fragment **102** in hand the synthesis was finished as follows: the head group was installed by Friedel-Crafts acylation to **103** and triethylsilane reduction to form the acetate **104**. The tail was added by alkylation with bromides **10a** or **10b**. The acetate group of compounds **105** and **106** was clearly quite labile as some transesterification was observed from just the methanol solvent used in the purification. Hydrolysis of the ester mixtures gave the desired carboxylic acids **107** and **108** respectively.



Scheme 15. Synthesis of 2,6-dimethyl-7-azaindoles **107** and **108** (8-9 mg scale).

Finally, a singly-methylate 7-azaindole **112** was synthesized according to Scheme 16. The core fragment **98** was alkylated with tail bromide **10c**. The azaindole nucleus **109** was then brominated in the 3-position and the head was introduced by palladium cross-coupling with the acetate zincate reagent. tert-Butyl ester deprotection with trifluoroacetic acid gave the final product **112**.

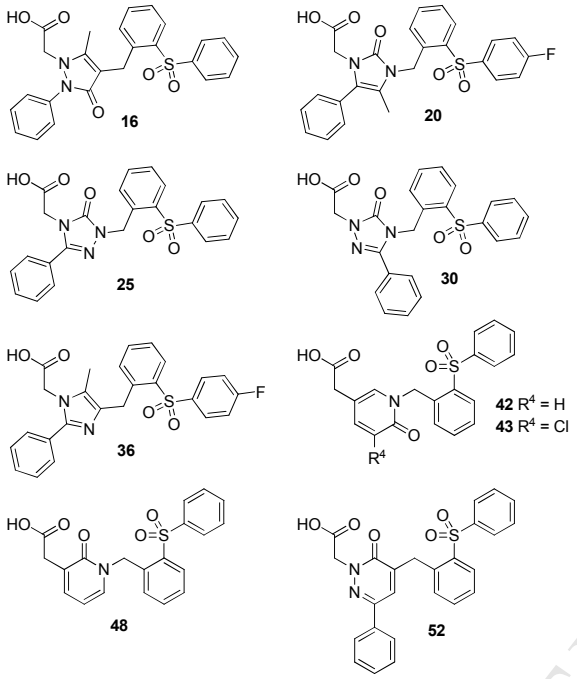


Scheme 16. Synthesis of 2-methyl-7-azaindole **112** (46 mg scale).

3. Results and Discussion

All potency data was determined by a [^{35}S]GTPγS binding assay. The monocycle cores were very disappointing from the outset (Table 2). We were hoping for a wide structural freedom in this part of the molecules, however imidazole **36** was the only compound with a single-digit nanomolar potency. The only other compounds which displayed sub-micromolar potencies were pyrazolone **16** and pyridone **43**, and even then, only just sub-micromolar.

Table 2



Monocyclic core SAR and SKR.

Cmpd	Core	GTPγS IC_{50} (nM)	Dissociation half-life (h)
16	Pyrazolone	970	n.d.
20	Imidazolone	10000	n.d.
25	Triazolone	2400	n.d.
30	Triazolone	inactive	n.d.
36	Imidazole	8	0.6
42	Pyridone	10000	n.d.
43	Pyridone	860	n.d.
48	Pyridone	inactive	n.d.
52	Pyridazinone	inactive	n.d.

n.d. not determined. Inactive refers to < 25% antagonism observed at 10 μM.

Almost all of the monocycles structure included a carbonyl group, a group which invariably helped in the synthesis of the diverse cores, but which impacted negatively on the potency. The SAR of the monocycles allowed us to generate some rules-of-thumb for the cores (Fig. 2):[37]

(1) A methyl group in the North of the core is beneficial. Polarity in the North is detrimental
(2) Polarity in the South West is not tolerated.
(3) Polarity in the South East is tolerated
(4) Lipophilicity somewhere in the South is beneficial.

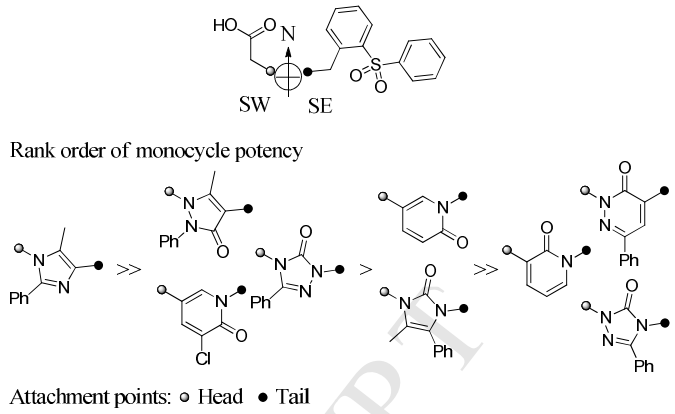
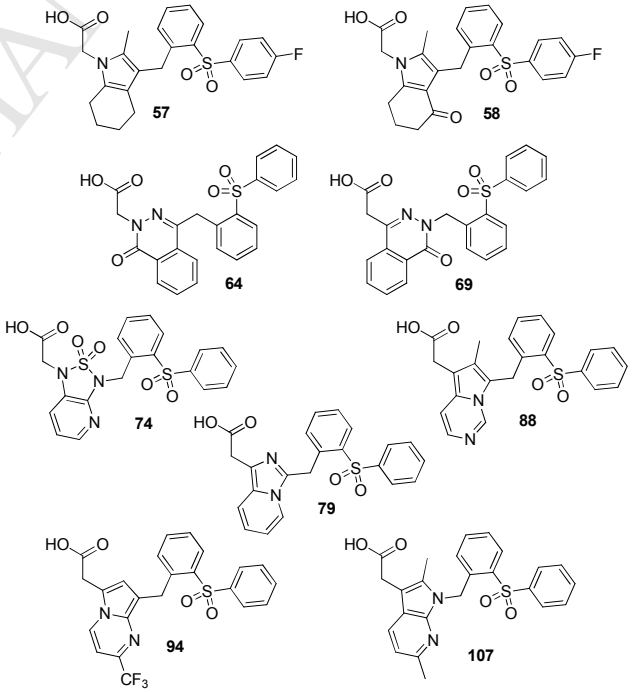


Fig. 3. Rank order of monocyclic cores and SAR map

Potent imidazole **36** was also testing for its receptor residence time, but its half-life was measured at only 0.6 h, below our minimum cut-off of 1 h. Hence we abandoned any further work on the monocyclic cores.

At the same time we were synthesizing and testing the bicyclic cores (Table 3).

Table 3



Bicyclic core SAR and SKR.

Cmpd	Core	GTPγS IC_{50} (nM)	Dissociation half-life (h)
57	Pyrrole	104	n.d.
58	Pyrrole	2	**21**
64	Phthalazinone	inactive	n.d.
69	Phthalazinone	65	0.04
74	Sulfamide	1600	n.d.
79	Imidazopyridine	3000	n.d.
88	Pyrrolopyrimidine	28	0.2
94	Pyrrolopyrimidine	47	0.05
107	Azaindole	14	1.3

n.d. not determined. Inactive refers to < 25% antagonism observed at 10 μM. Bold numbers indicate dissociation half-lives of ≥12h.

Pyrrole **57** which had given such synthetic problems was only moderately active. **58**, a close analogue of our PPA **4** was highly active at 2 nM. The pair of phthalazinones **64** and **69** were synthesized while we were still building our SAR rules of thumb, but these compounds also obeyed the rules: **64**, with polarity in the North and SouthWest portions of the core was inactive. **69** with polarity in the North and SouthEast of the core was fairly potent at 65 nM. Unfortunately, although not surprisingly, **69** suffered from a gradual decarboxylation upon standing, and accelerated decarboxylation upon heating, so this core was abandoned (Fig. 4).

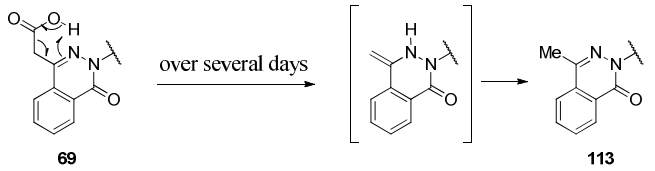


Fig. 4. Decarboxylation of phthalazinone **69**.

Thiadiazolopyridine dioxide **74** and imidazopyridine **79** also obeyed the SAR rules-of-thumb. Both cores possess an excess of polarity in the North of the core, the electron-rich sulfamide of **74**, and the strong hydrogen bond acceptor nitrogen of **79**. Both compounds were accordingly in the micromolar range. The remaining three 5,6-bicyclic cores, **88**, **94** and **107**, were all sufficiently potent.

We next measured the residence times of the most potent bicyclics. Pyrrole-derived **58** was a very long residence compound with a dissociation half-life of 21 h. This was maybe not too much of a surprise since it was a close analogue of long resident PPAs **4**, and it also possessed the para-fluoro substituent in the tail, a group we had shown to favour longer residence times.[12] Phthalazinones **69** and pyrrolo[1,2-a]pyrimidine **94**, were very short residence compounds, effectively losing all potency immediately after compound washout. The pyrrolo[1,2-c]pyrimidine **88** and azaindole **107** had half-lives which were at least measurable, with **107** possessing a half-life of just over 1 h.

Very few of the bicycles synthesized were apt for further investigation, either because of lack of potency or for lack of residence time. The GTPγS assay provided a semi-functional readout: activation of CRTh2 in membrane preparations by prostaglandin D_2 (PGD_2) triggers the binding of GTP to G-proteins. A functional readout was also available by measuring the activation (and antagonism thereof) of eosinophils in human blood – the eosinophil shape-change (ESC) assay. Only compound **88** was tested in the ESC assay and showed an IC_{50} of 12 nM, within experimental variation of the GTPγS IC_{50} of 28 nM. Since both assays gave similar results, we could be confident that the GTPγS IC_{50}s would be a true reflection of functional antagonism in vivo.

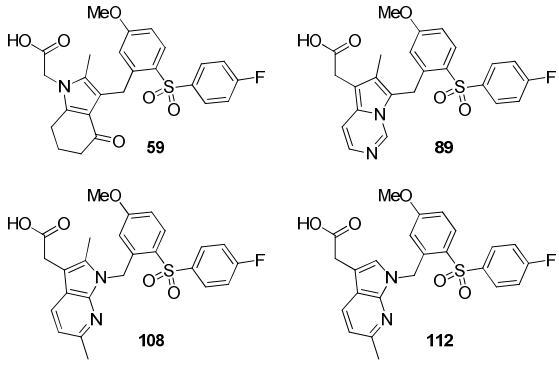
In addition to the SAR rules-of-thumb that applied across both the monocycles and the bicycles, a single observation stood out in terms of residence time and could be added to the list of Figure 2:

(5) a methyl group in the North of the core was beneficial for long(er) residence times.

Of the 4 compounds which displayed any kind of residence time, where measured, beyond a few minutes, **16**, **58**, **88** and **107** all possessed this same methyl group in the core. As a final optimization, we resynthesized the three bicyclic cores from this group of 4, but with the methoxy-fluoro substitution in the tail – a substitution pattern which had led to an approximate ten-fold increase in residence time in the PPA series[12] (Table 4).

All of the compounds were highly potent, as to be expected. Pyrrole **59** showed exactly the same potency and residence half-life as its analogue **58**. It seems that the methoxy-fluoro tail substitution of **59** offered no advantage over the mono-fluoro substitution of **58**. Even so, both of these compounds displayed dissociation half-lives of 21h, well above our desired cut-off of 12 h. The methoxy-fluoro substituted tail did improve the dissociation half-lives of both the other two cores tested. Pyrrolopyrimidine **89** had a half-life of 1.5 h, compared to 0.2 h for the unsubstituted tail analogue **88**, although this was still too short for our needs. Azaindole **108** showed a half-life of 13 h, and compared to 1.3 hours for unsubstituted tail analogue **107**. Thus **108** became the third compound of this investigation to achieve what we set out to discover, highly potent compounds with a residence half-life above 12 h. As a final investigation into the SKR, we synthesized azaindole **112**, identical to **108** except for the absence of the 2-methyl group in the North of the core. **112** was of a similar potency to **108**. The residence half-life fell off dramatically to just 30 min, just as the SKR rule-of-thumb stated.

Table 4



Methoxy-fluoro tail substitution SAR and SKR.

Cmpd	Core	GTPγS IC_{50} (nM)	Dissociation half-life (h)
59	Pyrrole	2	**21**
89	Pyrrolopyrimidine	5[a]	1.5
108	Azaindole	4	**13**
112	Azaindole	18	0.5

Bold numbers indicate dissociation half-lives of ≥12h. IC_{50} in ESC assay 6 nM.

4. Conclusions

The survey of different monocyclic and bicyclic cores revealed that the SAR was not as open as we had hoped for. Nevertheless, we could establish several rules-of-thumb for the structural requirements needed to obtain potent compounds, or at least to avoid weakly potent or inactive compounds. The more active compounds were also characterized for their receptor residence half-lives and again, a structural requisite of SKR – a methyl group in the North of the core in between the attachment points of the acetic acid and the tail chains – was also revealed. How this methyl group proportions longer residence times is unclear, however we can offer a speculation: the methyl group will have a steric influence over the possible conformations that these molecules can adopt. The conformation of binding to the receptor does not seem overly affected by the presence or absence of the methyl group. However, if the transition state conformation of the molecule as it makes its way from being unbound to its ultimate binding site requires either the head or tail to be squeezed close to the methyl group, this will imply and energetic penalty and a consequent slowing down of both the rates of association and dissociation. Whatever the reason may be, this structural feature could be employed empirically, and in combination with the methoxy-fluoro substitution pattern in the tail, be used to design potent and long resident CRTh2 antagonists.

5. Experimental Section

General:

Reaction products were purified, when necessary, by flash chromatography on silica gel (40-63 μm) with the solvent system indicated. Compounds obtained below 90% purity by HPLC or UPLC are generally referred to as in crude form.

Purifications in reverse phase were made in a Biotage SP1® or a Biotage Isolera automated purification system equipped with a C18 column and using a gradient of, unless otherwise stated, water-acetonitrile/MeOH (1:1) (0.1% v/v ammonium formate both phases) from 0% to 100% acetonitrile/MeOH (1:1) in 80 column volumes.
The conditions "formic acid buffer" refer to the use of 0.1% v/v formic acid in both phases.

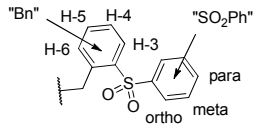
Preparative HPLC-MS were performed on a Waters instrument equipped with a 2767 injector/collector, a 2525 binary gradient pump, a 2996 PDA detector, a 515 pump as a make-up pump and a ZQ4000 Mass spectrometer detector.
Preparative HPLC was also carried out on an Agilent 1200 Series (AE-0010) with diode array detection and peak collection.

Gas chromatography was performed using a Thermo Trace Ultra gas chromatograph, coupled to a DSQ mass detector. Injections were performed on a split/splitless injector and a HP-1MS was the capillary column. Mass spectra were obtained by electron impact ionisation at 70 eV.

The HPLC chromatographic separations were obtained using a Waters 2795 system equipped with a Symmetry C18 (2.1 x 50 mm, 3.5 μM) column for methods 1, 2, 3 and 5 and a Symmetry C18 (2.1 x 100 mm, 3.5 μM) for method 4. A Waters 2996 diode array was used as a UV detector. Mass spectra of the chromatograms were acquired using positive and negative electrospray ionization in a Micromass ZMD or in a Waters ZQ detectors coupled to the HPLC. The mobile phases were (A): formic acid (0.5 ml), ammonia (0.125 ml) and water (1000 ml), (B): formic acid (0.4 ml), ammonia (0.1 ml), methanol (500 ml) and acetonitrile (500 ml). the following gradients were used.
Method 1 (5 min): 0% B, 0.2 min; 0 to 95% B, over 3 min; 95% B, 0.8 min. Method 2 (9 min): 0% B, 0.5 min; 0 to 95% B, over 6.5 min; 95% B, 1 min. Method 3 (15 min): 0 to 95% B, over 10.5 min; 95% B, 1,5 min. Method 4 (30 min): 0 to 95% B, over 20 min; 95% B, 4 min.
HPLC Chromatographic separations were also obtained using a Waters 2795 system equipped with a Symmetry C18 (2.1 x 50 mm, 3.5 μM) column for methods E. The mobile phases were (B): formic acid (0.7 ml) and acetonitrile (1000 ml) and (A): formic acid (1 ml) and water (1000 ml) (A), the gradients specified as follows: Method 5 (4.5 min): 5% to 100% B over 4.5 min.

The UPLC chromatographic separations were obtained using a Waters Acquity UPLC system coupled to a SQD mass spectrometer detector. The system was equipped with an ACQUITY UPLC BEH C-18 (2.1x50mm, 1.7 mm) column. The mobile phase was formic acid (0.4 ml), ammonia (0.1 ml), methanol (500 ml) and acetonitrile (500 ml) (B) and formic acid (0.5 ml), ammonia (0.125 ml) and water (1000 ml) (A). A gradient between 0 to 95% of B was used. The run time was 3 or 5 minutes. The injection volume was 0.5 microliter. Chromatograms were processed at 210 nM or 254 nM. Mass spectra of the chromatograms were acquired using positive and negative electrospray ionization.

^{1}H Nuclear Magnetic Resonance Spectra were recorded on a Varian Mercury plus operating at a frequency of 400MHz, Varian Gemini-2000 spectrometer operating at a frequency of 300MHz or a Varian VNMRS operating at 600MHz and equipped with a cold probe for the 1H spectra. Samples were dissolved in the specified deuterated solvent. Tetramethylsilane was used as reference. Chemical shifts δ in ppm, the following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), double doublet (dd), multiplet (m), broad signal (br. s).



Common identifiers of protons

1. Scheme 1

1.1. *2-(Phenylthio)benzaldehyde (**7a**)*

2-Fluorobenzaldehyde (9 ml, 90 mmol) and benzenethiol (8.8 ml, 90 mmol) were dissolved in 30 ml dimethylsulfoxide. Potassium carbonate (26 g, 190 mmol) was added and the mixture was heated at 100ºC for 4 h. The mixture was allowed to cool and was poured into water. The aqueous layer was extracted with ethyl acetate. The combined organics were washed with water and brine and were dried over sodium sulphate. Filtration and evaporation gave **7a** (18.5 g, 78.3 mmol, 92% yield) as a yellow oil. Used as such without further purification. Purity 91%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.08 - 7.12 (m, 1H, Ar), 7.29 - 7.46 (m, 7H, Ar), 7.88 (dd, *J*=1.4, 1.6 Hz, 1H, PhCHO H-6), 10.40 (s, 1H, CHO). HPLC/MS (9 min) retention time 6.53 min. LRMS: *m/z* 215 (M+1).

1.2. *2-[(4-Fluorophenyl)thio]benzaldehyde (**7b**)*

2-Fluorobenzaldehyde (1.86 g, 15.0 mmol) was treated with 4-fluorobenzenethiol (1.6 ml, 15.0 mmol) and potassium carbonate (4.67 g, 33.8 mmol) according to the method of **7a** to give **7b** (2.95 g, 11.8 mmol, 79% yield) as a yellow oil. Used as such without further purification. Purity 93%. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 6.87 (d, *J*=8.2 Hz, 1H, PhCHO H-3), 7.27 - 7.46 (m, 3H, Ar), 7.49 - 7.56 (m, 1H, Ar), 7.56 - 7.63 (m, 2H, Ar), 7.97 (d, *J*=7.4 Hz, 1H, PhCHO H-6), 10.22 (s, 1H, CHO). HPLC/MS (9 min) retention time 6.57 min. LRMS: *m*/*z* 233 (M+1).

1.3. *2-[(4 Fluorophenyl)thio]-5-methoxybenzaldehyde (**7c**)*

2–Fluoro-5-methoxybenzaldehyde (2.5 g, 16.2 mmol) was treated with 4-fluorobenzenethiol (2.1 g, 16.4 mmol) and potassium carbonate (4.5 g, 32.6 mmol) following the method of **7a**. The resulting residue was purified using the SP1 Purification System (ethyl acetate:hexane gradient, 0:100 rising to 5:95) to give **7c** (2.9 g, 10.8 mmol, 67% yield) as a yellow solid. Purity 98%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.86 (s, 3H, MeO), 7.02 – 6.95 (m, 2H, Ar), 7.08 (dd, *J*=3.0, 8.7 Hz, 1H PhCHO H-3), 7.25 – 7.18 (m, 2H, Ar), 7.28 (d, *J*=8.6 Hz, 1H, PhCHO H-4), 7.44 (d, *J*=3.0 Hz, 1H, PhCHO H-6), 10.48 (s, 1H, CHO), HPLC/MS (9 min) retention time 6.80 min. LRMS: *m*/*z* 263 (M+1).

1.4. *2-(Phenylsulfonyl)benzaldehyde (**8a**)*

Thioether **7a** (3.5 g, 16.3 mmol) was dissolved in 50 ml dichloromethane. 3-Chloroperbenzoic acid (77% purity, 11 g, 49 mmol) was added in portions and the mixture was stirred at room temperature overnight. The mixture was washed with sodium carbonate 5% solution, water and brine. The resulting organic layer was dried over sodium sulphate, filtered and evaporated. The residue was purified using the SP1 Purification System (ethyl acetate-hexane gradient, 0:100 rising to 30:70) to give **8a** (1.9 g, 7.7 mmol, 47% yield) as a white solid. Purity 100%. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 7.67 (t, *J*=7.6 Hz, 2H, SO_2Ph meta), 7.75 (t, *J*=7.4 Hz, 1H, PhCHO H-4), 7.88 - 7.99 (m, 3H, Ar), 8.02 (d, *J*=7.4 Hz, 2H, SO_2Ph ortho), 8.20 (d, *J*=7.8 Hz, 1H, PhCHO H-3), 10.68 (s, 1H, CHO). HPLC/MS (9 min) retention time 5.47 min. LRMS: *m*/*z* 247 (M+1).

1.5. *2-[(4-Fluorophenyl)sulfonyl]benzaldehyde (**8b**)*

Thioether **7b** (2.0 g, 7.96 mmol) was dissolved in 30 ml dichloromethane and the mixture was cooled in an ice-bath. 3-Chloroperbenzoic acid (77% purity, 4.1 g, 24 mmol) was added in portions and the mixture was stirred at room temperature for 2 h. The mixture was washed sequentially with 25% solution potassium hydrogen sulphate, 1N sodium hydroxide and brine. The resulting organic layer was dried over sodium sulphate, filtered and evaporated to give **8b** (1.88 g, 7.11 mmol, 89% yield) as a yellow solid. Purity 100%. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 7.51 (t, *J*=8.8 Hz, 2H, SO_2PhF meta), 7.87 - 7.99 (m, 3H, Ar), 8.07 - 8.16 (m, 2H, Ar), 8.20 (d, *J*=7.0 Hz, 1H, PhCHO H-3), 10.66 (s, 1H, CHO). GC/MS (18 min) retention time 10.0 min. LRMS: *m*/*z* 265 (M+1).

1.6. *2-[(4 Fluorophenyl)sulfonyl]-5-methoxybenzaldehyde (**8c**)*

Thioether **7c** (2.9 g, 10.8 mmol) was treated with 3-chloroperbenzoic acid (77% purity, 7.5 g, 33.5 mmol) following the method of **8a**. The resulting residue was partially purified using the SP1 Purification System (ethyl acetate:hexane gradient, 0:100 rising 25:75) to give **8c** (600 mg). Used as such without further purification. Purity 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.91 (s, 3H, MeO), 7.17 - 7.24 (m, 3H, Ar), 7.49 (d, *J*=2.7 Hz, 1H, PhCHO H-6), 7.87 - 7.93 (m, 2H, Ar), 8.14 (d, *J*=9.0 Hz, 1H, PhCHO H-3), 10.79 (s, 1H, CHO). HPLC/MS (9 min) retention time 5.88 min. LRMS: *m*/*z* 295 (M+1).

1.7. *[2-(Phenylsulfonyl)phenyl]methanol (**9a**)*

Aldehyde **8a** (1.98 g, 8.0 mmol) was suspended in 16 ml methanol. Sodium borohydride (150 mg, 3.86 mmol) was added in portions and the mixture was stirred at room temperature for 30 min. 5% Hydrochloric acid solution (4 ml) was added and the mixture was evaporated. The residue was taken up in water and the aqueous was extracted twice with dichloromethane. The combined organics were washed with brine and dried over sodium sulphate. Filtration and evaporation gave **9a** (1.9 g, 7.3 mmol, 95% yield) as a white solid. Purity 96%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.74 (s, 2H, CH_2), 7.49 - 7.58, (m, 4H, Ar), 7.61 (d, *J*=7.5 Hz, 1H, Ar), 7.64 (d, *J*=7.5 Hz, 1H, Ar), 7.90 (d, *J*=7.4 Hz, 2H, SO_2Ph ortho), 8.15 (d, *J*=7.8 Hz, 1H, Bn H-3). HPLC/MS (9 min) retention time 4.97 min. LRMS: *m*/*z* 249 (M+1).

1.8. *[2-(4-Fluorophenylsulfonyl)phenyl]methanol (**9b**)*

Aldehyde **8b** (1.0 g, 3.8 mmol) was treated with sodium borohydride (70 mg, 1.8 mmol) following the method of **9a** to give **9b** (1.0 g, 3.8 mmol, 100% yield) as a white solid. Purity 96%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.75 (s, 2H, CH_2), 7.21 (t, *J*=8.4 Hz, 2H, SO_2PhF meta), 7.53 (t, *J*=7.6 Hz, 1H, Bn H-4), 7.58 (d, *J*=7.4 Hz, 1H, Bn H-6), 7.64 (t, *J*=7.4 Hz, 1H, Bn H-5), 7.92 (dd, *J*=5.1, 9.0 Hz, 2H, SO_2PhF ortho), 8.11 (d, *J*=7.8 Hz, 1H, Bn H-3). HPLC/MS (9 min) retention time 5.17 min. LRMS: *m*/*z* 267 (M+1).

1.9. *[2-(4-Fluorophenylsulfonyl)-5-methoxyphenyl]methanol (**9c**)*

Crude Aldehyde **8c** (0.32 g, 1.1 mmol) was treated with sodium borohydride (20 mg, 0.53 mmol) following the

method of **9a** to give **9c** (0.32 g, 1.1 mmol, 19% yield over two steps) as a colourless oil. Purity 100%. ^{1}H NMR spectrum not recorded. UPLC/MS (3 min) retention time 1.46 min. LRMS: *m*/*z* 297 (M+1).

1.10. *1-(Bromomethyl)-2-(phenylsulfonyl)benzene (**10a**)*

Alcohol **9a** (1.9 g, 7.3 mmol) was suspended in 20 ml chlorobenzene. Thionyl bromide (1.46 ml, 18.3 mmol) was slowly added and the mixture was heated at 110ºC for 1 h. The mixture was concentrated under reduced pressure and the residue was partitioned between water and dichloromethane. The aqueous phase was basified with potassium carbonate and extracted three times with dichloromethane. The combined organics were washed with water and brine, dried over sodium sulphate and evaporated. The residue was purified by column chromatography (ethyl acetate-hexane gradient, 0:100 rising to 8:92) to give **10a** (1.95 g, 5.89 mmol, 80% yield) as an orange oil. Purity 94%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.89 (s, 2H, CH_2), 7.48 - 7.64 (m, 6H, Ar), 7.92 (d, *J*=7.4 Hz, 2H, SO_2Ph ortho), 8.19 (d, *J*=7.8 Hz, 1H, Bn H-3). HPLC/MS (9 min) retention time 6.03 min. LRMS: *m*/*z* 328, 330 (M+18).

1.11. *1-(Bromomethyl)-2-(4-fluorophenylsulfonyl)benzene (**10b**)*

Alcohol **9b** (1.1 g, 4.1 mmol) was suspended in 10 ml chlorobenzene. Thionyl bromide (0.73 ml, 9.4 mmol) was slowly added and the mixture was heated at 110ºC for 1 h. The mixture was concentrated under reduced pressure and the residue was partitioned between water and dichloromethane. The aqueous phase was basified with potassium carbonate and extracted three times with dichloromethane. The combined organics were washed with water, brine and dried over sodium sulphate and evaporated to give **10b** (1.1 g, 3.2 mmol, 77% yield) as a white solid. Purity 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.89 (s, 2H, CH_2), 7.21 (t, *J*=8.2 Hz, 2H, SO_2PhF meta), 7.51 (t, *J*=7.6 Hz, 1H, Bn H-4), 7.57 (d, *J*=7.5 Hz, 1H, Bn H-6), 7.62 (t, *J*=7.4 Hz, 1H Bn H-5), 7.95 (dd, *J*=5.3, 8.0 Hz, 2H, SO_2PhF ortho), 8.18 (d, *J*=7.8 Hz, 1H, Bn H-3). HPLC/MS (9 min) retention time 6.23 min. LRMS: *m*/*z* 346, 348 (M+18).

1.12. *1-(Bromomethyl)-2-(4-fluorophenylsulfonyl)-5-methoxybenzene (**10c**)*

Alcohol **9c** (0.25 g, 86 mmol) was treated with thionyl bromide (0.17 ml, 2.2 mmol) following the method of **10a**. The residue was purified by column chromatography (ethyl acetate-hexane gradient, 0:100 rising to 18:82) to give **10c** (0.21 g, 0.59 mmol, 69% yield) as a white solid. Purity 100%. NMR spectrum not recorded. UPLC/MS (3 min) retention time 1.79 min. LRMS: *m*/*z* 376, 378 (M+18).

1.13. *[2-(Phenylsulfonyl)phenyl]methylamine (**11a**)*

Aldehyde **8a** (2.0 g, 8.1 mmol) was dissolved in 20 ml ethanol. A solution of hydroxylamine hydrochloride (0.63 g, 9.1 mmol) and sodium bicarbonate (0.68 g, 8.1 mmol) dissolved in 20 ml water was added and the mixture was stirred for 2 h at room temperature. The mixture was partially evaporated and was partitioned between ethyl acetate and brine. The aqueous was extracted with ethyl acetate and the combined organics were evaporated under reduced pressure. The residue was dissolved in a mixture of 35 ml tetrahydrofuran and 40 ml 2N hydrochloric acid. Zinc dust (5.0 g, 76.5 mmol) was added and the mixture was stirred at reflux for 1 h. The mixture was allowed to cool and was filtered through a pad of Celite, washing through with dichloromethane. The aqueous phase was basified to pH >10 with 8N sodium hydroxide solution and the phases were separated. The aqueous was extracted with dichloromethane and the combined organics were washed with water, brine, dried over magnesium sulphate and evaporated under reduced pressure to give **11a** (1.9 g, 7.7 mmol, 95% yield) as a pale yellow oil. Purity 97%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.97 (s, 2H, CH_2), 7.47 (t, *J*=8.2 Hz, 1H, Bn H-6), 7.50 - 7.55 (m, 3H, Ar), 7.56 - 7.65 (m, 2H, Ar), 7.89 (d, *J*=7.4 Hz, 2H, SO_2Ph ortho), 8.18 (d, *J*=7.8 Hz, 1H, Bn H-3). HPLC/MS (9 min) retention time 3.32 min. LRMS: *m*/*z* 248 (M+1).

2. Scheme 2

2.1. *Ethyl 2-acetyl-3-[2-(phenylsulfonyl)phenyl]acrylate (**12**)*

Aldehyde **8a** (1.14 g, 4.6 mmol) was dissolved in 8 ml ethanol containing activated 4Å molecular sieves. Ethyl 3-oxobutanoate (0.60 g, 4.6 mmol), piperidine (0.39 g, 4.6 mmol) and acetic acid (0.27 g, 4.6 mmol) were added. The mixture was stirred at reflux for 2 h and then allowed to cool to room temperature. The mixture was filtered through a plug of Celite, washing through with ethyl acetate. The combined filtrate was evaporated under reduced pressure and the residue was purified using the Isolera system (ethyl acetate-hexane gradient, 0:100 rising to 50:50) to give **12** (1.48 g, 4.1 mmol, 90% yield) as a yellow solid and a 60:40 mixture of isomers. Purity 100%. ^{1}H NMR (400 MHz, $CDCl_3$) Major isomer: δ ppm 0.79 (t, *J*=7.0 Hz, 3H, OCH_2CH_3), 2.44 (s, 3H, COMe), 3.87 (q, *J*=7.0 Hz, 2H, OCH_2CH_3), 7.35 (d, *J*=6.6 Hz, 1H, Ar), 7.42 - 7.64 (m, 5H, Ar), 7.82 (d, *J*=7.4 Hz, 2H, SO_2Ph ortho), 8.26 (d, *J*=7.4 Hz, 1H, vinylPh H-3), 8.27 (s, 1H, vinyl H). Minor isomer: δ ppm 1.38 (t, *J*=7.0 Hz, 3H, OCH_2CH_3), 1.65 (s, 3H, COMe), 4.34 (q, *J*=7.2 Hz, 2H, OCH_2CH_3), 7.28 (d, *J*=7.4 Hz, 1H, Ar), 7.42 - 7.64 (m, 5H, Ar), 7.90 (d, *J*=7.4 Hz, 2H, SO_2Ph ortho), 8.17 (s, 1H, vinyl H), 8.32 (d, *J*=7.4 Hz, 1H, vinylPh H-3). HPLC/MS (9 min) retention time 5.98 (major) and 6.18 (minor) min. LRMS: *m*/*z* 359 (M+1).

2.2. *Ethyl 3-oxo-2-[2-(phenylsulfonyl)benzyl]butanoate (**13**)*

Alkene **12** (1.48 g, 4.1 mmol) was dissolved in 30 ml ethanol and 30 ml tetrahydrofuran. 10% Palladium on carbon (0.44 g) was added and the mixture was agitated under a hydrogen atmosphere (20 psi) for 20 min. The mixture was filtered through a plug of Celite, washing through with tetrahydrofuran. The combined filtrate was evaporated under reduced pressure and the residue was purified using the Isolera system (ethyl acetate-hexane gradient, 0:100 rising to 35:65) to give **13** (1.37 g, 3.80 mmol, 92% yield) as a pale yellow oil. Purity 96%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.22 (t, *J*=7.2 Hz, 3H, OCH_2CH_3), 2.25 (s, 3H, COMe), 3.20 (dd, *J*=8.2, 14.1 Hz, 1H, CH_AH_BPh), 3.38 (dd, *J*=5.7, 13.9 Hz, 1H, CH_AH_BPh), 4.08 - 4.20 (m, 3H, OCH_2CH_3 and COCHCO), 7.29 (dd, *J*=1.6, 7.4 Hz, 1H, Bn H-6), 7.41 - 7.49 (m, 2H, Ar), 7.51 (t, *J*=7.0 Hz, 2H, SO_2Ph meta), 7.59 (t, *J*=7.2 Hz, 1H, SO_2Ph para), 7.84 (d, *J*=7.0 Hz, 2H, SO_2Ph ortho), 8.19 (dd, *J*=1.8, 7.6 Hz, 1H, Bn H-3). HPLC/MS (9 min) retention time 6.20 min. LRMS: *m*/*z* 359 (M-1).

2.3. *5-Methyl-2-phenyl-4-[2-(phenylsulfonyl)benzyl]-1,2-dihydro-3H-pyrazol-3-one (**14**)*

Dicarbonyl **13** (0.50 g, 1.4 mmol) was dissolved in 10 ml glacial acetic acid. Sodium acetate (0.57 g, 6.9 mmol) and phenylhydrazine (0.17 g, 1.67 mmol) were added and the mixture was stirred at 70 ºC for 90 min. The mixture was allowed to cool and was partitioned between ethyl acetate and water. The aqueous phase was extracted twice with ethyl acetate. The combined organics were washed with brine, dried over sodium sulphate, filtered and evaporated. The residue was triturated with ether to give a precipitate which was collected by filtration and dried in a stream of air to give **14** (0.39 g, 0.97 mmol, 69% yield) as a white solid. Purity 94%. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.51 (s, 3H, pyrazolone Me), 3.81 (s, 2H, CH_2Ph), 7.11 - 7.26 (m, 2H, Ar), 7.42 (t, *J*=7.8 Hz, 2H, NPh meta), 7.54 (t, *J*=7.6 Hz, 1H, Ar), 7.58 - 7.80 (m, 6H, Ar), 7.92 (d, *J*=7.4 Hz, 2H, SO_2Ph ortho), 8.19 (d, *J*=7.7 Hz, 1H, Bn H-3), 11.00 (br. s., 1H, NH). UPLC/MS (3 min) retention time 1.57 min. LRMS: *m*/*z* 405 (M+1).

2.4. *Ethyl {5-methyl-3-oxo-2-phenyl-4-[2-(phenylsulfonyl)benzyl]-2,3-dihydro-1H-pyrazol-1-yl}acetate (**15**)*

Pyrazolone **14** (140 mg, 0.35 mmol) was dissolved in 2.5 ml anhydrous dimethyformamide. Potassium carbonate (53 mg, 0.38 mmol) was added and the mixture was stirred for 45 min. Ethyl bromoacetate (42 µl, 0.38 mmol) was added and the mixture was stirred for 1 h. The mixture was partitioned between ethyl acetate and water. The aqueous phase was extracted three times with ethyl acetate. The combined organics were washed with brine, dried over sodium sulphate, filtered and evaporated. The residue was partially purified using the Isolera system (methanol-dichloromethane gradient, 0:100 rising to 50:50) to give 45 mg crude product. This was re-purified by reverse-phase chromatography using the Isolera to give **15** (16 mg, 0.033 mmol, 9% yield) as a white solid. Purity 100%. Regiochemistry was confirmed by nOe experiment. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.17 (t, *J*=6.2 Hz, 3H, OCH_2CH_3), 2.04 (s, 3H, pyrazolone Me), 3.93 (s, 2H, CH_2Ph), 4.10 (q, *J*=6.8 Hz, 2H, OCH_2CH_3), 4.21 (s, 2H, CH_2COEt), 7.23 - 7.60 (m, 11H, Ar), 7.88 (d, *J*=6.0 Hz, 2H, SO_2Ph ortho), 8.24 (d, *J*=6.6 Hz, 1H, CH_2Ph H-3). UPLC/MS (3 min) retention time 1.69 min. LRMS: *m*/*z* 491 (M+1).

2.5. *{5-Methyl-3-oxo-2-phenyl-4-[2-(phenylsulfonyl)benzyl]-2,3-dihydro-1H-pyrazol-1-yl}acetic acid (**16**)*

Ester **15** (16 mg, 0.033 mmol) was dissolved in 0.5 ml tetrahydrofuran and 0.5 ml water. Lithium hydroxide monohydrate (5.5 mg, 0.13 mmol) was added and the mixture was stirred for 90 min. The organics were evaporated and the remaining aqueous was acidified with 0.5N hydrochloric acid forming a precipitate. The solid was collected by filtration, was washed with water and was dried under vacuum to give **16** (6.6 mg, 0.013 mmol, 43% yield) as a white solid. Purity 97%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.92 (s, 3H, Me), 3.92 (s, 2H, CH_2Ph), 4.12 (s, 2H, CH_2COOH), 7.26 - 7.45 (m, 8H, Ar), 7.48 (d, *J*=7.7 Hz, 2H, SO_2Ph meta), 7.55 (t, *J*=7.2 Hz, 1H, SO_2Ph para), 7.85 (d, *J*=8.0 Hz, 2H, SO_2Ph ortho), 8.18 (d, *J*=7.1 Hz, 1H, CH_2Ph H-3). HPLC/MS (30 min) retention time 13.50 min. LRMS: *m*/*z* 463 (M+1).

3. Scheme 3

3.1. *2-Amino-1-phenylpropan-1-one hydrochloride (**17**)*

Sodium diformylamide (1.1 g, 11.6 mmol) was suspended in 20 ml acetonitrile. 2-Bromo-1-phenylpropanone (2.0 g, 9.4 mmol) was added drop-wise and with stirring. The mixture was then stirred at 75 ºC for 36 h. The mixture was hot filtered and the solid was washed twice with acetonitrile. The combined organics were evaporated under reduced pressure and the residue was suspended in 9 ml 5N hydrochloric acid. The mixture was stirred at reflux for 45 min and was then evaporated under reduced pressure. The residue was re-evaporated twice from isopropanol and was then triturated with ether to give a precipitate. The solid was collected by filtration, washed twice with ether and dried in vacuo to give **17** (1.4 g, 7.5 mmol, 80% yield) as a white solid. Purity 100%. ^{1}H NMR (400 MHz, D_2O) δ ppm 1.42 (d, *J*=7.0 Hz, 3H, Me), 5.02 (q, *J*=7.0 Hz, 1H, CH), 7.44 (t, *J*=7.2 Hz, 2H, Ph meta), 7.60 (t, *J*=7.2 Hz, 1H, Ph para), 7.84 (d, *J*=7.4 Hz, 2H, Ph ortho). HPLC/MS (9 min) retention time 1.13 min. LRMS: *m*/*z* 150 (M+1).

3.2. *Ethyl (4-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-imidazol-1-yl)acetate trifluoroacetate (**18**)*

Amine salt **17** (250 mg, 1.35 mmol) was suspended in 15 ml acetone and the mixture cooled in an ice bath. Ethyl 2-isocyanatoacetate (192 mg, 1.49 mmol) was added drop-wise and with stirring, followed by triethylamine (0.75 ml, 5.4 mmol). The mixture was stirred at 0 ºC for 3 h. 2 ml Trifluoroacetic acid was added and the mixture was stirred for a further 1 h at room temperature. The mixture was partitioned between chloroform and saturated sodium bicarbonate solution. The organics were dried over sodium sulphate, filtered and evaporated to give **18** (345 mg, 0.88 mmol, 65% yield) as a pale yellow solid. Purity 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.20 (t, *J*=7.2 Hz, 3H, OCH_2CH_3), 2.07 (s, 3H, Me), 4.14 (q, *J*=7.3 Hz, 2H, OCH_2CH_3), 4.31 (s, 2H, CH_2CO), 7.25 (d, *J*=7.5 Hz, 2H, Ph ortho), 7.35 (t, *J*=7.2 Hz, 1H, Ph para), 7.41 (t, *J*=7.2 Hz, 2H, Ph meta), 9.57 (br. s., 1H, NH). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -75.68 (s, 3F). HPLC/MS (9 min) retention time 5.38 min. LRMS: *m*/*z* 261 (M+1).

3.3. *Ethyl (3-{2-[(4-fluorophenyl)sulfonyl]benzyl}-4-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-imidazol-1-yl)acetate (**19**)*

Imidazolone salt **18** (150 mg, 0.40 mmol) was dissolved in 5 ml dimethylformamide. Triethylamine (60 µl, 0.43 mmol) was added and the mixture was stirred for 15 min. Bromide **10b** (400 mg, 1.22 mmol) and potassium carbonate (170 mg, 1.23 mmol) were added and the mixture was stirred at room temperature overnight. The mixture was partitioned between ethyl acetate and water. The aqueous phase was extracted twice with ethyl acetate. The combined organics were washed with brine, dried over sodium sulphate, filtered and evaporated. The residue was purified by reverse-phase chromatography to give **19** (65 mg, 0.13 mmol, 32% yield) as a white solid. Purity 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.20 (t, *J*=7.0 Hz, 3H, OCH_2CH_3), 1.75 (s, 3H, Me), 4.13 (q, *J*=7.0 Hz, 2H, OCH_2CH_3), 4.35 (s, 2H, CH_2CO), 5.22 (s, 2H, CH_2Ph), 7.15 (d, *J*=7.8 Hz, 1H, Bn H-6), 7.19 - 7.26 (m, 4H, Ar), 7.35 - 7.46 (m, 3H, Ar), 7.50 (t, *J*=7.6 Hz, 1H, Ar), 7.60 (t, *J*=6.6 Hz, 1H, Ar), 7.94 (dd, *J*=4.9, 8.8 Hz, 2H, SO_2Ph ortho), 8.23 (d, *J*=7.8 Hz, 1H, Bn H-3). HPLC/MS (9 min) retention time 6.77 min. LRMS: *m*/*z* 509 (M+1).

3.4. *(3-{2-[(4-Fluorophenyl)sulfonyl]benzyl}-4-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-imidazol-1-yl)acetic acid (**20**)*

Ester **19** (65 mg, 0.13 mmol) was dissolved in 3 ml tetrahydrofuran and 3 ml water. Lithium hydroxide monohydrate (30 mg, 0.71 mmol) was added and the mixture was stirred overnight. The organics were evaporated and residue was purified by reverse-phase chromatography to give **20** (34 mg, 0.070 mmol, 55% yield) as a white solid. Purity 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.73 (s, 3H, Me), 4.29 (s, 2H, $COCH_2$), 5.24 (s, 2H, CH_2Ph), 7.13 (m, 1H, Bn H-6), 7.16 - 7.23 (m, 2H, Ar), 7.23 - 7.29 (m, 3H, Ar), 7.35 - 7.44 (m, 3H, Ar), 7.45 - 7.53 (m, 1H, Ar), 7.60 (m, 1H, Ar), 7.91 - 7.97 (m, 2H, SO_2Ph ortho), 8.19 - 8.24 (m, 1H, Bn H-3). HPLC/MS (30 min) retention time 15.98 min. LRMS: *m*/*z* 481 (M+1).

4. Scheme 4

4.1. *Ethyl N-[(2-benzoylhydrazino)carbonyl]glycinate (**21**)*

Benzohydrazide (0.53 g, 3.9 mmol) was dissolved in 10 ml tetrahydrofuran under nitrogen and the mixture stirred at 50 ºC. Ethyl 2-isocyanatoacetate (0.50 g, 3.9 mmol) was added drop-wise and with stirring. The mixture was then stirred at 50 ºC overnight, forming a precipitate. The solid was collected by filtration, was washed with ether and dried in a stream of air to give **21** (1.00 g, 3.8 mmol, 97% yield) as a white solid. Purity 100%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.19 (t, *J*=7.0 Hz, 3H, OCH_2CH_3), 3.78 (d, *J*=5.9 Hz, 2H, CH_2CO), 4.09 (q, *J*=7.3 Hz, 2H, OCH_2CH_3), 6.86 (br. s., 1H, NH), 7.48 (t, *J*=7.4 Hz, 2H, Ph meta), 7.56 (t, *J*=7.4 Hz, 1H, Ph para), 7.90 (d, *J*=7.4 Hz, 2H, Ph ortho), 8.20 (br. s., 1H, NH), 10.22 (s, 1H, NH). HPLC/MS (9 min) retention time 3.93 min. LRMS: *m*/*z* 266 (M+1).

4.2. *(5-Oxo-3-phenyl-1,5-dihydro-4H-1,2,4-triazol-4-yl)acetic acid (**22**)*

Acyl semicarbazide **21** (0.50 g, 1.88 mmol) was suspended in 10 ml 5N sodium hydroxide solution and the mixture was stirred at reflux overnight. The mixture was allowed to cool and was acidified with 5N hydrochloric acid. The aqueous was extracted with ethyl acetate, the organics were washed with brine, dried over sodium sulphate, filtered and evaporated to give crude **22** (0.25 g). Purity 71%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.43 (s, 2H, CH_2CO), 7.51 (t, *J*=7.4 Hz, 2H, Ph meta), 7.63 (t, *J*=7.4 Hz, 1H, Ph para), 7.95 (d, *J*=7.4 Hz, 2H, Ph ortho), 12.03 (s, 1H, NH), 13.05 (br. s., 1H, OH). HPLC/MS (9 min) retention time 3.85 min. LRMS: *m*/*z* 220 (M+1).

4.3. *Ethyl (5-oxo-3-phenyl-1,5-dihydro-4H-1,2,4-triazol-4-yl)acetate (**23**)*

Crude Triazolone **22** (0.25 g) was dissolved in 4 ml ethanol. 0.2 ml Concentrated sulphuric acid was added and the mixture was stirred at relux overnight. The mixture was evaporated under reduced pressure. The residue was partitioned between dichloromethane and saturated sodium bicarbonate solution. The organics were washed with water, dried over sodium sulphate, filtered and evaporated to give

crude **23** (150 mg) as an oil. Purity 60%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.23 (t, *J*=7.3 Hz, 3H, OCH_2CH_3), 4.20 (q, *J*=7.3 Hz, 2H, OCH_2CH_3), 4.48 (s, 2H, CH_2CO), 7.44 (t, *J*=7.8 Hz, 2H, Ph meta), 7.56 (t, *J*=7.4 Hz, 1H, Ph para), 8.05 (d, *J*=7.4 Hz, 2H, Ph ortho), 9.48 (br. s., 1H, NH). HPLC/MS (9 min) retention time 4.78 min. LRMS: *m*/*z* 248 (M+1).

4.4. *Ethyl {5-oxo-3-phenyl-1-[2-(phenylsulfonyl)benzyl]-1,5-dihydro-4H-1,2,4-triazol-4-yl}acetate (**24**)*

Crude triazolone **23** (150 mg) was dissolved in 10 ml acetonitrile. Bromide **10a** (115 mg, 0.37 mmol) and potassium carbonate (100 mg, 0.72 mmol) were added and the mixture was stirred at reflux overnight. The mixture was evaporated under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic phase was washed with water, brine, dried over sodium sulphate, filtered and evaporated. The residue was purified using the Isolera system (ethyl acetate-hexane gradient, 0:100 rising to 60:40) to give **24** (140 mg, 0.29 mmol, 16% yield over three steps) as a white solid. Purity 98%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.23 (t, *J*=7.2 Hz, 3H, OCH_2CH_3), 4.19 (q, *J*=7.0 Hz, 2H, OCH_2CH_3), 4.51 (s, 2H, CH_2CO), 5.46 (s, 2H, NCH_2Ph), 7.19 (d, *J*=7.8 Hz, 1H, Bn H-6), 7.45 - 7.62 (m, 10H, Ar), 7.95 (d, *J*=7.4 Hz, 2H, SO_2Ph ortho), 8.22 (d, *J*=7.4 Hz, 1H, Bn H-3). HPLC/MS (9 min) retention time 6.37 min. LRMS: *m*/*z* 478 (M+1).

4.5. *{5-Oxo-3-phenyl-1-[2-(phenylsulfonyl)benzyl]-1,5-dihydro-4H-1,2,4-triazol-4-yl}acetic acid (**25**)*

Ester **24** (140 mg, 0.29 mmol) was dissolved in 5 ml tetrahydrofuran and 5 ml water. Lithium hydroxide monohydrate (75 mg, 1.8 mmol) was added and the mixture was stirred for 3 h. The organics were evaporated and the remaining aqueous was acidified with 2N hydrochloric acid forming a oily residue. The aqueous was extracted with ethyl acetate and the organics dried over sodium sulphate, filtered and evaporated. The residue was sonnicated in ether to give a solid which was collected by filtration, washed with ether and was dried under vacuum to give **25** (85 mg, 0.19 mmol, 64% yield) as a white solid. Purity 97%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.46 (s, 2H, CH_2CO), 5.23 (s, 2H, NCH_2Ph), 7.10 (d, *J*=7.4 Hz, 1H, Bn H-6), 7.42 – 7.51 (m, 4H, Ar), 7.57 – 7.71 (m, 6H, Ar), 7.94 (d, *J*=7.4 Hz, 2H, SO_2Ph ortho), 8.16 (d, *J*=7.4 Hz, 1H, Bn H-3). HPLC/MS (30 min) retention time 14.82 min. LRMS: *m*/*z* 450 (M+1).

4.6. *1-(Isocyanatomethyl)-2-(phenylsulfonyl)benzene (**26**)*

Triphosgene (0.60 g, 2.0 mmol) was dissolved in 20 ml dichloromethane and the mixture cooled in an ice bath. A solution of amine **11a** (0.50 g, 2.0 mmol) dissolved in 5 ml tetrahydrofuran was added drop-wise and with stirring. A mixture of triethylamine (0.60 ml, 2.1 mmol) dissolved in 5 ml tetrahydrofuran was then added drop-wise and with stirring. The mixture was removed from the ice-bath and was stirred for 2.5 h, warming to room temperature. Pentane was added while stirring to form a precipitate. The mixture was filtered and the filtrate was evaporated to give **26** (0.53 g, 1.94 mmol, 96% yield) as a colourless oil. Used as such without further purification. Purity 95%. NMR spectrum not recorded. HPLC/MS (9 min) sample dissolved in methanol: retention time 5.35 min. LRMS: *m*/*z* 305 (M+MeOH+1).

4.7. *2-Benzoyl-N-[2-(phenylsulfonyl)benzyl]hydrazinecarboxamide (**27**)*

Benzohydrazide (265 mg, 1.95 mmol) was dissolved in 10 ml tetrahydrofuran under nitrogen and the mixture was stirred at 50 ºC. Isocyanate **26** (530 mg, 1.94 mmol) was added drop-wise and the mixture was stirred at 50 ºC overnight. The mixture was allowed to cool and was evaporated under reduced pressure. The oily residue was taken up in ether and sonicated. The ether was decanted and the process repeated until a solid was obtained. The solid was collected by filtration and was dried in a stream of air to give **27** (790 mg, 1.93 mmol, 99% yield) as a white solid. Purity 93%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.55 (d, *J*=3.5 Hz, 2H, CH_2Ph), 6.58 (t, *J*=3.5 Hz, 1H, $NHCH_2$), 7.39 - 7.60 (m, 9H, Ar), 7.63 (d, *J*=7.4 Hz, 1H, Ar), 7.85 (app t, *J*=7.6 Hz, 4H, Ar), 8.09 (d, *J*=7.8 Hz, 1H, Bn H-6), 9.00 (br. s., 1H, NH). HPLC/MS (9 min) retention time 5.35 min. LRMS: *m*/*z* 410 (M+1).

4.8. *5-Phenyl-4-[2-(phenylsulfonyl)benzyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (**28**)*

Semicarbazide **27** (400 mg, 0.98 mmol) was suspended in 8 ml 5N sodium hydroxide solution and was stirred at reflux overnight. A further 4 ml 5N sodium hydroxide solution was added and the mixture was stirred at reflux for a further night. The mixture was allowed to cool and was acidified with concentrated hydrochloric acid. The mixture was extracted with dichloromethane and the organic phase was washed with water, brine, dried over sodium sulphate, filtered and evaporated to give crude **28** (280 mg) as a solid. Purity 85%. NMR spectrum not recorded. HPLC/MS (9 min) retention time 5.68 min. LRMS: *m*/*z* 392 (M+1).

4.9. *tert-Butyl {5-oxo-3-phenyl-4-[2-(phenylsulfonyl)benzyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}acetate (**29**)*

Crude triazolone **28** (280 mg) was dissolved in 10 ml acetonitrile. Potassium carbonate (170 mg, 1.23 mmol) and tert-butyl bromoacetate (118 mg, 0.60 mmol) were added and the mixture was stirred at reflux for 24 h. The mixture allowed to cool and was evaporated under reduced pressure. The residue was partitioned between ethyl acetate and water. The aqueous phase was extracted twice with ethyl acetate. The combined organics were washed with water, brine, dried over

sodium sulphate, filtered and evaporated. The residue was purified using the SP1 purification system (ethyl acetate-hexane gradient, 20:80 rising to 40:60) to give **29** (180 mg, 0.36 mmol, 36% yield over two steps) as a white solid. Purity 93%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.49 (s, 9H, tBu), 4.58 (s, 2H, CH_2CO), 5.31 (s, 2H, CH_2Ph), 7.19 (d, *J*=7.4 Hz, 1H, Bn H-6), 7.23 - 7.31 (m, 4H, Ar), 7.37 (t, *J*=7.2 Hz, 1H, Bn H-4), 7.48 (t, *J*=7.8 Hz, 2H, SO_2Ph meta), 7.52 - 7.65 (m, 3H, Ar), 7.84 (d, *J*=7.4 Hz, 2H, SO_2Ph ortho), 8.25 (d, *J*=7.8 Hz, 1H, Bn H-3). HPLC/MS (9 min) retention time 6.70 min. LRMS: *m*/*z* 506 (M+1).

4.10. *{5-Oxo-3-phenyl-4-[2-(phenylsulfonyl)benzyl]-4,5-dihydro-1H-1,2,4-triazol-1-yl}acetic acid (**30**)*

Ester **29** (180 mg, 0.36 mmol) was dissolved in 3 ml dichloromethane. 3 ml Trifluoroacetic acid was added and the mixture was stirred for 90 min at room temperature. The mixture was evaporated under reduced pressure and the residue was taken up in a little water, frozen and lyophilized. The solid obtained was suspended in a little ether and was broken up by sonication. The solid was collected by filtration and dried in a stream of air to give **30** (100 mg, 0.23 mmol, 66% yield) as a white solid. Purity 100%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.60 (s, 2H, CH_2CO), 5.19 (s, 2H, CH_2Ph), 7.06 - 7.13 (m, 1H, Ar), 7.13 - 7.22 (m, 4H, Ar), 7.30 - 7.42 (m, 1H, Ar), 7.52 - 7.74 (m, 5H, Ar), 7.87 (d, *J*=7.4 Hz, 2H, SO_2Ph ortho), 8.23 (d, *J*=7.4 Hz, 1H, Bn H-3). HPLC/MS (30 min) retention time 14.25 min. LRMS: *m*/*z* 450 (M+1).

5. Scheme 5

5.1. *(4E)-4-{2-[(4-Fluorophenyl)sulfonyl]benzylidene}-2-phenyl-1,3-oxazol-5(4H)-one (**31**)*

A mixture of hippuric acid (1.7 g, 9.49 mmol), aldehyde **8b** (2.51 g, 9.49 mmol), sodium acetate (1.32 g, 16.1 mmol) and acetic anhydride (2.7 ml, 28.6 mmol) was stirred together at 100 ºC under argon for 2 h. The mixture was allowed to cool, was diluted with 8 ml ethanol and the resulting suspension was stirred for a further 1 h at room temperature. The solid was collected by filtration and was washed successively with ethanol and water. The solid was dried at 40 ºC under reduced pressure overnight to give **31** (2.45 g, 6.0 mmol, 63% yield) as a pale yellow solid. Purity 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.17 (t, *J*=8.6 Hz, 2H, oxazolinone-Ph meta), 7.53 (t, *J*=7.6 Hz, 2H, SO_2PhF meta), 7.64 (t, *J*=7.6 Hz, 2H, C=CPh H-4 and H-5 coincident), 7.75 (t, *J*=7.6 Hz, 1H, oxazolinone-Ph para), 7.95 (dd, *J*=4.9, 8.8 Hz, 2H, SO_2PhF ortho), 8.10 (s, 1H, vinyl H), 8.13 (d, *J*=7.4 Hz, 2H, oxazolinone-Ph ortho), 8.37 (d, *J*=7.8 Hz, 1H, C=CPh H-6), 8.75 (d, *J*=7.8 Hz, 1H, C=CPh H-3). HPLC/MS (9 min) retention time 7.25 min. LRMS: *m*/*z* 408 (M+1).

5.2. *(2E)-2-(Benzoylamino)-3-{2-[(4-fluorophenyl)sulfonyl]phenyl}acrylic acid (**32**)*

Azlactone **31** (2.18 g, 5.35 mmol) was suspended in 10 ml tetrahydrofuran and the mixture was stirred at reflux (bath temperature 100 ºC). 104 ml of a 1% w/v solution of potassium hydroxide was added slowly while still in the oil bath and the mixture was then stirred for 20 min at 80 ºC. The mixture was hot filtered and the filtrate was partially evaporated under reduced pressure. The filtrate was allowed to cool and was acidified to pH 2 with concentrated hydrochloric acid, forming a precipitate. The solid was collected by filtration, was washed with water and was dried at 40 ºC under reduced pressure overnight to give **32** (1.86 g, 4.37 mmol, 82% yield) as a white solid. Purity 100%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.42 - 7.52 (m, 4H, COPh meta and SO_2PhF meta, coincident), 7.56 (t, *J*=6.8 Hz, 1H, Ar), 7.60 - 7.65 (m, 1H, Ar), 7.69 (m, 2H, Ar), 7.81 (d, *J*=7.4 Hz, 2H, COPh ortho), 7.86 (s, 1H, vinyl H), 7.92 - 8.01 (m, 2H, SO_2PhF ortho), 8.17 (d, *J*=7.4 Hz, 1H, C=CPh H-3), 9.81 (br. s., 1H, NH), 13.06 (br. s., 1H, COOH). HPLC/MS (30 min) retention time 12.32 min. LRMS: *m*/*z* 426 (M+1).

5.3. *N-Benzoyl-2-[(4-fluorophenyl)sulfonyl]phenylalanine (**33**)*

Acrylic acid **32** (1.86 g, 4.37 mmol) was suspended in 65 ml acetic acid and the mixture was stirred at 80 ºC to dissolve the solid. Zinc dust (3.0 g, 46 mmol) was added and the mixture was stirred vigorously at 80 ºC for 8 h. The mixture was hot filtered through a plug of Celite, washing through with tetrahydrofuran once cool. The filtrate was re-filtered through filter paper and was partially evaporated under reduced pressure to remove the tetrahydrofuran. The organics were diluted by slow addition of water to form a precipitate. The solid was collected by filtration, was washed with water and was dried at 40 ºC under reduced pressure overnight to give **33** (1.71 g, 4.00 mmol, 92% yield) as a white solid. Purity 100%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.10 (dd, *J*=11.3, 13.7 Hz, 1H, CH_ACH_BPh), 3.62 (dd, *J*=3.7, 13.9 Hz, 1H, CH_ACH_BPh), 4.65 (ddd, *J*=3.7, 8.6, 11.3 Hz, 1H, CHCO), 7.43 - 7.48 (m, 3H, Ar), 7.49 - 7.55 (m, 4H, Ar), 7.59 (t, *J*=6.8 Hz, 1H, COPh para), 7.77 (d, *J*=7.0 Hz, 2H, COPh ortho), 7.98 (dd, *J*=4.9, 8.8 Hz, 2H, SO_2PhF ortho), 8.10 (d, *J*=7.0 Hz, 1H, Bn H-3), 8.73 (d, *J*=8.6 Hz, 1H, NH), 12.73 - 12.91 (br. s., 1H, COOH). HPLC/MS (9 min) retention time 7.17 min. LRMS: *m*/*z* 428 (M+1).

5.4. *N-(1-{2-[(4-Fluorophenyl)sulfonyl]benzyl}-2-oxopropyl)benzamide (**34**)*

Carboxylic acid **33** (600 mg, 1.40 mmol) was suspended in acetic anhydride (0.53 ml, 5.6 mmol). Triethylamine (0.28 ml, 2.0 mmol) and 4-(N,N-dimethylamino)pyridine (7 mg, 0.06 mmol) were added and the mixture was stirred at 60 ºC for 30

min, evolving a gas. Once no more gas was evolved, 2 ml acetic acid were added and the mixture was stirred at 60 ºC for a further 30 min. The mixture was allowed to cool and was evaporated under reduced pressure. The residue was re-suspended in 2N sodium hydroxide, forming a paste. The paste was triturated with ether to form a solid. The solid was collected by filtration and was dried at 40 ºC under reduced pressure to give **34** (374 mg, 0.88 mmol, 63% yield) as a white solid. Purity 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.32 (s, 3H, Me), 3.18 (dd, *J*=4.3, 14.1 Hz, 1H, C*H*$_A$CH$_B$Ph), 3.39 (dd, *J*=11.7, 14.1 Hz, 1H, CH$_A$C*H*$_B$Ph), 4.94 (ddd, *J*=4.7, 7.2, 11.5 Hz, 1H, CHCO), 7.22 (t, *J*=8.6 Hz, 2H, SO_2PhF meta), 7.39 - 7.44 (m, 3H, Ar), 7.45 - 7.53 (m, 2H, Ar), 7.58 (t, *J*=7.2 Hz, 1H, COPh para), 7.80 (d, *J*=7.4 Hz, 2H, COPh ortho), 7.85 - 7.92 (m, 3H, SO_2PhF ortho and NH), 8.08 (d, *J*=7.4 Hz, 1H, Bn H-3). HPLC/MS (9 min) retention time 6.08 min. LRMS: *m*/*z* 426 (M+1).

5.5. *2-(4-{2-[(4-Fluorophenyl)sulfonyl]benzyl}-5-methyl-2-phenyl-1H-imidazol-1-yl)ethanol (**35**)*

Ketone **34** (150 mg, 0.35 mmol) was suspended in 4 ml xylene. Ethanolamine (32 µl, 0.53 mmol) and 2.6 ml acetic acid were added and the mixture was stirred at 130 ºC for 5 h. Further ethanolamine (64 µl, 1.06 mmol) was added and the mixture was stirred at 130 ºC for a further 4 h. The mixture was allowed to cool and was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic phase was dried over sodium sulphate, filtered and evaporated. The residue was purified by reverse-phase chromatography to give **35** (11 mg, 0.024 mmol, 7% yield) as a solid. Purity 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.06 (s, 3H, Me), 3.75 (t, *J*=5.9 Hz, 2H, NC*H*$_2$CH$_2$OH), 4.09 (t, *J*=5.9 Hz, 2H, NCH$_2$C*H*$_2$OH), 4.18 (s, 2H, CH$_2$Ph), 7.16 (t, *J*=8.6 Hz, 2H, SO_2PhF meta), 7.30 (d, *J*=7.8 Hz, 1H, Ar), 7.34 - 7.52 (m, 5H, Ar), 7.57 (d, *J*=7.4 Hz, 2H, imidazole-Ph ortho), 7.91 (dd, *J*=5.1, 9.0 Hz, 2H, SO_2PhF ortho), 8.21 (d, *J*=7.8 Hz, 1H, Bn H-3). HPLC/MS (9 min) retention time 4.23 min. LRMS: *m*/*z* 451 (M+1).

5.6. *(4-{2-[(4-Fluorophenyl)sulfonyl]benzyl}-5-methyl-2-phenyl-1H-imidazol-1-yl)acetic acid (**36**)*

A solution of Jones' reagent was prepared by dissolving chromium trioxide (67 mg, 0.63 mmol) and concentrated sulphuric acid (58 µl) and 0.25 ml water at 0 ºC. Alcohol **35** (8 mg, 0.018 mmol) was dissolved in 0.8 ml acetone and cooled to 0 ºC. Jones reagent solution (30 µl) was added and the mixture was stirred for 3 h, warming to room temperature. The mixture was evaporated under reduced pressure and the residue was purified by preparative HPLC to give **36** (3.9 mg, 0.0083 mmol, 37% yield) as a solid. Purity 95%. ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.84 (s, 3H, Me), 4.03 (s, 2H, CH_2Ph), 4.27 (br. s., 2H, CH_2CO), 7.30 (d, *J*=7.6 Hz, 1H, Ar), 7.33 (d, *J*=7.0 Hz, 1H, Ar), 7.37 (t, *J*=7.3 Hz, 2H, SO_2PhF meta), 7.39 - 7.45 (m, 4H, Ar), 7.49 (t, *J*=7.6 Hz, 1H, Ar), 7.59 (t, *J*=7.3 Hz, 1H, Ar), 7.92 (m, 2H, SO_2PhF ortho), 8.12 (d, *J*=7.6 Hz, 1H, Bn H-3), 8.19 (br. s., 1H, COOH). HPLC/MS (30 min) retention time 10.67 min. LRMS: *m*/*z* 465 (M+1).

6. Scheme 6

6.1. *(6-Oxo-1,6-dihydropyridin-3-yl)acetic acid (**37**)*

(6-Chloropyridin-3-yl)acetic acid (2.2 g, 12.8 mmol) was suspended in 22 ml glacial acetic acid and 6 ml water. The mixture was stirred at 160 ºC under microwave irradiation for 8 h. The mixture was allowed to cool and was evaporated under reduced pressure. The residue was re-evaporated from toluene to give **37** (1.96 g, 12.8 mmol, 100% yield) as a pale brown solid. Purity 92%. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.38 (s, 2H, CH_2), 6.33 (d, *J*=9.3 Hz, 1H, H-5), 7.28 (s, 1H, H-2), 7.38 (dd, *J*=2.5, 9.3 Hz, 1H, H-4). UPLC/MS (3 min) retention time 0.42 min. LRMS: *m*/*z* 152 (M-1).

6.2. *Ethyl (6-oxo-1,6-dihydropyridin-3-yl)acetate (**38**)*

Acid **37** (1.96 g, 12.8 mmol) was suspended in 40 ml ethanol and 16 drops of concentrated sulphuric acid were added. The mixture was stirred at reflux for 5 h and was then left to cool. The mixture was evaporated under reduced pressure and the residue partitioned between brine and dichloromethane. The aqueous phase was extracted with dichloromethane and the combined organics were dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure to give **38** (1.95 g, 10.8 mmol, 84% yield) as a pale yellow solid. Purity 94%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.27 (t, *J*=7.0 Hz, 3H, OCH$_2$C*H*$_3$), 3.40 (s, 2H, CH_2CO), 4.16 (q, *J*=7.0 Hz, 2H, OC*H*$_2$CH$_3$), 6.63 (d, *J*=9.1 Hz, 1H, H-5), 7.36 (s, 1H, H-2), 7.50 (d, *J*=9.0 Hz, 1H, H-4). UPLC/MS (3 min) retention time 0.81 min. LRMS: *m*/*z* 182 (M+1).

6.3. *Ethyl (5-chloro-6-oxo-1,6-dihydropyridin-3-yl)acetate (**39**)*

Pyridone **38** (300 mg, 1.79 mmol) was dissolved in 6 ml dimethylformamide and the mixture cooled in an ice-bath. N-Chlorosuccinimide (287 mg, 2.15 mmol) was added portion-wise and with stirring. The mixture was alowed to warm to room temperature and was stirred for 3 h. The mixture was partitioned between water and ethyl acetate. The aqueous phase was extracted with ethyl acetate and the combined organics were dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The residue was partially purified by flash chromatography to give crude **39** (150 mg) as a solid. Purity 85%. NMR spectrum not recorded. UPLC/MS (3 min) retention time 1.02 min. LRMS: *m*/*z* 216 (M+1).

6.4. *Ethyl {6-oxo-1-[2-(phenylsulfonyl)benzyl]-1,6-dihydropyridin-3-yl}acetate (**40**)*

Pyridone **38** (100 mg, 0.56 mmol) was dissolved in 4 ml dimethylformamide. Bromide **10a** (288 mg, 0.93 mmol) and potassium carbonate (84 mg, 0.60 mmol) were added and the mixture was stirred at 70 ºC overnight. The mixture was evaporated under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic phase was washed twice with water, dried over magnesium sulphate, filtered and evaporated. The residue was purified by flash chromatography using the Isolera system (ethyl acetate-hexane gradient, 0:100 rising to 100:0) to give **40** (98 mg, 0.24 mmol, 44% yield) as a colourless oil. Purity 100%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.26 (t, *J*=7.1 Hz, 3H, OCH_2CH_3), 3.31 (s, 2H, CH_2CO), 4.16 (q, *J*=7.1 Hz, 2H, OCH_2CH_3), 5.47 (s, 2H, NCH_2Ph), 6.61 (d, *J*=9.3 Hz, 1H, pyridone H-5), 7.15 (d, *J*=1.9 Hz, 1H, pyridone H-2), 7.19 (d, *J*=7.4 Hz, 1H, Bn H-6), 7.35 (dd, *J*=2.5, 9.3 Hz, 1H, pyridine H-4), 7.45 - 7.60 (m, 4H, Ar), 7.64 (t, *J*=7.1 Hz, 1H, Ar), 7.92 (d, *J*=7.1 Hz, 2H, SO_2Ph ortho), 8.24 (dd, *J*=1.2, 7.6 Hz, 1H, Bn H-3). UPLC/MS (3 min) retention time 1.56 min. LRMS: *m*/*z* 412 (M+1).

6.5. *Ethyl {5-chloro-6-oxo-1-[2-(phenylsulfonyl)benzyl]-1,6-dihydropyridin-3-yl}acetate (**41**)*

Crude pyridone **39** (100 mg) was dissolved in 3 ml dimethylformamide under argon and the mixture was cooled in an ice-bath. Sodium hydride (60% dispersion in oil, 20 mg, 0.50 mmol) was added and the mixture was stirred at 0 ºC for 30 min. A solution of bromide **10a** (194 mg, 0.62 mmol) dissolved in 1 ml dimethylformamide was added and the mixture was stirred at room temperature for 2 h. The mixture was partitioned between ethyl acetate and water. The organic phase was dried over magnesium sulphate, filtered and evaporated. The residue was purified by flash chromatography using the Isolera system (diethyl ether-hexane gradient) to give **41** (50 mg, 0.11 mmol, 9% yield over two steps) as a colourless oil. Purity 95%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.26 (t, *J*=7.1 Hz, 3H, OCH_2CH_3), 3.29 (s, 2H, CH_2CO), 4.16 (q, *J*=7.1 Hz, 2H, OCH_2CH_3), 5.51 (s, 2H, NCH_2Ph), 7.20 (br. s., 1H, pyridone H-2), 7.25 (d, *J*=7.1 Hz, 1H, Bn H-3), 7.45 - 7.69 (m, 6H, Ar), 7.88 (d, *J*=7.1 Hz, 2H, SO_2Ph ortho), 8.20 (d, *J*=7.5 Hz, 1H, Bn H-3). UPLC/MS (3 min) retention time 1.68 min. LRMS: *m*/*z* 446 (M+1).

6.6. *{6-Oxo-1-[2-(phenylsulfonyl)benzyl]-1,6-dihydropyridin-3-yl}acetic acid (**42**)*

Ester **40** (95 mg, 0.23 mmol) was dissolved in 1.5 ml tetrahydrofuran and 1.5 ml water. Lithium hydroxide monohydrate (14 mg, 0.33 mmol) was added and the mixture was stirred for 1 h at room temperature. The organics were evaporated under reduced pressure. The solution was diluted with water and acidified to pH 3-4 with 2N hydrochloric acid. The aqueous phase was extracted twice with dichloromethane and the combined organics were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to give **42** (83 mg, 0.22 mmol, 94% yield) as a white solid. Purity 99%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.34 (s, 2H, CH_2CO), 5.46 (s, 2H, NCH_2Ph), 6.64 (d, *J*=9.3 Hz, 1H, pyridone H-5), 7.17 (d, *J*=1.9 Hz, 1H, pyridone H-2), 7.20 (d, *J*=7.4 Hz, 1H, Bn H-6), 7.34 (dd, *J*=2.5, 9.3 Hz, 1H, pyridone H-4), 7.45 - 7.59 (m, 4H, Ar), 7.63 (t, *J*=7.1 Hz, 1H, Ar), 7.89 (d, *J*=7.1 Hz, 2H, SO_2Ph ortho), 8.21 (dd, *J*=1.5, 7.6 Hz, 1H, Bn H-3). HPLC/MS (30 min) retention time 11.20 min. LRMS: *m*/*z* 384 (M+1).

6.7. *{5-Chloro-6-oxo-1-[2-(phenylsulfonyl)benzyl]-1,6-dihydropyridin-3-yl}acetic acid (**43**)*

Ester **41** (50 mg, 0.11 mmol) was dissolved in 1 ml tetrahydrofuran and 1.5 ml water. Lithium hydroxide monohydrate (7 mg, 0.17 mmol) was added and the mixture was stirred for 3 h at room temperature. The organics were evaporated under reduced pressure. The solution was diluted with water and was washed with ethyl acetate. The aqueous phase was acidified to pH 3 with 2N hydrochloric acid forming a turbid solution. The aqueous phase was extracted twice with dichloromethane and the combined organics were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to give **43** (23 mg, 0.060 mmol, 53% yield) as a white solid. Purity 99%. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.3 (approx, CH_2CO signal under water peak), 5.43 (s, 2H, NCH_2Ph), 6.77 (d, *J*=7.4 Hz, 1H, Bn H-6), 7.54 (d, *J*=1.9 Hz, 1H, pyridine H-2), 7.58 - 7.71 (m, 4H, Ar), 7.74 (d, *J*=7.4 Hz, 1H, Ar), 7.79 (d, *J*=2.2 Hz, 1H, Ar), 7.98 (d, *J*=7.4 Hz, 2H, SO_2Ph ortho), 8.19 (d, *J*=7.4 Hz, 1H, Bn H-3). HPLC/MS (30 min) retention time 12.17 min. LRMS: *m*/*z* 418 (M+1).

7. Scheme 7

7.1. *(2-Methoxypyridin-3-yl)methanol (**44**)*

Sodium borohydride (0.17 g, 4.5 mmol) was dissolved in 20 ml ethanol under argon and the mixture cooled to -40 ºC in a cryo-cool. A solution of 2-methoxynicotinaldehyde (2.0 g, 14.6 mmol) dissolved in 4 ml ethanol was added drop-wise and with stirring. The mixture was stirred at -40 ºC for 45 min. 10 ml Brine was added carefully and the mixture was then allowed to warm to room temperature. The organics were evaporated under reduced pressure. The mixture was partitioned between ethyl acetate and water. The aqueous phase was extracted with ethyl acetate and the combined organics were dried over magnesium sulphate, filtered and evaporated to give **44** (1.90 g, 13.7 mmol, 94% yield) as a pale yellow oil. Purity 100%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.30 (t, *J*=6.5 Hz, 1H, OH), 4.00 (s, 3H, MeO), 4.66 (d,

J=6.3 Hz, 2H, CH_2), 6.90 (dd, *J*=5.0, 7.1 Hz, 1H, H-5), 7.58 (d, *J*=7.1 Hz, 1H, H-4), 8.11 (d, *J*=4.9 Hz, 1H, H-6). UPLC/MS (3 min) retention time 0.77 min. LRMS: *m*/*z* 140 (M+1).

7.2. *3-(Chloromethyl)-2-methoxypyridine (**45**)*

Alcohol **44** (1.0 g, 7.2 mmol) was dissolved in 35 ml dichloromethane. Thionyl chloride (9.4 ml, 18 mmol) was added drop-wise and with stirring and the mixture was stirred for 1 h at room temperature. The mixture was concentrated under reduced pressure. The residue was re-suspended in dichloromethane and saturated sodium bicarbonate solution was added carefully. The mixture was stirred for 10 min and the organic phase was then separated, dried over magnesium sulphate, filtered and evaporated to give **45** (1.05 g, 6.7 mmol, 93% yield) as a pale yellow oil. Purity 95%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 4.01 (s, 3H, MeO), 4.60 (s, 2H, CH_2), 6.90 (dd, *J*=5.1, 7.0 Hz, 1H, H-5), 7.65 (d, *J*=7.1 Hz, 1H, H-4), 8.13 (d, *J*=4.7 Hz, 1H, H-6). UPLC/MS (3 min) retention time 1.46 min. LRMS: *m*/*z* no ionization.

7.3. *(2-Methoxypyridin-3-yl)acetonitrile (**46**)*

Chloride **45** (0.50 g, 3.2 mmol) was dissolved in 2 ml dimethylformamide. Sodium cyanide (0.31 g, 6.33 mmol) was added and the mixture was agitated at 50 ºC for 3 h and then at 70 ºC overnight. The mixture was allowed to cool and was partitioned between ethyl acetate and water. The organic phase was washed twice with water, was dried over magnesium sulphate, filtered and evaporated. The residue was purified using the Isolera (ethyl acetate-hexane, 25:75) to give **46** (0.37 g, 2.50 mmol, 79% yield) as a pale yellow oil. Purity 96%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.67 (s, 2H, CH_2), 4.00 (s, 3H, MeO), 6.93 (dd, *J*=5.1, 7.3 Hz, 1H, H-5), 7.68 (d, *J*=7.4 Hz, 1H, H-4), 8.15 (d, *J*=4.1 Hz, 1H, H-6). UPLC/MS (3 min) retention time 1.08 min. LRMS: *m*/*z* 149 (M+1).

7.4. *Ethyl (2-oxo-1,2-dihydropyridin-3-yl)acetate (**47**)*

Nitrile **46** (0.23 g, 1.55 mmol) was dissolved in 3 ml ethanol in a sealed tube. Acetyl chloride (1.1 ml, 15.4 mmol) was added drop-wise and with stirring (Exotherm !). The vessel was then sealed and the mixture was stirred at 50 ºC overnight. The mixture was allowed to cool and was evaporated under reduced pressure. The residue was triturated with ether to give a solid. The solid was collected by filtration and dried in a stream of air to give **47** (0.37 g, 2.50 mmol, 79% yield) as a white solid. Purity 75%. NMR spectrum not recorded. UPLC/MS (3 min) retention time 0.83 min. LRMS: *m*/*z* 182.

7.5. *{2-Oxo-1-[2-(phenylsulfonyl)benzyl]-1,2-dihydropyridin-3-yl}acetic acid (**48**)*

Pyridone **47** (0.30 g, 1.66 mmol) was dissolved in 5 ml dimethylformamide and the mixture was cooled in an ice-bath. Sodium hydride (60% dispersion in oil, 0.17 g, 4.3 mmol) was added portion-wise and with stirring and the mixture was stirred for 30 min at 0 ºC. Bromide **10a** (0.77 g, 2.5 mmol) dissolved in 4 ml dimethylformamide was added and the mixture was stirred for 2 h at room temperature. The mixture was partitioned between ethyl acetate and water. The aqueous was extracted with ethyl acetate and was then acidified with 2N hydrochloric acid forming a suspension. The mixture was extracted with dichloromethane and the organic phase was dried over magnesium sulphate, filtered and evaporated to give **48** (0.13 g, 0.34 mmol, 21% yield) as a white solid. Purity 97%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.66 (s, 2H, CH_2CO), 5.59 (s, 2H, CH_2Ph), 6.39 (t, *J*=7.0 Hz, 1H, pyridone H-5), 7.06 - 7.16 (m, 1H, Ar), 7.23 - 7.31 (m, 1H, Ar), 7.39 - 7.49 (m, 2H, Ar), 7.50 - 7.68 (m, 4H, Ar), 7.90 (d, *J*=7.4 Hz, 2H, SO_2Ph ortho), 8.22 (d, *J*=7.4 Hz, 1H, Bn H-3). HPLC/MS (30 min) retention time 11.83 min. LRMS: *m*/*z* 384 (M+1).

8. Scheme 8

8.1. *(3Z)-5-Phenyl-3-[2-(phenylsulfonyl)benzylidene]furan-2(3H)-one (**49**)*

4-Oxo-4-phenylbutanoic acid (200 mg, 1.12 mmol) and aldehyde **8a** (275 mg, 1.12 mmol) were mixed under nitrogen atmosphere. 5 ml Acetic anhydride and 10 drops of triethylamine were added and the mixture was stirred at reflux for 3 h. The mixture was poured over ice-water. Ethyl acetate was added and the organic phase was separated. The aqueous was extracted three times with ethyl acetate and the combined organics were washed twice with water, twice with brine, dried over magnesium sulphate, filtered and evaporated. The residue was triturated with acetonitrile to give a solid. The solid was collected by filtration to give **49** (110 mg, 0.28 mmol, 25% yield) as a bright yellow solid. Purity 94%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.40 (s, 1H, furanone H), 7.33 - 7.52 (m, 6H, Ar), 7.53 - 7.74 (m, 5H, Ar), 7.90 (d, *J*=7.0 Hz, 2H, $PhSO_2$ ortho), 7.97 (s, 1H, vinyl H), 8.38 (d, *J*=7.8 Hz, 1H, C=CPh H-3). HPLC/MS (9 min) retention time 7.00 min. LRMS: *m*/*z* 406 ($M+NH_4^+$).

8.2. *6-Phenyl-4-[2-(phenylsulfonyl)benzyl]pyridazin-3(2H)-one (**50**)*

Lactone **49** (110 mg, 0.28 mmol) was dissolved in 2 ml ethanol. 2 ml Hydrazine hydrate was added and the mixture was stirred at reflux for 4 h. The mixture was allowed to cool and was evaporated under reduced pressure. The residue was partitioned between ethyl acetate and water. The aqueous was extracted three times with ethyl acetate and the combined organics were washed three times with water, twice with brine, dried over magnesium sulphate, filtered and evaporated

to give crude pyridazinone **50** (99 mg) as a pale yellow solid. Purity 74%. NMR spectrum not recorded. HPLC/MS (9 min) retention time 6.15 min. LRMS: *m*/*z* 403 (M+1).

8.3. *tert-Butyl [6-oxo-3-phenyl-5-[2-(phenylsulfonyl)benzyl]pyridazin-1(6H)-yl]acetate (**51**)*

Crude pyridazinone **50** (99 mg) was dissolved in 4 ml dimethylformamide. tert-Butyl 2-bromoacetate (82 µl, 0.55 mmol) and potassium carbonate (75 mg, 0.55 mmol) were added and the mixture was stirred at room temperature for 2 h. The mixture was poured over ice-water forming a precipitate. The solid was collected by filtration and was dissolved in dichloromethane, dried over magnesium sulphate, filtered and evaporated. The residue was purified using the SP1 purification system (ethyl acetate-hexane gradient, 0:100 rising to 60:40) to give **51** (70 mg, 0.14 mmol, 46% yield over two steps) as a colourless oil. Purity 98%. NMR spectrum not recorded. HPLC/MS (9 min) retention time 7.15 min. LRMS: *m*/*z* 517 (M+1).

8.4. *[6-Oxo-3-phenyl-5-[2-(phenylsulfonyl)benzyl]pyridazin-1(6H)-yl]acetic acid (**52**)*

Ester **51** (70 mg, 0.14 mmol) was dissolved in 2 ml dichloromethane and 1 ml trifluoroacetic acid and the mixture was stirred for 2 h at room temperature. The mixture was evaporated under reduced pressure and the residue was triturated with ether to give a solid. The solid was collected by filtration and was dried at 40 ºC under reduced pressure to give **52** (54 mg, 0.12 mmol, 87% yield) as a white solid. Purity 100%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.22 (s, 2H, CH_2CO), 4.86 (s, 2H, CH_2Ph), 6.56 (s, 1H, pyridazinone H), 7.36 - 7.48 (m, 9H, Ar), 7.66 - 7.71 (m, 1H, Ar), 7.72 - 7.77 (m, 3H, Ar), 8.29 (dd, *J*=1.6, 7.8 Hz, 1H, Bn H-3), 13.14 (s, 1H, COOH). HPLC/MS (30 min) retention time 15.47 min. LRMS: *m*/*z* 461 (M+1).

9. Scheme 9

9.1. *2-(2-Oxopropyl)cyclohexanone (**53**)*

Lithium hexamethyldisilazide (1M in tetrahydrofuran, 12 ml, 12 mmol) was diluted with 20 ml anhydrous toluene under nitrogen atmosphere and the mixture was cooled to 0 ºC. Cyclohexanone (1 g, 10.2 mmol) dissolved in 20 ml anhydrous toluene was added drop-wise and with stirring and the mixture was stirred for 5 min at 0 ºC. Chloroacetone (0.82 ml, 10.3 mmol) dissolved in 10 ml anhydrous toluene was added drop-wise and with stirring and the mixture was stirred at 0 ºC for 10 min. The mixture was evaporated under reduced pressure to give crude **53** (1.2 g). Purity 41% by gas chromatography. Used as such without further purification.

9.2. *Ethyl (2-methyl-4,5,6,7-tetrahydro-1H-indol-1-yl)acetate (**54**)*

The crude sample of **53** (1.2 g) was dissolved in 5 ml ethanol. Ethyl 2-aminoacetate hydrochloride (0.45 g, 3.2 mmol) and sodium acetate (0.52 g, 6.3 mmol) were added and the mixture was stirred overnight at room temperature. The mixture was evaporated under reduced pressure and the residue was re-suspended in dichloromethane, filtered and the filtrate evaporated under reduced pressure. The residue was partially purified by reverse-phase chromatography crude **54** (0.08 g) as a red oil. Purity 48%. Used as such without further purification. HPLC/MS (30 min) retention time 14.77 min. LRMS: *m*/*z* 222 (M+1).

9.3. *2-(2-Oxopropyl)cyclohexane-1,3-dione (**55**)*

Cyclohexane-1,3-dione (1 g, 8.9 mmol) was dissolved in 12 ml chloroform. Chloroacetone (0.71 ml, 8.9 mmol) and potassium carbonate (1.23 g, 8.9 mmol) were added and the mixture was stirred for 2 h, forming a dark brown gum. The solvents were decanted and the gummy residue was extracted several times with ethyl acetate. The combined organics were evaporated under reduced pressure and the residue was purified using the SP-1 purification system (ethyl acetate-hexane gradient, 0:100 rising to 100:0) to give **55** (0.31 g, 1.8 mmol, 21% yield) as a pale yellow oil. Purity 92%. ^{1}H NMR (400 MHz, $CDCl_3$) mixture of keto and enol tautomers. Keto form (partial) δ ppm 3.08 (d, *J*=5.1 Hz, 2H, MeCO*C*H_2CH), 3.75 (t, *J*=4.9 Hz, 1H, MeCOCH$_2$*CH*). Enol form (partial) δ ppm 3.43 (s, 2H, MeCO*C*H_2). HPLC/MS (9 min) retention time 3.22 min. LRMS: *m*/*z* 169 (M+1).

9.4. *Ethyl (2-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)acetate (**56**)*

Triketone **55** (0.30 mg, 1.8 mmol) was dissolved in 3 ml ethanol. Ethyl 2-aminoacetate hydrochloride (0.23 g, 1.64 mmol) and sodium acetate (0.27 g, 3.3 mmol) were added and the mixture was stirred overnight at room temperature. The mixture was evaporated under reduced pressure and the residue was re-suspended in dichloromethane, filtered and the filtrate evaporated under reduced pressure. The residue was purified using the SP-1 purification system (ethyl acetate-hexane gradient, 0:100 rising to 65:35) to give **56** (0.265 g, 1.12 mmol, 68% yield). Purity 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.30 (t, *J*=7.2 Hz, 3H, COCH$_2$*CH*$_3$), 2.08 - 2.17 (m, 2H, CH$_2$*CH*$_2$CH$_2$CO), 2.18 (s, 3H, Me), 2.45 (d, *J*=7.0 Hz, 2H, *CH*$_2$CH$_2$CH$_2$CO), 2.67 (t, *J*=6.1 Hz, 2H, CH$_2$CH$_2$*CH*$_2$CO), 4.25 (q, *J*=7.0 Hz, 2H, CO*CH*$_2$CH$_3$), 4.51 (s, 2H, NCH$_2$), 6.30 (s, 1H, pyrrole H). HPLC/MS (9 min) retention time 4.77 min. LRMS: *m*/*z* 236 (M+1).

9.5. *(3-{2-[(4-Fluorophenyl)sulfonyl]benzyl}-2-methyl-4,5,6,7-tetrahydro-1H-indol-1-yl)acetic acid (**57**)*

Crude ester **54** (80 mg) was dissolved in 1 ml anhydride acetic. Hydriodic acid (57% solution, 0.27 ml, 2.0 mmol) was added drop-wise and with stirring (exotherm). Hypophosphorous acid (50% solution, 0.07 ml, 0.7 mmol) was added followed by aldehyde **8b** (46 mg, 0.17 mmol) and the dark red mixture was stirred for 1 h at room temperature. The mixture was partitioned between dichloromethane and water. The aqueous phase was extracted twice with dichloromethane and the combined organics were dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The residue was partially purified by reverse-phase chromatography to give 9 mg of a crude sample of the ethyl ester of **57**. Purity 76%. HPLC/MS (9 min) retention time 7.40 min. LRMS: *m*/*z* 470 (M+1).

The ester was dissolved in 0.5 ml tetrahydrofuran and 0.25 ml water. Lithium hydroxide monohydrate (3 mg, 0.07 mmol) was added and the mixture was stirred for 1 h at room temperature. The mixture was acidified to pH 4 with acetic acid and was stirred for 2 h, forming a precipitate. This was collected by filtration, washed with a little water and dried at 35 ºC in vacuo to give crude **57** (2 mg) as a pale green solid. Purity 83%. The solid was further purified by analytical HPLC to give **57** (0.7 mg, 1.6 µmol, 0.02% yield over three steps). NMR spectrum not recorded. HPLC/MS (30 min) retention time 17.43 min. LRMS: *m*/*z* 442 (M+1).

9.6. *(3-{2-[(4-Fluorophenyl)sulfonyl]benzyl}-2-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)acetic acid (**58**)*

Ester **56** (100 mg, 0.43 mmol) was dissolved in 0.8 ml anhydride acetic. Hydriodic acid (57% solution, 0.67 ml, 5.1 mmol) was added drop-wise and with stirring (exotherm). Hypophosphorous acid (50% solution, 0.22 ml, 2.1 mmol) was added followed by aldehyde **8b** (146 mg, 0.55 mmol). The mixture was stirred for 3 d at room temperature. The mixture was partitioned between dichloromethane and water. The aqueous phase was extracted twice with dichloromethane and the combined organics were dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The residue was purified by reverse-phase chromatography to give **58** (67 mg, 0.15 mmol 34% yield) as a white solid. Purity 99%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.54 (s, 3H, Me), 1.95 (quin, *J*=6.0 Hz, 2H, $CH_2CH_2CH_2CO$), 2.19 (t, *J*=6.1 Hz, 2H, $CH_2CH_2CH_2CO$), 2.64 (t, *J*=5.7 Hz, 2H, $CH_2CH_2CH_2CO$), 4.13 (s, 2H, CH_2Ph), 4.54 (s, 2H, NCH_2), 6.87 (d, *J*=7.4 Hz, 1H, Bn H-6), 7.40 - 7.57 (m, 4H, Ar), 7.97 (dd, *J*=5.1, 8.6 Hz, 2H, SO_2PhF ortho), 8.13 (d, *J*=7.8 Hz, 1H, Bn H-3). HPLC/MS (30 min) retention time 13.98 min. LRMS: *m*/*z* 456 (M+1).

9.7. *(3-{2-[(4-Fluorophenyl)sulfonyl]-5-methoxybenzyl}-2-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)acetic acid (**59**)*

Ester **56** (150 mg, 0.64 mmol) was dissolved in 1.5 ml anhydride acetic. Hydriodic acid (57% solution, 1.2 ml, 9.1 mmol) was added drop-wise and with stirring (exotherm). Hypophosphorous acid (50% solution, 0.33 ml, 3.3 mmol) was added followed by crude aldehyde **8c** (265 mg). The mixture was stirred for 3 d at room temperature. The mixture was partitioned between dichloromethane and water. The aqueous phase was extracted twice with dichloromethane and the combined organics were dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The residue was purified using the SP-1 purification system (ethyl acetate-hexane gradient, 0:100 rising to 50:50) to give the ethyl ester of **59** (0.26 g, 0.51 mmol, 79% yield). Purity 96%. HPLC/MS (9 min) retention time 6.42 min. LRMS: *m*/*z* 514 (M+1).

The ester was dissolved in 3 ml tetrahydrofuran and 1.5 ml water. Lithium hydroxide monohydrate (63 mg, 1.5 mmol) was added and the mixture was stirred for 45 min at room temperature. The organics were evaporated under reduced pressure and the remaining aqueous was acidified to pH 4 with acetic acid and was stirred for 2 h, forming a precipitate. This was collected by filtration, washed with a little water and dried at 35 ºC in vacuo to give **59** (180 mg, 0.37 mmol 58% overall yield) as a white solid. Purity 100%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.59 (s, 3H, Me), 1.91 - 2.02 (m, 2H, $CH_2CH_2CH_2CO$), 2.16 - 2.26 (m, 2H, $CH_2CH_2CH_2CO$), 2.63 - 2.72 (m, 2H, $CH_2CH_2CH_2CO$), 3.68 (s, 3H, OMe), 4.08 (s, 2H, NCH_2), 4.65 (s, 2H, CH_2Ph), 6.31 (m, 1H, Bn H-6), 7.01 (d, *J*=8.2 Hz, 1H, Bn H-4), 7.46 (t, *J*=8.2 Hz, 2H, SO_2PhF meta), 7.93 (t, *J*=4.7 Hz, 2H, SO_2PhF ortho), 8.11 (d, *J*=8.6 Hz, 1H, Bn H-3). HPLC/MS (30 min) retention time 14.25 min. LRMS: *m*/*z* 486 (M+1).

10. Scheme 10

10.1. *(3-Oxo-1,3-dihydro-2-benzofuran-1-yl)(triphenyl)phosphonium bromide (**60**)*

3-Bromoisobenzofuran-1(3H)-one (0.5 g, 2.35 mmol) was suspended in 2 ml acetonitrile. Triphenylphosphine (0.62 g, 2.35 mmol) was added and the mixture was stirred at reflux for 2.5 h. The mixture was allowed to cool and was filtered. The solid was washed with ether and was dried at 40 ºC under reduced pressure to give crude **60** (0.56 g) as a white solid. Purity 85%. Used as such without further purification. NMR spectrum not recorded. HPLC/MS (4.5 min) retention time 2.99 min. LRMS: *m*/*z* 395 (cation M+).

10.2. *(3Z)-3-[2-(Phenylsulfonyl)benzylidene]-2-benzofuran-1(3H)-one (**61**)*

Crude phosphine salt **60** (0.56 g) was suspended in 10 ml dichloromethane. Aldehyde **8a** (0.29 g, 1.17 mmol) was added. Triethylamine (0.16 ml, 1.17 mmol) was added drop-wise and with stirring and the mixture was stirred at room temperature for 2.5 h. The mixture was acidified with 1N

hydrochloric acid. The organic phase was separated, dried over magnesium sulphate, filtered and evaporated. The residue was purified using the SP1 purification system (ethyl acetate-hexane gradient, 15:85 rising to 70:30) to give **61** (0.14 g, 0.37 mmol, 16% yield over two steps) as a yellow solid. Purity 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.18 (d, *J*=7.8 Hz, 1H, Bn H-6), 7.00 (s, 1H, vinyl H), 7.02 - 7.10 (m, 3H, Ar), 7.15 (t, *J*=7.3 Hz, 1H, Ar), 7.39 (t, *J*=7.5 Hz, 1H, SO_2Ph para), 7.48 (d, *J*=7.5 Hz, 1H, phthalazinone H-8), 7.65 - 7.74 (m, 4H, Ar), 7.77 (d, *J*=7.8 Hz, 1H, Bn H-3), 8.47 (dd, *J*=2.2, 7.0 Hz, 1H, phthalazinone H-5). HPLC/MS (4.5 min) retention time 3.86 min. LRMS: *m*/*z* 363 (M+1).

10.3. *4-[2-(Phenylsulfonyl)benzyl]phthalazin-1(2H)-one (**62**)*

Lactone **61** (0.14 g, 0.37 mmol) was suspended in 5 ml methanol. Hydrazine hydrate (54 µl, 1.2 mmol) was added and the mixture was stirred at reflux for 1 h. The mixture was evaporated under reduced pressure and the residue was partitioned between dichloromethane and water. The organic phase was dried over magnesium sulphate, filtered and evaporated. to give **62** (76 mg, 0.20 mmol, 54% yield) as a white solid. Purity 97%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.54 (s, 2H, CH_2), 7.29 (d, *J*=7.2 Hz, 1H, Bn H-6), 7.41 (t, *J*=7.8 Hz, 2H, PhSO_2 meta), 7.50 - 7.65 (m, 4H, Ar), 7.72 (d, *J*=7.6 Hz, 2H, PhSO_2 ortho), 7.78 - 7.85 (m, 2H, Ar), 8.18 - 8.25 (m, 2H, phthalazinone H-5 and Bn H-3), 8.21 (s, 1H), 12.21 (s, 1H, NH). HPLC/MS (4.5 min) retention time 3.64 min. LRMS: *m*/*z* 377 (M+1).

10.4. *Ethyl [1-oxo-4-[2-(phenylsulfonyl)benzyl]phthalazin-2(1H)-yl]acetate (**63**)*

Sodium hydride (60% dispersion in oil, 16 mg, 0.40 mmol) was suspended in 1 ml dimethylformamide Phthalazinone **62** (76 mg, 0.20 mmol) dissolved in 1 ml dimethylformamide was added and the mixture was stirred at room temperature for 50 min. Ethyl 2-bromoacetate (34 µl, 0.30 mmol) was added and the mixture was stirred for 20 min. The mixture was partitioned between ethyl acetate and water. The organic phase was dried over magnesium sulphate, filtered and evaporated. The residue was purified using the SP1 purification system (ethyl acetate-hexane gradient) to give **63** (40 mg, 0.086 mmol, 22% yield) as a colourless oil. Purity 96%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.28 (t, *J*=7.1 Hz, 3H, OCH_2CH_3), 4.22 (q, *J*=7.2 Hz, 2H, OCH_2CH_3), 4.55 (s, 2H, CH_2Ph), 4.80 (s, 2H, CH_2CO), 7.12 (dd, *J*=2.0, 7.5 Hz, 1H, Bn H-6), 7.38 - 7.46 (m, 3H, Ar), 7.47 (t, *J*=8.1 Hz, 2H, SO_2Ph meta), 7.57 (t, *J*=7.5 Hz, 1H, SO_2Ph para), 7.62 (td, *J*=7.8, 1.2 Hz, 1H, Bn H-4), 7.70 (t, *J*=7.3 Hz, 1H, Ar), 7.86 (d, *J*=7.4 Hz, 2H, SO_2Ph ortho), 8.34 (dd, *J*=2.1, 7.2 Hz, 1H, phthalazinone H-5), 8.41 (d, *J*=7.4 Hz, 1H, Bn H-3). HPLC/MS (4.5 min) retention time 3.99 min. LRMS: *m*/*z* 463 (M+1).

10.5. *[1-Oxo-4-[2-(phenylsulfonyl)benzyl]phthalazin-2(1H)-yl]acetic acid (**64**)*

Ester **63** (40 mg, 0.086 mmol) was dissolved in 3 ml tetrahydrofuran and 1.5 ml water. Lithium hydroxide monohydrate (8 mg, 0.34 mmol) was added and the mixture was stirred for 90 min at room temperature. The organics were evaporated under reduced pressure. The solution was diluted with water and was washed with ethyl acetate. The aqueous phase was acidified to pH 3 with 2N hydrochloric acid forming a turbid solution. The aqueous phase was extracted twice with ethyl acetate and the combined organics were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The residue was purified by reverse-phase chromatography to give **64** (28 mg, 0.064 mmol, 74% yield) as a white solid. Purity 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.57 (s, 2H, CH_2CO), 4.81 (s, 2H, CH_2Ph), 7.11 (d, *J*=6.4 Hz, 1H, Bn H-6), 7.39 - 7.52 (m, 5H, Ar), 7.55 (t, *J*=7.4 Hz, 1H, SO_2Ph para), 7.66 (t, *J*=7.1 Hz, 1H, Ar), 7.72 (t, *J*=7.4 Hz, 1H, Ar), 7.83 (d, *J*=7.4 Hz, 2H, SO_2Ph ortho), 8.33 (d, *J*=9.2 Hz, 1H, phthalazinone H-5), 8.41 (d, *J*=7.6 Hz, 1H, Bn H-3). HPLC/MS (30 min) retention time 13.98 min. LRMS: m/z 435 (M+1).

10.6. *Ethyl (triphenylphosphoranylidene)acetate (**65**)*

Ethyl 2-bromoacetate (1.4 ml, 12.6 mmol) and triphenylphosphine (3.3 g, 12.6 mmol) were dissolved in in 15 ml benzene and the mixture was stirred at reflux overnight forming a precipitate. The mixture was allowed to cool and the solid was collected by filtration. The solid was washed with benzene and was re-dissolved in dichloromethane. The organics were shaken with 10% sodium hydroxide solution, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to give **65** (3.81 g, 10.9 mmol, 87% yield) as a white solid. Purity 98%. NMR spectrum not recorded. HPLC/MS (4.5 min) retention time 3.06 min. LRMS: m/z 349 (M+1).

10.7. *Ethyl (2Z)-(3-oxo-2-benzofuran-1(3H)-ylidene)acetate (**66**)*

Phthalic anhydride (0.50 g, 3.37 mmol) and Wittig reagent **65** (1.29 g, 3.70 mmol) were dissolved in 8 ml dioxane and the mixture was stirred at reflux for 2 h. The mixture was allowed to cool and was evaporated under reduced pressure. The residue was purified by flash chromatography (ethyl acetate-hexane gradient, 0:100 rising to 80:20) to give **66** (0.42 g, 1.9 mmol, 57% yield) as a yellow solid. Purity 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.37 (t, *J*=7.1 Hz, 3H, OCH_2CH_3), 4.30 (q, *J*=7.0 Hz, 2H, OCH_2CH_3), 6.16 (s, 1H, vinyl H), 7.71 (t, *J*=7.4 Hz, 1H, H-5 or H-6), 7.82 (t, *J*=7.7 Hz, 1H, H-6 or

H-5), 7.97 (d, *J*=7.6 Hz, 1H, H-4), 9.06 (d, *J*=8.0 Hz, 1H, H-7). HPLC/MS (4.5 min) retention time 4.10 min. LRMS: m/z 219 (M+1).

10.8. *Ethyl (4-oxo-3,4-dihydrophthalazin-1-yl)acetate (**67**)*

Lactone **66** (0.39 g, 1.77 mmol) was dissolved in 6 ml ethanol. Hydrazine monohydrate (0.26 ml, 5.32 mmol) was added and the mixture was stirred at 60 ºC for 2 h. The mixture was evaporated under reduced pressure and the residue was purified using the Biotage purification system (ethyl acetate-hexane gradient) to give **67** (116 mg, 0.50 mmol, 28% yield) as a yellow solid. Purity 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.24 (t, *J*=7.1 Hz, 3H, OCH_2CH_3), 3.97 (s, 2H, CH_2CO_2), 4.20 (q, *J*=7.2 Hz, 2H, OCH_2CH_3), 7.75 (d, *J*=8.0 Hz, 1H, H-8), 7.80 (t, *J*=6.9 Hz, 1H, H-6 or H-7), 7.85 (t, *J*=7.6 Hz, 1H, H-7 or H-6), 8.48 (d, *J*=7.6 Hz, 1H, H-5). HPLC/MS (4.5 min) retention time 3.12 min. LRMS: m/z 233 (M+1).

10.9. *Ethyl {4-oxo-3-[2-(phenylsulfonyl)benzyl]-3,4-dihydrophthalazin-1-yl}acetate (**68**)*

Phthalazinone **67** (98 mg, 0.42 mmol) was dissolved in 1.4 ml dimethylformamide. Sodium hydride (60% dispersion in oil, 34 mg, 0.85 mmol) was added and the mixture was stirred at room temperature for 1 h. Bromide **10a** (197 mg, 0.63 mmol) was added and the mixture was stirred for 1 h. The mixture was partitioned between dichloromethane and brine. The aqueous was extracted twice with dichloromethane and the combined organics were dried over magnesium sulphate, filtered and evaporated. The residue was partially purified using the Biotage purification system (ethyl acetate-hexane gradient, 0:100 rising to 100:0). The residue obtained was re-purified by reverse-phase chromatography to give **68** (35 mg, 0.075 mmol, 18% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.21 (t, *J*=7.1 Hz, 3H, OCH_2CH_3), 3.87 (s, 2H, CH_2CO_2), 4.15 (q, *J*=7.0 Hz, 2H, OCH_2CH_3), 5.77 (s, 2H, CH_2Ph), 6.97 (dd, *J*=3.9, 5.1 Hz, 1H, Bn H-6), 7.43 – 7.47 (m, 2H, Bn H-4 and H-5), 7.54 (t, *J*=7.8 Hz, 2H, SO_2Ph meta), 7.60 (t, *J*=7.0 Hz, 1H, SO_2Ph para), 7.70 (d, *J*=8.0 Hz, 1H, phthalazinone H-8), 7.77 (t, *J*=7.1 Hz, 1H, phthalazinone H-6 or H-7), 7.83 (t, *J*=7.2 Hz, 1H, phthalazinone H-7 or H-6), 7.98 (d, *J*=7.2 Hz, 2H, SO_2Ph ortho), 8.22 - 8.27 (m, 1H, phthalazinone H-5), 8.43 (d, *J*=7.4 Hz, 1H, Bn H-3). HPLC/MS (4.5 min) retention time 3.95 min. LRMS: m/z 463 (M+1).

10.10. *{4-Oxo-3-[2-(phenylsulfonyl)benzyl]-3,4-dihydrophthalazin-1-yl}acetic acid (**69**)*

Ester **68** (35 mg, 0.076 mmol) was dissolved in 2 ml tetrahydrofuran and 2 ml water. Lithium hydroxide monohydrate (4 mg, 0.17 mmol) was added and the mixture was stirred at room temperature for 2 h. The solution was diluted with water and was washed with ethyl acetate. The aqueous phase was acidified to pH 3 with 1N hydrochloric acid forming a turbid solution. The aqueous phase was extracted twice with ethyl acetate and the combined organics were dried over anhydrous magnesium sulphate, filtered and evaporated to give **69** (33 mg, 0.76 mmol, 100% yield) as a white solid. Purity 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.89 (s, 2H, CH_2CO), 5.76 (s, 2H, CH_2Ph), 6.97 (dd, *J*=3.8, 5.2 Hz, 1H, Bn H-6), 7.26-7.46 (m, 2H, Bn H-4 and H-5), 7.51 (t, *J*=7.8 Hz, 2H, SO_2Ph meta), 7.57 (t, *J*=7.2 Hz, 1H, SO_2Ph para), 7.70 (d, *J*=7.8 Hz, 1H, phthalazinone H-8), 7.78 (t, *J*=7.1 Hz, 1H, phthalazinone H-6 or H-7), 7.83 (t, *J*=6.9 Hz, 1H, phthalazinone H-7 or H-6), 7.95 (d, *J*=7.2 Hz, 2H, SO_2Ph ortho), 8.17 - 8.25 (m, 1H, phthalazinone H-5), 8.44 (d, *J*=7.4 Hz, 1H, Bn H-3). HPLC/MS (30 min) retention time 13.63 min. LRMS: m/z 435 (M+1).

11. Scheme 11

11.1. *3-Nitro-N-[2-(phenylsulfonyl)benzyl]pyridin-2-amine (**70**)*

Chloro-3-nitropyridine (250 mg, 1.58 mmol) was dissolved in diisopropylethylamine (0.33 ml, 1.9 mmol) in 2.5 ml ethanol. Amine **11a** (468 mmol, 1.9 mmol) was added and the mixture was stirred and heated at 140 ºC under microwave irradiation for 30 min. The mixture was allowed to cool and was partitioned between water and ethyl acetate, forming a precipitate. The solid was collected by filtration, washed with ether and dried in a stream of air to give **70** (502 mg, 1.36 mmol, 86% yield). Purity 95%. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 4.99 (d, *J*=6.0 Hz, 2H, CH_2), 6.73 (dd, *J*=4.4, 8.2 Hz, 1H, pyridine H-5), 7.47 (d, *J*=7.4 Hz, 1H, Bn H-6), 7.51 - 7.69 (m, 4H, SO_2Ph meta and 2×Ar), 7.72 (t, *J*=7.4 Hz, 1H, SO_2Ph para), 7.93 (d, *J*=7.4 Hz, 2H, SO_2Ph ortho), 8.10 - 8.18 (m, 2H, Bn H-3 and Ar), 8.40 (d, *J*=8.2 Hz, 1H, pyridine H-6), 8.93 (t, *J*=5.8 Hz, 1H, NH). UPLC/MS (3 min) retention time 1.81 min. LRMS: *m*/z 370 (M+1).

11.2. *N-2-[2-(Phenylsulfonyl)benzyl]pyridine-2,3-diamine (**71**)*

Nitropyridine **70** (450 mg, 1.22 mmol) was suspended in 10 ml ethanol and 10 ml tetrahydrofuran. 10% Palladium on carbon (145 mg) was added and the mixture was stirred under a hydrogen atmosphere (1 atm) for 1 h at room temperature. The mixture was filtered through a plug of Celite, washing through with methanol. The combined filtrate was evaporated under reduced pressure to give **71** (402 mg, 1.19 mmol, 97% yield) as a pale brown semi-solid. Purity 97%. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 4.72 (br. s., 2H, NH_2), 4.77 (d, *J*=5.5 Hz, 2H, CH_2), 6.19 (t, *J*=5.5 Hz, 1H, NH), 6.33 (dd, *J*=5.1, 7.3 Hz, 1H, pyridine H-5), 6.70 (d, *J*=7.4 Hz, 1H, pyridine H-6), 7.12 (d, *J*=4.9 Hz, 1H, pyridine H-4), 7.43 (d, *J*=7.7 Hz, 1H, Bn H-6), 7.53 (t, *J*=7.6 Hz, 1H, Bn Ar), 7.63 (t, *J*=7.2 Hz,

2H, SO_2Ph meta), 7.64 - 7.70 (m, 1H, Bn Ar), 7.73 (t, *J*=7.2 Hz, 1H, SO_2Ph para), 7.94 (d, *J*=7.4 Hz, 2H, SO_2Ph ortho), 8.12 (d, *J*=7.7 Hz, 1H, Bn H-3). UPLC/MS (3 min) retention time 0.93 min. LRMS: *m/z* 340 (M+1).

11.3. *3-[2-(Phenylsulfonyl)benzyl]-1,3-dihydro[1,2,5]thiadiazolo[3,4-b]pyridine 2,2-dioxide (**72**)*

Diamine **71** (100 mg, 0.29 mmol) was suspended in 1 ml pyridine. Sulphuric diamide (102 mg, 1.06 mmol) was added and the mixture was stirred and heated at 160 ºC for 15 min under microwave irradiation. The mixture was allowed to cool and was poured over water. The mixture was extracted three times with ethyl acetate, the combined organics were washed with brine, dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The residue was partially purified using the Isolera purification system (methanol-dichloromethane gradient, 0:100 rising to 10:90) to give crude **72** (35 mg). Purity 85%. ^{1}H NMR spectrum not recorded. UPLC/MS (3 min) retention time 1.46 min. LRMS: *m/z* 402 (M+1).

11.4. *Ethyl [2,2-dioxido-3-[2-(phenylsulfonyl)benzyl][1,2,5]thiadiazolo[3,4-b]pyridin-1(3H)-yl]acetate (**73**)*

Crude sulfamide **72** (35 mg) was dissolved in 1 ml anhydrous dimethylformamide. Potassium carbonate (48 mg, 0.35 mmol) was added and the mixture was stirred for 15 min. Ethyl bromoacetate (42 µl, 0.38 mmol) was added and the mixture was stirred for 2.5 h. The mixture was partitioned between ethyl acetate and water. The aqueous phase was extracted three times with ethyl acetate. The combined organics were washed with brine, dried over sodium sulphate, filtered and evaporated to give crude **73** (45 mg). Purity 53%. Used as such without further purification. ^{1}H NMR spectrum not recorded. UPLC/MS (3 min) retention time 1.76 min. LRMS: *m/z* 488 (M+1).

11.5. *[2,2-Dioxido-3-[2-(phenylsulfonyl)benzyl][1,2,5]thiadiazolo[3,4-b]pyridin-1(3H)-yl]acetic acid (**74**)*

Crude ester **73** (45 mg) was dissolved in 1 ml tetrahydrofuran and 1 ml water. Lithium hydroxide monohydrate (8 mg, 0.19 mmol) was added and the mixture was stirred for 90 min at room temperature. The organics were evaporated under reduced pressure. The remaining aqueous solution was diluted with water and was washed three times with ethyl acetate. The aqueous phase was acidified with 2N hydrochloric acid forming a turbid solution. The aqueous phase was extracted three times with ethyl acetate and the combined organics were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The residue was purified using the Isolera purification system (methanol-dichloromethane gradient, 0:100 rising to 10:90) to give **74** (2.5 mg, 0.0054 mmol, 2% yield over three steps). Purity 98%. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.99 (s, 2H, CH_2CO), 5.26 (s, 2H, CH_2Ph), 6.94 (dd, *J*=5.0, 7.7 Hz, 1H, thiadiazolopyridine H-6), 7.11 (d, *J*=7.7 Hz, 1H, thiadiazolopyridine H-6), 7.49 (d, *J*=7.4 Hz, 1H, Bn H-6), 7.56 (d, *J*=5.2 Hz, 1H, thiadiazolopyridine H-8), 7.63 - 7.72 (m, 4H, SO_2Ph meta + 2Ar), 7.76 (t, *J*=7.3 Hz, 1H, SO_2Ph para), 7.98 (d, *J*=7.7 Hz, 2H, SO_2Ph ortho), 8.18 (d, *J*=7.4 Hz, 1H, Bn H-3). HPLC/MS (30 min) retention time 14.52 min. LRMS: *m/z* 460 (M+1).

12. Scheme 12

12.1. *Ethyl (2Z)-3-amino-3-pyridin-2-ylacrylate (**75**)*

Sodium ethoxide (6.4 g, 94 mmol) was dissolved in 80 ml ethanol. Ethyl malonate (10 g, 75 mmol) dissolved in 20 ml ethanol was added and the mixture was strirred for 1 h forming a precipitate. The solid was collected by filtration and dried at 40 ºC under vacuum to give sodium ethyl malonate (6.62 g, 43 mmol, 57% yield). 2-Cyanopyridine (2.7 g, 25.9 mmol) was dissolved in 55 ml dichloroethane under nitrogen in a flask fitted with a Dean-Stark head. Sodium ethyl malonate (6.62 g, 43 mmol), zinc(II) chloride (2.62 g, 13 mmol) and diisopropylethylamine (0.45 ml, 2.6 mmol) were added and the mixture was stirred at reflux for 4 h. The mixture was allowed to cool and 25 ml saturated ammonium chloride solution was added. The organic phase was separated, dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The residue was purified using the SP-1 purification system (ethyl acetate-hexane gradient, 0:100 rising to 20:80) to give **75** (4.37 g, 22.7 mmol, 88% yield). Purity 100%. ^{1}H NMR spectrum not recorded. HPLC/MS (9 min) retention time 5.35 min. LRMS: *m/z* 193 (M+1).

12.2. *Ethyl 3-amino-3-pyridin-2-ylpropanoate (**76**)*

Amino acrylate **75** (2.0 g, 10.4 mmol) was dissolved in 65 ml ethanol containing 1.2 ml acetic acid. Palladium hydroxide (20% on carbon, 1.1 g, 1.6 mmol) was added and the mixture was stirred under hydrogen atmosphere (14 psi) for 4 h. The mixture was filtered through a plug of Celite and the filtrate was evaporated under reduced pressure. The residue was partitioned between dichloromethane and saturated potassium carbonate solurtion. The organic phase was washed with water, brine, dried over anhydrous sodium sulphate, filtrered and evaporated under reduced pressure to give **76** (1.48 g, 7.6 mmol, 73% yield) as a pale yellow oil. Purity 100%. ^{1}H NMR spectrum not recorded. UPLC/MS (3 min) retention time 0.58 min. LRMS: *m/z* 195 (M+1).

12.3. *Ethyl [3-(2-iodobenzyl)imidazo[1,5-a]pyridin-1-yl]acetate (**77**)*

Aminoester **76** (0.92 g, 4.50 mmol) and 2-(2-iodophenyl)acetic acid (1.36 g, 5.2 mmol) were dissolved in 23 ml butyl acetate. 1-Propanephosphonic anhydride solution (T3P, 7 ml, 11.7 mmol) was added and the mixture was stirred for 1 h at room termpature and then 1 h at reflux. The mixture was allowed to cool to room temperature and was washed twice with 4% sodium bicarbonate solution. The organics were dried over anhydrous sodium sulphate, filtrered and evaporated under reduced pressure. The residue was purified using the SP-1 purification system (ethyl acetate-hexane gradient, 0:100 rising to 30:70) to give **77** (1.1 g, 2.62 mmol, 58% yield) as a pale yellow solid. Purity 100%. ^{1}H NMR spectrum not recorded. UPLC/MS (3 min) retention time 1.76 min. LRMS: *m*/*z* 421 (M+1).

12.4. *Ethyl {3-[2-(phenylsulfonyl)benzyl]imidazo[1,5-a]pyridin-1-yl}acetate (**78**)*

Iodide **77** (200 mg, 0.48 mmol) was dissolved in 1 ml dimethylsulphoxide under nitrogen. Benzene sulphinic acid sodium salt (94 mg, 0.5 mmol), copper(I) triflate-benzene complex (13 mg, 0.02 mmol) and N,N'-dimethylethylenediamine (5 µl, 0.05 mmol) were added and the mixture was stirred at 110 ºC overnight. The mixture was allowed to cool, was diluted with ethyl acetate and was filtered through a plug of Celite. The filtrate was washed twice with water, brine, dried over anhydrous sodium sulphate, filtrered and evaporated under reduced pressure. The residue was purified using the SP-1 purification system (ethyl acetate-hexane gradient, 0:100 rising to 50:50) to give **78** (30 mg, 0.069 mmol, 15% yield). Purity 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.26 (t, *J*=7.2 Hz, 3H, OCH_2CH_3), 3.89 (s, 2H, CH_2CO_2), 4.17 (q, *J*=7.0 Hz, 2H, OCH_2CH_3), 4.61 (s, 2H, CH_2Ph), 6.39 (t, *J*=6.6 Hz, 1H, imidazopyridine H-6), 6.64 (dd, *J*=6.4, 9.2 Hz, 1H, imidazopyridine H-7), 6.86 (d, *J*=7.0 Hz, 1H, Bn H-6), 7.36 - 7.48 (m, 4H, Ar), 7.51 (t, *J*=7.6 Hz, 2H, $PhSO_2$ meta), 7.60 (t, *J*=7.4 Hz, 1H, $PhSO_2$ para), 7.88 (d, *J*=7.4 Hz, 2H, $PhSO_2$ ortho), 8.31 (d, *J*=7.4 Hz, 1H, Bn H-3). UPLC/MS (3 min) retention time 1.66 min. LRMS: *m*/*z* 435 (M+1).

12.5. *{3-[2-(Phenylsulfonyl)benzyl]imidazo[1,5-a]pyridin-1-yl}acetic acid (**79**)*

Ester **78** (30 mg, 0.07 mmol) was dissolved in 1.5 ml tetrahydrofuran and 1.5 ml water. Lithium hydroxide monohydrate (12 mg, 0.29 mmol) was added and the mixture was stirred for 2 h at room temperature. The organics were evaporated under reduced pressure. The solution was diluted with water and was washed with ethyl acetate. The aqueous phase was acidified to pH 4 with acetic acid and was stirred for 90 min forming a turbid solution. The mixture was extracted three times with ethyl acetate and the combined organics were dried over anhydrous sodium sulphate, filtrered and evaporated under reduced pressure. The residue was purified by preparative HPLC to give **79** (6 mg, 0.014 mmol, 21% yield). Purity 86%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.63 (s, 2H, CH_2CO_2), 4.57 (s, 2H, CH_2Ph), 6.54 (t, *J*=6.6 Hz, 1H, imidazopyridine H-6), 6.68 (dd, *J*=6.4, 9.2 Hz, 1H, imidazopyridine H-7), 7.03 (d, *J*=7.8 Hz, 1H, Bn H-6), 7.51 (t, *J*=8.0 Hz, 2H, $PhSO_2$ meta), 7.54 - 7.68 (m, 5H, Ar), 7.79 (d, *J*=7.8 Hz, 2H, $PhSO_2$ ortho), 8.19 (d, *J*=7.4 Hz, 1H, Bn H-3). HPLC/MS (30 min) retention time 10.97 min. LRMS: *m*/*z* 407 (M+1).

13. Scheme 13

13.1. *4-Bromo-1H-pyrrole-2-carbaldehyde (**80**)*

1H-Pyrrole-2-carbaldehyde (20 g, 210 mmol) was dissolved in 250 ml tetrahydrofuran and the mixture was cooled to -78 ºC. N-Bromosuccinimide (37 g, 210 mmol) was added portion-wise over 1 h with stirring and the mixture was stirred for a further 6.5 at -78 ºC. The mixture was allowed to warm to 0 ºC and was partitioned between water and hexane and protected from the light. The aqueous phase was extracted with cold hexane and the combined organics were washed with water, dried over anhydrous sodium sulphate and filtered. The organics were concentrated under reduced pressure until a precipitate formed. The solid was cold-filtered, washed with cold hexane and dried under vacuum to give 12.8 g of **80**. The filtrates were concentrated again under reduced pressure until further precipitate formed. This was collected by filtration as before and combined with the first obtained solid to give **80** (18.9 g, 109 mmol, 53% yield). Purity 96%. Stored at 4 ºC in the dark. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.96 - 6.99 (m, 1H, H-3), 7.11 - 7.14 (m, 1H, H-5), 9.47 (s, 1H, CHO), 9.88 (br. s., 1H, NH). UPLC/MS (3 min) retention time 1.18 min. LRMS: *m*/*z* 172, 174 (M-1).

13.2. *6-Bromo-3-[(4-methylphenyl)sulfonyl]pyrrolo[1,2-c]pyrimidine (**81**)*

Aldehyde **80** (3.1 g, 13.0 mmol) was dissolved in 160 ml anhydrous tetrahydrofuran under argon. Toluenesulfonylmethyl isocyanide (3.8 g, 19.5 mmol) and 1,8-diazabicycloundec-7-ene (2.9 g, 19.4 mmol) were added and the mixture was stirred for 3 h at room temperature. The mixture was adjusted to pH 6-7 with acetic acid and was evaporated under reduced pressure. The residue was purified by flash chromatography using the Isolera system (ethyl acetate-hexane gradient, 0:100 rising to 100:0) to give **81** (3.43 g, 9.8 mmol, 75% yield) as a beige solid. Purity 100%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.42 (s, 3H, Me), 6.85 (s, 1H, H-5), 7.34 (d, *J*=8.0 Hz, 2H, SO_2Ph meta), 7.52 (s, 1H, H-7), 7.94 (d, *J*=8.0 Hz, 2H, SO_2Ph ortho), 8.18 (s, 1H, H-4), 8.65 (s, 1H, H-1). UPLC/MS (3 min) retention time 1.78 min. LRMS: *m*/*z* 351, 353 (M+1).

13.3. *6-Methyl-3-[(4-methylphenyl)sulfonyl]pyrrolo[1,2-c]pyrimidine (**82**)*

Bromide **81** (5.0 g, 14.3 mmol) was dissolved in 11 ml dimethoxyethane under nitrogen. Potassium carbonate (6.0 g, 43.4 mmol), trimethyl boroxine (2.2 ml, 16.0 mmol) and [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (0.61 g, 0.69 mmol) were added. The mixture was subjected to a vacuum-nitrogen cycle and was then heated at 120 ºC under microwave irradiation for 30 min. the mixture was allowed to cool and was filtered through a plug of Celite, washing through with dichloromethane. The mixture was evaporated under reduced pressure and the residue was triturated with ether and dichloromethane to give **82** (3.7 g, 12.9 mmol, 90% yield) as a brown solid. Purity 93%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.35 (s, 3H, ArMe), 2.41 (s, 3H, SO_2PhMe), 6.64 (s, 1H, H-5), 7.29 (s, 1H, H-7), 7.32 (d, *J*=8.0 Hz, 2H, SO_2Ph meta), 7.94 (d, *J*=8.2 Hz, 2H, SO_2Ph ortho), 8.14 (s, 1H, H-4), 8.62 (s, 1H, H-1). UPLC/MS (3 min) retention time 1.70 min. LRMS: *m*/*z* 287 (M+1).

13.4. *6-Methylpyrrolo[1,2-c]pyrimidine (**83**)*

Disodium phosphate (0.60 g, 4.2 mmol) and 5% sodium/mercury amalgam (0.94 g, 2.1 mmol) were suspended in 12 ml anhydrous methanol and the mixture was degassed with a stream of argon. Sulphone **82** (300 mg, 1.05 mmol) dissolved in 8 ml tetrahydrofuran was added over 5 min and the mixture was stirred vigorously overnight under argon. Further 5% sodium/mercury amalgam (0.94 g, 2.1 mmol) was added and the mixture was stirred vigorously for 2 h. The mixture was partitioned between water and ether. The aqueous phase was extracted twice with ether and the combined organics were dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The residue was purified using the Isolera purification system (ether-hexane gradient) to give **83** (87 mg, 0.66 mmol, 63% yield) as a yellow oil. Purity 95%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.34 (s, 3H, Me), 6.27 (br. s., 1H, H-5), 7.14 (d, *J*=6.3 Hz, 1H, H-4), 7.17 (s, 1H, H-7), 7.35 (d, *J*=6.3 Hz, 1H, H-3), 8.69 (s, 1H, H-1). UPLC/MS (3 min) retention time 1.00 min. LRMS: *m*/*z* 133 (M+1).

13.5. *6-Methyl-7-[2-(phenylsulfonyl)benzyl]pyrrolo[1,2-c]pyrimidine (**84**)*

Pyrrolopyrimidine **83** (370 mg, 2.8 mmol) was dissolved in 7 ml anhydride acetic under nitrogen and the mixture was cooled to 0 ºC. Hydriodic acid (57% solution, 3.3 ml, 25.0 mmol) was added drop-wise and with stirring over 20 min (exotherm), warming to room temperature. Hypophosphorous acid (50% solution, 1.37 ml, 13.2 mmol) was added followed by aldehyde **8a** (580 mg, 2.4 mmol) and the mixture was stirred for 100 min at room temperature. The mixture was partitioned between ethyl acetate and ice-water. The aqueous phase was extracted twice with ethyl acetate. The combined organics were washed with 4% sodium bicarbonate solution, brine, dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The residue was purified using the Isolera purification system (ether-hexane gradient) to give **84** (299 mg, 0.83 mmol, 35% yield) as a pale yellow solid. Purity 94%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.17 (s, 3H, Me), 4.45 (s, 2H, CH_2), 6.31 (s, 1H, pyrrolopyrimidine H-5), 6.55 (d, *J*=7.4 Hz, 1H, Bn H-6), 7.11 (dd, *J*=1.4, 6.3 Hz, 1H, pyrrolopyrimidine H-4), 7.29 (d, *J*=6.3 Hz, 1H, pyrrolopyrimidine H-3), 7.37 (td, *J*=7.6, 1.2 Hz, 1H, Bn H-4), 7.45 (t, *J*=7.3 Hz, 1H, Bn H-5), 7.60 (t, 2H, SO_2Ph meta), 7.61 (d, *J*=1.4 Hz, pyrrolopyrimidine H-1), 7.68 (t, *J*=7.4 Hz, 1H, SO_2Ph para), 7.97 (d, *J*=7.4 Hz, 2H, SO_2Ph ortho), 8.31 (dd, *J*=1.4, 7.7 Hz, 1H, Bn-3). UPLC/MS (3 min) retention time 1.85 min. LRMS: *m*/*z* 363 (M+1).

13.6. *7-{2-[(4-Fluorophenyl)sulfonyl]-5-methoxybenzyl}-6-methylpyrrolo[1,2-c]pyrimidine (**85**)*

Pyrrolopyrimidine **83** (220 mg, 1.67 mmol) was dissolved in 4 ml anhydride acetic under nitrogen and the mixture was cooled to 0 ºC. Hydriodic acid (57% solution, 2.1 ml, 15.9 mmol) was added drop-wise and with stirring over 20 min (exotherm), warming to room temperature. Hypophosphorous acid (50% solution, 0.86 ml, 8.3 mmol) was added followed by crude aldehyde **8c** (440 mg) and the mixture was stirred for 2 h at room temperature. The mixture was partitioned between ethyl acetate and ice-water. The aqueous phase was extracted twice with ethyl acetate. The combined organics were washed with 4% sodium bicarbonate solution, brine, dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The residue was purified using the Isolera purification system (ether-hexane gradient) to give **85** (196 mg, 0.48 mmol, 32% yield) as a white solid. Purity 96%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.18 (s, 3H, ArMe), 3.68 (s, 3H, OMe), 4.41 (s, 2H, CH_2), 6.08 (s, 1H, pyrrolopyrimidine H-5), 6.31 (s, 1H, Bn H-6), 6.90 (dd, *J*=2.3, 8.7 Hz, 1H, pyrrolopyrimidine H-4), 7.13 (d, *J*=6.3 Hz, 1H, pyrrolopyrimidine H-3), 7.19 - 7.36 (m, 3H, Ar), 7.86 (s, 1H, pyrrolopyrimidine H-1), 7.90 - 8.00 (m, 2H, SO_2Ph ortho), 8.27 (d, *J*=8.8 Hz, 1H, Bn H-3). UPLC/MS (3 min) retention time 1.91 min. LRMS: *m*/*z* 411 (M+1).

13.7. *Ethyl {6-methyl-7-[2-(phenylsulfonyl)benzyl]pyrrolo[1,2-c]pyrimidin-5-yl}acetate (**86**)*

Aluminium trichloride (0.16 g, 1.25 mmol) was dissolved in 2 ml chlorobenzene and the mixture was degassed with nitrogen and cooled to 0 ºC. Ethyl 2-chloro-2-oxoacetate (0.14 ml, 1.25 mmol) was added drop-wise and with stirring and the mixture stirred for 15 min at 0 ºC giving a bright yellow solution. Pyrrolopyrimidine **84** (0.15 g, 0.41 mmol) dissolved

in 1 ml chlorobenzene was added drop-wise and with vigorous stirring at 0 ºC, giving a dark red solution. The mixture was stirred at 0 ºC for 3 h and then overnight at room temperature. The mixture was partitioned between ethyl acetate and 16% aqueous ammonia solution. The aqueous phase was extratcted with ethyl acetate and the combined organics were washed with brine, dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure to give 190 mg of the crude oxoacetate. used directly without further purification. UPLC/MS (5 min) retention time 2.18 min. LRMS: *m*/*z* 463 (M+1).

The crude oxoacetate (190 mg) was dissolved in 1.6 ml trifluoroacetic acid under argon. Triethylsilane (2.0 ml, 12.6 mmol) as added and the mixture was stirred at 80 ºC overnight. The mixture was allowed to cool and was basified with dilute aqueous ammonia. The mixture was extracted three times with ethyl acetate and the combined organics were washed brine, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The residue was purified using the Isolera purification system (ether-hexane gradient, 50:50 rising to 100:0) to give **86** (53 mg, 0.12 mmol, 29% yield over two steps) as a pale yellow solid. Purity 97%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.26 (t, *J*=7.1 Hz, 3H, $COCH_2CH_3$), 2.14 (s, 3H, ArMe), 3.69 (s, 2H, CH_2CO), 4.16 (q, *J*=7.0 Hz, 2H, $COCH_2CH_3$), 4.46 (s, 2H, CH_2Ph), 6.57 (d, *J*=7.4 Hz, 1H, Bn H-6), 7.15 (d, *J*=6.6 Hz, 1H, pyrrolopyrimidine H-4), 7.31 (d, *J*=6.6 Hz, 1H, pyrrolopyrimidine H-3), 7.38 (t, *J*=6.9 Hz, 1H, Bn H-4), 7.46 (t, *J*=7.6 Hz, 1H, Bn H-5), 7.58 (s, 1H, pyrrolopyrimidine H-1), 7.60 (t, *J*=7.2 Hz, 2H, SO_2Ph meta), 7.69 (t, *J*=7.2 Hz, 1H, SO_2Ph para), 7.97 (d, *J*=7.1 Hz, 2H, SO_2Ph ortho), 8.32 (d, *J*=8.0 Hz, 1H, Bn H-3). UPLC/MS (3 min) retention time 1.87 min. LRMS: *m*/*z* 449 (M+1).

13.8. *Ethyl (7-{2-[(4-fluorophenyl)sulfonyl]-5-methoxybenzyl}-6-methylpyrrolo[1,2-c]pyrimidin-5-yl)acetate (**87**)*

Aluminium trichloride (0.14 g, 1.05 mmol) was dissolved in 2 ml chlorobenzene and the mixture was degassed with nitrogen and cooled to 0 ºC. Ethyl 2-chloro-2-oxoacetate (0.12 ml, 1.05 mmol) was added drop-wise and with stirring and the mixture stirred for 10 min at 0 ºC, giving a bright yellow solution. Pyrrolopyrimidine **85** (0.15 g, 0.35 mmol) dissolved in 1.5 ml chlorobenzene was added drop-wise and with vigorous stirring at 0 ºC, giving a dark red solution. The mixture was then stirred overnight at room temperature. The mixture was partitioned between ethyl acetate and 16% aqueous ammonia solution. The aqueous phase was extratcted with ethyl acetate and the combined organics were washed brine, dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure to give crude oxoacetate (190 mg). Used directly without further purification. UPLC/MS (3 min) retention time 1.92 min. LRMS: *m*/*z* 511 (M+1).

The crude oxoacetate (190 mg) was dissolved in 1.5 ml trifluoroacetic acid under nitrogen. Triethylsilane (2.0 ml, 12.6 mmol) was added and the mixture was stirred at 80 ºC overnight. The mixture was allowed to cool and was basified with dilute aqueous ammonia. The mixture was extracted three times with chloroform and the combined organics were washed brine, dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The residue was purified using the Isolera purification system (ether-hexane gradient, 30:70 rising to 100:0) to give **87** (34 mg, 0.068 mmol, 19% over two steps) as a pale yellow solid. Purity 100%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.25 (t, *J*=7.1 Hz, 3H, $COCH_2CH_3$), 2.12 (s, 3H, ArMe), 3.68 (s, 5H, OMe and CH_2CO), 4.14 (q, *J*=7.1 Hz, 2H, $COCH_2CH_3$), 4.40 (s, 2H, CH_2Ph), 6.08 (s, 1H, Bn H-6), 6.89 (dd, *J*=2.5, 8.8 Hz, 1H, Bn H-4), 7.16 (d, *J*=6.3 Hz, 1H, pyrrolopyrimidine H-4), 7.21 - 7.30 (m, 2H, SO_2Ph meta), 7.33 (d, *J*=6.6 Hz, 1H, pyrrolopyrimidine H-3), 7.82 (s, 1H, pyrrolopyrimidine H-1), 7.89 - 8.01 (m, 2H, SO_2Ph para), 8.27 (d, *J*=8.8 Hz, 1H, Bn H-3). UPLC/MS (3 min) retention time 1.93 min. LRMS: *m*/*z* 497 (M+1).

13.9. *{6-Methyl-7-[2-(phenylsulfonyl)benzyl]pyrrolo[1,2-c]pyrimidin-5-yl}acetic acid (**88**)*

Ester **86** (53 mg, 0.12 mmol) was dissolved in 1 ml tetrahydrofuran and 1 ml water. Lithium hydroxide monohydrate (20 mg, 0.48 mmol) was added and the mixture was stirred for 1 h at room temperature. The organics were evaporated under reduced pressure. The solution was diluted with water and was washed with ethyl acetate. The aqueous phase was neutralized to pH 7 with 1N hydrochloric acid, forming a precipitate. The solid was collected by filtration, was washed with a little water and was dried at 40 ºC under vacuum to give **88** (50 mg, 0.12 mmol, 99% yield) as a white solid. Purity 99%. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.89 (s, 3H, Me), 3.62 (s, 2H, CH_2CO), 4.48 (s, 2H, CH_2Ph), 6.59 (d, *J*=6.0 Hz, 1H, Bn H-6), 7.23 (d, *J*=6.0 Hz, 1H, pyrrolopyrimidine H-4), 7.34 (d, *J*=6.0 Hz, 1H, pyrrolopyrimidine H-3), 7.45 - 7.62 (m, 3H, Ar), 7.68 (t, *J*=7.1 Hz, 2H, SO_2Ph meta), 7.78 (t, *J*=7.0 Hz, 1H, SO_2Ph para), 7.92 - 8.08 (m, 3H, SO_2Ph ortho and pyrrolopyrimidine H-1), 8.24 (d, *J*=6.3 Hz, 1H, Bn H-3). HPLC/MS (30 min) retention time 13.92 min. LRMS: *m*/*z* 421 (M+1).

13.10. *(7-{2-[(4-Fluorophenyl)sulfonyl]-5-methoxybenzyl}-6-methylpyrrolo[1,2-c]pyrimidin-5-yl)acetic acid (**89**)*

Ester **87** (34 mg, 0.068 mmol) was dissolved in 0.8 ml tetrahydrofuran and 0.8 ml water. Lithium hydroxide monohydrate (32 mg, 0.76 mmol) was added and the mixture

was stirred for 3 h at room temperature. The organics were evaporated under reduced pressure. The solution was diluted with water and was washed twice with chloroform. The aqueous phase was evaporated under reduced pressure and the residue was purified using the Isolera purification system (methanol-dichloromethane, 10:90) to give **89** (20 mg, 0.042 mmol, 61% yield) as a white solid. Purity 97%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.12 (s, 3H, ArMe), 3.66 (s, 3H, OMe), 3.72 (s, 2H, CH_2CO), 4.39 (s, 2H, CH_2Ph), 6.06 (s, 1H, Bn H-6), 6.89 (dd, *J*=2.5, 8.8 Hz, 1H, Bn H-4), 7.14 (d, *J*=6.6 Hz, 1H, pyrrolopyrimidine H-4), 7.23 (t, *J*=7.4 Hz, 2H, SO_2Ph meta), 7.34 (d, *J*=6.3 Hz, 1H, pyrrolopyrimidine H-3), 7.84 (s, 1H, pyrrolopyrimidine H-1), 7.89 - 7.98 (m, 2H, SO_2Ph ortho), 8.26 (d, *J*=8.8 Hz, 1H, Bn H-3). HPLC/MS (30 min) retention time 14.55 min. LRMS: *m*/*z* 469 (M+1).

14. Scheme 19

14.1. *Methyl pent-4-ynoate (**90**)*

Pent-4-ynoic acid (11.7 g, 119 mmol) was dissolved in 100 ml methanol and the mixture was cooled to -5 ºC in a salt-ice bath. Thionyl chloride (10 ml, 137 mmol) dissolved in 80 ml methanol was added over 30 min with stirring. The mixture was stirred for a further 2 h at room temperature. The mixture was concentrated to around 50 ml volume and was diluted with dichloromethane. The organics were washed sequentially with water, 4% sodium bicarbonate solution, water and brine, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to give **90** (13.3 g, 119 mmol, 100% yield) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.47 - 2.62 (m, 4H, 2×CH_2), 3.65 (s, 1H, acetylene H), 3.71 (s, 3H, Me). UPLC/MS (3 min) no chromophore, no ionization.

14.2. *Methyl 5-[4-(trifluoromethyl)pyrimidin-2-yl]pent-4-ynoate (**91**)*

2-Chloro-4-(trifluoromethyl)pyrimidine (2.0 ml, 16.6 mmol), alkyne **90** (2.23 g, 19.9 mmol), and copper(I) iodide (0.13 g, 0.66 mmol) were suspended together in 150 ml triethylamine in a Schlenk tube. The mixture was subjected to three vacuum-argon cycles. Bis(triphenylphosphine)palladium(II) dichloride (0.23 g, 0.33 mmol) was added and the mixture was subjected to a further three vacuum-argon cycles. The mixture was stirred at 80 ºC overnight. The mixture was allowed to cool and was poured into saturated ammonium chloride solution. The mixture was extracted twice with ethyl acetate. The organics were washed twice with water, once with brine, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The residue was purified using the Isolera purification system (ether-hexane gradient, 0:100 rising to 50:50) to give **91** (2.91 g, 11.3 mmol, 68% yield) as a pale yellow oil which crystallized over time. Purity 95%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.72 (t, *J*=8.2 Hz, 2H, CH_2), 2.83 (t, *J*=8.2 Hz, 2H, CH_2), 3.73 (s, 3H, Me), 7.55 (d, *J*=5.3 Hz, 1H, H-5), 8.95 (d, *J*=4.7 Hz, 1H, H-6). HPLC/MS (9 min) retention time 5.58 min. LRMS: *m*/*z* 259 (M+1).

14.3. *Methyl [2-(trifluoromethyl)pyrrolo[1,2-a]pyrimidin-6-yl]acetate (**92**)*

In five separate batches, a total of alkyne **91** (5×170 mg, 3.3 mmol), copper(I) bromide (5×95 mg, 3.3 mmol) and triethylamine (5×0.095 ml, 3.3 mmol) were suspended together in 5×16 ml dimethylacetamide. Each batch was stirred and heated at 180 ºC for 1 h under microwave irradiation. The mixtures were allowed to cool and were poured into cold saturated ammonium chloride solution. Ether was added and the whole mixture was filtered through a plug of Celite, washing through with ether. The biphasic filtrate was separated and the aqueous was extracted three times with ether. The combined organics were washed with brine, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The residue was partially purified by reverse-phase chromatography using the Isolera purification system to give crude **92**. The crude residue was re-purified using the Isolera purification system (ether-hexane gradient, 0:100 rising to 40:60) to give **92** (278 mg, 1.08 mmol, 33% yield). Purity 100%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.72 (s, 3H, OMe), 3.97 (s, 2H, CH_2), 6.88 (d, *J*=3.5 Hz, 1H, H-7), 6.89 (d, *J*=7.6 Hz, 1H, H-3), 7.07 (d, *J*=4.1 Hz, 1 H, H-8), 8.33 (d, *J*=7.6 Hz, 1H, H-4). UPLC/MS (3 min) retention time 1.54 min. LRMS: *m*/*z* 259 (M+1).

14.4. *Methyl [8-[2-(phenylsulfonyl)benzyl]-2-(trifluoromethyl)pyrrolo[1,2-a]pyrimidin-6-yl]acetate (**93**)*

Pyrrolopyrimidine **92** (215 mg, 0.83 mmol) was dissolved in 2.5 ml anhydride acetic under argon and the mixture was cooled to 0 ºC. Hydriodic acid (57% solution, 1.1 ml, 8.33 mmol) was added drop-wise and with stirring (exotherm), warming to room temperature. Hypophosphorous acid (50% solution, 0.50 ml, 4.8 mmol) was added followed by aldehyde **8a** (195 mg, 0.79 mmol) and the mixture was stirred for 2 h at room temperature. The mixture was partitioned between ethyl acetate and water. The organic phase was washed twice with water, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The residue was re-dissolved in 1.3N hydrochloric acid in methanol and the mixture was stirred for 1 h at room temperature. The mixture was concentrated under reduced, was diluted with dichloromethane and washed with saturated sodium bicarbonate solution. The organics were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure and the residue was purified using the Isolera purification system (ether-hexane gradient, 0:100 rising to 100:0) to give **93** (132 mg, 0.27 mmol, 34% yield) as a

yellow oil. Purity 100%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.69 (s, 3H, OMe), 3.83 (s, 2H, CH_2CO), 4.49 (s, 2H, CH_2Ph), 6.70 (s, 1H, pyrrolopyrimidine H-7), 6.81 (d, *J*=7.0 Hz, 1H, Bn H-6), 7.33 – 7.42 (m, 4H, Ar), 7.44 (t, *J*=7.0 Hz, 2H, SO_2Ph meta), 7.53 (t, *J*=7.0 Hz, 1H, SO_2Ph para), 7.88 (d, *J*=7.6 Hz, 2H, SO_2Ph ortho), 8.19 (d, *J*=7.6 Hz, 1H, pyrrolopyrimidine H-4), 8.25 (d, *J*=7.6 Hz, 1H, Bn H-3). HPLC/MS (9 min) retention time 6.80 min. LRMS: *m*/*z* 489 (M+1).

14.5. *[8-[2-(Phenylsulfonyl)benzyl]-2-(trifluoromethyl)pyrrolo[1,2-a]pyrimidin-6-yl]acetic acid (**94**)*

Ester **93** (20 mg, 0.041 mmol) was dissolved in 0.5 ml tetrahydrofuran and 0.5 ml water. Lithium hydroxide monohydrate (7 mg, 0.17 mmol) was added and the mixture was stirred for 60 min at room temperature. The organics were evaporated under reduced pressure. The remaining aqueous solution was diluted with a little water was acidified with 1N hydrochloric acid forming a turbid solution. The aqueous phase was extracted three times with dichloromethane and the combined organics were evaporated under reduced pressure to give **94** (15 mg, 0.031 mmol, 76% yield) as a yellow foam. Purity 91%. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.93 (s, 2H, CH_2CO), 4.41 (s, 2H, CH_2Ph), 6.45 (s, 1H, pyrrolopyrimidine H-7), 7.05 (d, *J*=7.6 Hz, 1H, Bn H-6), 7.29 (d, *J*=7.6 Hz, 1H, pyrrolopyrimidine H-3), 7.47 (t, *J*=7.6 Hz, 2H, SO_2Ph meta), 7.52 - 7.67 (m, 3H, Ar), 7.78 (d, *J*=7.6 Hz, 2H, SO_2Ph ortho), 8.18 (d, *J*=7.6 Hz, 1H, Bn H-3), 8.64 (d, *J*=7.6 Hz, 1H, pyrrolopyrimidine H-4). UPLC/MS (5 min) retention time 2.92 min. LRMS: *m*/*z* 475 (M+1).

15. Scheme 15

15.1. *2-Methyl-1H-pyrrolo[2,3-b]pyridine (**95**)*

tert-Butyl 3-methylpyridin-2-ylcarbamate (5.07 g, 23.6 mmol) was dissolved in 100 ml tetrahydrofuran under nitrogen and the mixture was cooled to -10 ºC. n-Butyllithium (2.5M in hexanes, 28 ml, 70 mmol) was added over 15 min with stirring, forming a dark red solution and the mixture was stirred for a further 1 h at -10 ºC. N-Methoxy-N-methylacetamide (3.80 g, 35.7 mmol) was added and the mixture was stirred at room temperature for 1 h. The mixture was cooled to -10 ºC, quenched with 13 ml concentrated hydrochloric acid and then stirred at 50 ºC for 90 min. The biphasic mixture was allowed to cool and the organic phase was extracted twice with 2N hydrochloric acid. The combined aqueous was basified with 32% sodium hydroxide solution and extracted three times with ethyl acetate. The organics were washed with brine, dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The residue was purified using the Isolera purification system (ethyl acetate-hexane gradient, 0:100 rising to 50:50) to give **95** (2.5 g, 18.9 mmol, 80% yield) as a pale yellow solid. Purity 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.55 (s, 3H, Me), 6.17 (s, 1H, H-3), 7.03 (dd, *J*=4.9, 7.6 Hz, 1H, H-5), 7.82 (d, *J*=7.4 Hz, 1H, H-4), 8.21 (d, *J*=4.7 Hz, 1H, H-6), 11.96 (br. s., 1H, NH). UPLC/MS (3 min) retention time 0.68 min. LRMS: *m*/*z* 133 (M+1).

15.2. *2-Methyl-1H-pyrrolo[2,3-b]pyridine 7-oxide (**96**)*

Azaindole **95** (152 mg, 1.15 mmol) was dissolved in 5 ml dimethoxyethane and was cooled to 0 ºC. meta-Chloroperbenzoic acid (77% max purity, 360 mg, 1.8 mmol) was added and the mixture was stirred at room temperature for 1 h. The mixture was concentrated to around 2 ml under reduced pressure and was diluted with 5 ml water, forming a precipitate. The solid was collected by filtration and was purified by reverse-phase chromatography using the Biotage system to give **96** (130 mg, 0.88 mmol, 76% yield) as a yellow solid. Purity 93%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.51 (s, 3H, Me), 6.21 (s, 1H, H-3), 6.99 (t, *J*=7.0 Hz, 1H, H-5), 7.52 (d, *J*=7.8 Hz, 1H, H-4), 8.10 (d, *J*=6.3 Hz, 1H, H-6), 12.64 (br. s., 1H, NH). UPLC/MS (3 min) retention time 0.82 min. LRMS: *m*/*z* 149 (M+1).

15.3. *Ethyl 6-chloro-2-methyl-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (**97**)*

N-oxide **96** (102 mg, 0.69 mmol) was dissolved in 4.5 ml tetrahydrofuran under nitrogen and the mixture cooled to -10 ºC. Hexamethyldisilazane (0.15 ml, 0.72 mmol) was added and the mixture was stirred for 30 min at -10 ºC. Separately, ethyl chloroformate (0.35 ml, 3.7 mmol) was dissolved in 0.5 ml tetrahydrofuran and cooled to -78 ºC. The solutions were combined at -78 ºC and the mixture was then stirred at room temperature overnight. Further hexamethyldisilazane (0.15 ml, 0.72 mmol) and ethyl chloroformate (0.35 ml, 3.7 mmol) were added and the mixture was stirred overnight. The mixture was evaporated under reduced pressure and the residue re-dissolved in ethyl acetate. The organics were washed three times with saturated sodium bicarbonate solution, dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The residue was purified using the Isolera purification system (ether-hexane gradient, 0:100 rising to 30:70) to give **97** (42 mg, 0.18 mmol, 26% yield) as a white solid. Purity 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.51 (t, *J*=7.0 Hz, 3H, OCH_2CH_3), 2.61 (s, 3H, ArMe), 4.55 (q, *J*=7.0 Hz, 2H, OCH_2CH_3), 6.27 (s, 1H, H-3), 7.17 (d, *J*=8.2 Hz, 1H, H-5), 7.68 (d, *J*=8.2 Hz, 1H, H-4). UPLC/MS (3 min) retention time 1.73 min. LRMS: *m*/*z* 239 (M+1).

15.4. *6-Methyl-1-[(4-methylphenyl)sulfonyl]-1H-pyrrolo[2,3-b]pyridine (**99**)*

Sodium hydride (60% dispersion in oil, 2.27 g, 56.8 mmol) was suspended in 50 ml dimethylformamide under nitrogen and the mixture was cooled to 0 ºC. 6-Methyl-1H-pyrrolo[2,3-b]pyridine **98** (5 g, 37.8 mmol) dissolved in 50 ml dimethylformamide was added over 30 min with stirring and the mixture was then stirred for 1 h at 0 ºC. Tosyl chloride (9.38 g, 49.2 mmol) was added portion-wise with stirring and the mixture was then stirred overnight at room temperature. The mixture was diluted with water and was extracted several times with ether. The combined organics were washed with brine, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to give **99** (10.8 g, 37.8 mmol, 99% yield) as a white solid. Purity 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.37 (s, 3H, SO_2PhMe), 2.63 (s, 3H, azaindole 6-Me), 6.50 (d, *J*=3.9 Hz, 1H, H-3), 7.01 (d, *J*=8.2 Hz, 1H, H-5), 7.26 (d, *J*=8.2 Hz, 2H, SO_2Ph meta), 7.62 (d, *J*=3.9 Hz, 1H, H-2), 7.68 (d, *J*=7.8 Hz, 1H, H-4), 8.12 (d, *J*=8.2 Hz, 2H, SO_2Ph ortho). UPLC/MS (3 min) retention time 1.81 min. LRMS: *m*/*z* 287 (M+1).

15.5. *2,6-Dimethyl-1-[(4-methylphenyl)sulfonyl]-1H-pyrrolo[2,3-b]pyridine (**100**)*

Azaindole **99** (1.36 g, 4.75 mmol) was dissolved in 50 ml tetrahydrofuran under nitrogen and the mixture was cooled to 0 ºC. n-Butyllithium (2.5M in hexanes, 3.8 ml, 9.5 mmol) was added over 15 min with stirring, forming a dark orange solution and the mixture was stirred for a further 30 min at 0 ºC. Methyl iodide (0.37 ml, 5.9 mmol) dissolved in 2 ml tetrahydrofuran was added drop-wise and the mixture was stirred at 0 ºC for 2 h. The mixture was diluted with saturated ammonium chloride solution and was extracted three times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The residue was purified by reverse-phase chromatogtraphy using the Isolera purification system to give **100** (0.33 g, 1.1 mmol, 23% yield) as a bright yellow solid. Purity 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.37 (s, 3H, SO_2PhMe), 2.61 (s, 3H, azaindole 6-Me), 2.71 (s, 3H, azaindole 2-Me), 6.20 (s, 1H, H-3), 6.95 (d, *J*=7.8 Hz, 1H, H-5), 7.25 (d, *J*=8.2 Hz, 2H, SO_2Ph meta), 7.53 (d, *J*=7.8 Hz, 1H, H-4), 8.07 (d, *J*=8.2 Hz, 2H, SO_2Ph ortho). UPLC/MS (3 min) retention time 1.90 min. LRMS: *m*/*z* 301 (M+1).

15.6. *2,6-Dimethyl-1-[(2,4-dimethylphenyl)sulfonyl]-1H-pyrrolo[2,3-b]pyridine (**101**)*

Chromatography of the reaction mixture of **100** also gave **101** (0.72 g, 2.3 mmol, 48% yield) as a bright yellow solid. Purity 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.33 (s, 3H, Me), 2.42 (s, 3H, Me), 2.42 (s, 3H, Me), 2.74 (s, 3H, azaindole 2-Me), 6.23 (s, 1H, azaindole H-3), 6.89 (d, *J*=7.8 Hz, 1H, azaindole H-5), 6.96 (s, 1H, SO_2Ph H-3), 7.14 (d, *J*=7.8 Hz, 1H, SO_2Ph H-5), 7.54 (d, *J*=7.8 Hz, 1H, azaindole H-4), 8.20 (d, *J*=8.2 Hz, 1H, SO_2Ph H-6). UPLC/MS (3 min) retention time 2.01 min. LRMS: *m*/*z* 315 (M+1).

15.7. *2,6-Dimethyl-1H-pyrrolo[2,3-b]pyridine (**102**)*

Method A: Chloroazaindole **97** (44 mg, 0.18 mmol) was dissolved in 1.5 ml dimethoxyethane under nitrogen in a Schlenk tube. Potassium carbonate (78 mg, 0.57 mmol), trimethyl boroxine (31 µl, 0.22 mmol) were added and the mixture was subjected to three vacuum-argon cycles. [1,1′-Bis(diphenylphosphino)ferrocene]-dichloropalladium(II), complex with dichloromethane (9 mg, 0.01 mmol) was added and the mixture was subjected to a further three vacuum-argon cycles. The mixture was then stirred at 115 ºC overnight. The mixture was allowed to cool and was filtered through a plug of Celite, washing through with dichloromethane and the combined filtrates were evaporated under reduced pressure. The residue was resuspended in 2.5 ml methanol and 5 ml 2N sodium hydroxide solution and the mixture was stirred for 3 h at room temperature. The organics were evaporated and the aqueous was extracted three times with dichloromethane. The combined organics were washed twice with water, dried over anhydrous sodium sulphate, filtered and and evaporated under reduced pressure to give **102** (17 mg, 0.11 mmol, 61% yield) as a pale brown solid. Purity 96%.

Method B: Tosylate **100** (607 mg, 2.02 mmol) was dissolved in 25 ml methanol. 8 N Sodium hydroxide solution (7.6 ml, 61 mmol) was added and the mixture was stirred at 65 ºC for 2 h. The mixture was allowed to cool and the organics were evaporated under reduced pressure. The aqueous was diluted with saturated ammonium chloride solution and was extracted three times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure to give **102** (294 mg, 2.01 mmol, 99% yield) as a pale yellow solid. Purity 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.49 (s, 3H, azaindole 6-Me), 2.64 (s, 3H, azaindole 2-Me), 6.11 (s, 1H, H-3), 6.90 (d, *J*=7.8 Hz, 1H, H-5), 7.69 (d, *J*=7.8 Hz, 1H, H-4), 9.82 (br. s., 1H, NH). UPLC/MS (3 min) retention time 0.70 min. LRMS: *m*/*z* 147 (M+1).

15.8. *Ethyl (2,6-dimethyl-1H-pyrrolo[2,3-b]pyridin-3-yl)(oxo)acetate (**103**)*

Aluminium trichloride (0.83 g, 6.2 mmol) was dissolved in 5 ml nitromethane and the mixture was cooled to -10 ºC. Azaindole **102** (0.29 g, 1.99 mmol) dissolved in 5 ml dichloroethane was added drop-wise and with stirring at -10 ºC. Ethyl 2-chloro-2-oxoacetate (0.29 ml, 2.6 mmol) was added drop-wise and the mixture was then stirred at -5 ºC for 3 h. The mixture was carefully quenched with 20 ml water and then acidified to pH 3-4 with 2N hydrochloric acid. The aqueous phase was extracted three times with dichloromethane and the combined organics were dried over

anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The residue was purified using the Biotage purification system (ethyl acetate-hexane gradient, 0:100 rising to 100:0) to give **103** (0.31 g, 1.24 mmol, 62% yield) as a white solid. Purity 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.44 (t, *J*=7.2 Hz, 3H, OCH_2CH_3), 2.69 (s, 3H, azaindole 6-Me), 2.77 (s, 3H, azaindole 2-Me), 4.47 (q, *J*=7.0 Hz, 2H, OCH_2CH_3), 7.12 (d, *J*=7.8 Hz, 1H, H-5), 8.24 (d, *J*=8.2 Hz, 1H, H-4), 11.60 (br. s., 1H, NH). UPLC/MS (3 min) retention time 1.40 min. LRMS: *m*/*z* 247 (M+1).

15.9. *Ethyl (2,6-dimethyl-1H-pyrrolo[2,3-b]pyridin-3-yl)acetate (**104**)*

Triethylsilane (0.70 ml, 4.4 mmol) was diluted with 2 ml trifluoroacetic acid. Dicarbonyl **103** (304 mg, 1.23 mmol) dissolved in 2 ml trifluoroacetic acid was added drop-wise and the mixture was stirred at 60 ºC overnight. The mixture was allowed to cool and was evaporated under reduced pressure. The residue was taken up in 10 ml ethanol and 10 ml 4% sodium bicarbonate solution and the mixture was stirred for 2 h. The mixture was extracted three times with dichloromethane and the combined organics were dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure to give **104** (210 mg, 0.90 mmol, 72% yield) as a white solid. Purity 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.23 (t, *J*=6.4 Hz, 3H, OCH_2CH_3), 2.45 (s, 3H, azaindole 6-Me), 2.64 (s, 3H, azaindole 2-Me), 3.64 (s, 2H, CH_2CO_2), 4.12 (q, *J*=6.5 Hz, 2H, OCH_2CH_3), 6.92 (d, *J*=7.8 Hz, 1H, H-5), 7.74 (d, *J*=7.4 Hz, 1H, H-4), 9.92 (br. s., 1H, NH). UPLC/MS (3 min) retention time 0.97 min. LRMS: *m*/*z* 233 (M+1).

15.10. *Ethyl {2,6-dimethyl-1-[2-(phenylsulfonyl)benzyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}acetate (**105**)*

Azaindole **104** (35 mg, 0.15 mmol) was dissolved in 1 ml anhydrous dimethylformamide and the mixture was cooled to 0 ºC. 2-tert-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP, 60 µl, 0.17 mmol) was added drop-wise and the mixture was stirred at 10 ºC for 30 min. Bromide **10a** (56 mg, 0.18 mmol) dissolved in 1 ml anhydrous dimethylformamide was added and the mixture was stirred overnight at room temperature. The mixture was poured onto ice-water and the aqueous was extracted three times with ether. The combined organics were washed with brine, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure evaporated. The residues was purified by reverse-phase chromatography using the Biotage purification system to give **105** (21 mg, 0.045 mmol, 27% yield). Purity 90% ethyl ester + 10% methyl ester. Ethyl ester: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.21 (t, *J*=7.2 Hz, 3H, OCH_2CH_3), 1.88 (s, 3H, azaindole 2-Me), 2.46 (s, 3H, azaindole 6-Me), 3.63 (s, 2H, CH_2CO_2), 4.11 (q, *J*=7.3 Hz, 2H, OCH_2CH_3), 5.73 (s, 2H, CH_2Ph), 6.38 (d, *J*=7.8 Hz, 1H, Bn H-6), 6.90 (d, *J*=7.8 Hz, 1H, azaindole H-5), 7.35 (t, *J*=7.0 Hz, 1H, Bn H-4), 7.43 (t, *J*=7.6 Hz, 1H, Bn H-5), 7.58 (t, *J*=7.4 Hz, 2H, SO_2Ph meta), 7.65 (t, *J*=7.0 Hz, 1H, SO_2Ph para), 7.72 (d, *J*=7.8 Hz, 1H, azaindole H-4), 7.99 (d, *J*=7.4 Hz, 2H, SO_2Ph ortho), 8.26 (dd, *J*=1.2, 7.8 Hz, 1H, Bn H-3). UPLC/MS (3 min) retention time 2.01 min. LRMS: *m*/*z* 463 (M+1).

Methyl ester: UPLC/MS (3 min) retention time 1.96 min. LRMS: *m*/*z* 449 (M+1).

15.11. *Ethyl (1-{2-[(4-fluorophenyl)sulfonyl]-5-methoxybenzyl}-2,6-dimethyl-1H-pyrrolo[2,3-b]pyridin-3-yl)acetate (**106**)*

Azaindole **104** (35 mg, 0.15 mmol) was dissolved in 1 ml anhydrous dimethylformamide and the mixture was cooled to 0 ºC. 2-tert-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP, 60 µl, 0.17 mmol) was added drop-wise and the mixture was stirred at 10 ºC for 30 min. Bromide **10b** (68 mg, 0.18 mmol) dissolved in 1 ml anhydrous dimethylformamide was added and the mixture was stirred overnight at room temperature. The mixture was poured onto ice-water and the aqueous was extracted three times with ether. The combined organics were washed with brine, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure evaporated. The residues was partially purified by reverse-phase chromatography using the Isolera purification system to give **106** (26 mg). Purity 78% ethyl ester + 9% methyl ester. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.21 (t, *J*=7.2 Hz, 3H, OCH_2CH_3), 2.01 (s, 3H, azaindole 2-Me), 2.44 (s, 3H, azaindole 6-Me), 3.58 (s, 3H, MeO), 3.64 (s, 2H, CH_2CO_2), 4.10 (q, *J*=7.0 Hz, 2H, OCH_2CH_3), 5.66 (s, 2H, CH_2Ph), 5.85 (d, *J*=2.3 Hz, 1H, Bn H-6), 6.86 (dd, *J*=2.3, 8.6 Hz, Bn H-4), 6.88 (d *J*=7.8 Hz, azaindole H-4), 7.24 (t, *J*=8.4 Hz, 2H, SO_2PhF meta), 7.71 (d, *J*=8.2 Hz, 1H, azaindole H-5), 7.99 (dd, *J*=5.1, 8.6 Hz, 2H, SO_2PhF ortho), 8.20 (d, *J*=8.6 Hz, 1H, Bn H-3). UPLC/MS (3 min) retention time 2.06 min. LRMS: *m*/*z* 511 (M+1).

Methyl ester: UPLC/MS (3 min) retention time 2.03 min. LRMS: *m*/*z* 497 (M+1).

15.12. *{2,6-Dimethyl-1-[2-(phenylsulfonyl)benzyl]-1H-pyrrolo[2,3-b]pyridin-3-yl}acetic acid (**107**)*

Ester **105** (21 mg, 0.045 mmol) was dissolved in 1 ml tetrahydrofuran and 1 ml water. Lithium hydroxide monohydrate (20 mg, 0.47 mmol) was added and the mixture was stirred at room temperature for 2 h. The organics were evaporated under reduced pressure. The remaining aqueous was diluted with water and was washed three times with ethyl

acetate. The aqueous phase was acidified with 5N hydrochloric acid forming a turbid solution and was extracted three times with ethyl acetate. The combined organics were dried over anhydrous magnesium sulphate, filtered and evaporated. The residue was purified by preparative HPLC to give **107** (8 mg, 0.018 mmol, 42% yield) as a white solid. Purity 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.84 (s, 3H, azaindole 2-Me), 2.44 (s, 3H, azaindole 6-Me), 3.60 (s, 2H, CH_2CO_2), 5.71 (s, 2H, CH_2Ph), 6.36 (d, *J*=7.4 Hz, 1H, Bn H-6), 6.79 - 6.89 (m, 1H, azaindole H-5), 7.28 - 7.34 (m, 1H, Bn H-4), 7.40 (t, *J*=7.0 Hz, 1H, Bn H-5), 7.56 (t, *J*=7.2 Hz, 2H, SO_2Ph meta), 7.60 - 7.71 (m, 2H, SO_2Ph para and azaindole H-4), 7.97 (d, *J*=7.8 Hz, 2H, SO_2Ph ortho), 8.24 (d, *J*=7.8 Hz, 1H, Bn H-3). UPLC/MS (5 min) retention time 2.86 min. LRMS: *m*/*z* 433 (M-1).

15.13. *(1-{2-[(4-Fluorophenyl)sulfonyl]-5-methoxybenzyl}-2,6-dimethyl-1H-pyrrolo[2,3-b]pyridin-3-yl)acetic acid (**108**)*

Crude ester **106** (26 mg) was dissolved in 1 ml tetrahydrofuran and 1 ml water. Lithium hydroxide monohydrate (23 mg, 0.54 mmol) was added and the mixture was stirred at room temperature for 2 h. The organics were evaporated under reduced pressure. The remaining aqueous was diluted with water and was washed three times with ethyl acetate. The aqueous phase was acidified with 5N hydrochloric acid forming a turbid solution and was extracted three times with ethyl acetate. The combined organics were dried over anhydrous magnesium sulphate, filtered and evaporated. The residue was purified by preparative HPLC to give **108** (9 mg, 0.019 mmol, 12% yield over two steps) as a white solid. Purity 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.00 (s, 3H, azaindole 2-Me), 2.44 (s, 3H, azaindole 6-Me), 3.53 (s, 3H, MeO), 3.66 (s, 2H, CH_2CO_2), 5.66 (s, 2H, CH_2Ph), 5.83 (d, *J*=2.3 Hz, 1H, Bn H-6), 6.86 (dd, *J*=2.3, 8.6 Hz, Bn H-4), 6.88 (d *J*=7.8 Hz, azaindole H-4), 7.23 (t, *J*=8.4 Hz, 2H, SO_2PhF meta), 7.68 (d, *J*=7.8 Hz, 1H, azaindole H-5), 7.98 (2 H, dd, *J*=5.1, 8.6 Hz, SO_2PhF ortho), 8.18 (d, *J*=8.6 Hz, 1H, Bn H-3). UPLC/MS (5 min) retention time 2.96 min. LRMS: *m*/*z* 483 (M+1).

16. Scheme 16

16.1. *1-{2-[(4-Fluorophenyl)sulfonyl]-5-methoxybenzyl}-6-methyl-1H-pyrrolo[2,3-b]pyridine (**109**)*

Azaindole **98** (55 mg, 0.42 mmol) was dissolved in 2 ml anhydrous dimethylformamide under nitrogen. Sodium hydride (60% dispersion in oil, 22 mg, 0.54 mmol) was added and the mixture was stirred for 45 min at room temperature. Bromide **10c** (180 mg, 0.50 mmol) dissolved in 2 ml anhydrous dimethylformamide was added and the mixture was stirred for 3 h. The mixture was poured over ice-water and was extracted three times with ether. The combined organics were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to give crude **109** (170 mg) as a yellow oil. Used as such without further purification. Purity 90%. NMR spectrum not recorded. UPLC/MS (3 min) retention time 1.97 min. LRMS: *m*/*z* 411 (M+1).

16.2. *3-Bromo-1-{2-[(4-fluorophenyl)sulfonyl]-5-methoxybenzyl}-6-methyl-1H-pyrrolo[2,3-b]pyridine (**110**)*

Crude azaindole **109** (170 mg) was dissolved in 4 ml ethyl acetate and the mixture cooled to 0 ºC. N-Bromosuccinimide (74 mg, 0.42 mmol) was added and the mixture was stirred at 0 ºC for 1 h. The mixture was partitioned between water an ethyl acetate. The aqueous phase was extracted twice with ethyl acetate and the combined organics were washed with brine, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The residue was purified using the Biotage purification system (ethyl acetate-hexane gradient, 0:100 rising to 30:70) to give **110** (110 mg, 0.22 mmol, 53% yield over two steps) as a yellow semi-solid. Purity 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.54 (s, 3H, azaindole 6-Me). 3.69 (s, 3H, MeO), 5.68 (s, 2H, CH_2Ph), 6.51 (d, *J*=2.6 Hz, 1H, Bn H-6), 6.92 (dd, *J*=2.6, 8.9 Hz, 1H, Bn H-4), 6.98 (s, 1H, azaindole H-2), 6.99 (d, *J*=7.8 Hz, 1H, azaindole H-4), 7.17 (t, *J*=8.6 Hz, 2H, SO_2PhF meta), 7.70 (d, *J*=8.0 Hz, 1H, azaindole H-5), 7.89 (dd, *J*=4.9, 8.8 Hz, 2H, SO_2PhF ortho), 8.17 (d, *J*=8.8 Hz, 1H, Bn H-3). UPLC/MS (3 min) retention time 2.13 min. LRMS: *m*/*z* 489, 491 (M+1).

16.3. *Ethyl (1-{2-[(4-fluorophenyl)sulfonyl]-5-methoxybenzyl}-6-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)acetate (**111**)*

Bromoazaindole **110** (110 mg, 0.22 mmol) was dissolved in 1 ml tetrahydrofuran under nitrogen. (2-tert-Butoxy-2-oxoethyl)zinc(II) chloride (0.5M in ether, 1.34 ml, 0.67 mmol), 1,2,3,4,5-pentaphenyl-1′-(di-tert-butylphosphino)ferrocene (Q-Phos, 8 mg, 0.01 mmol) and bis(dibenzylideneacetone) palladium(0) (6.5 mg, 0.01 mmol) were added and the mixture was stirred and heated at 100 ºC for 2 h under microwave irradiation. The mixture was allowed to cool and diluted with ether and water. The mixture was filtered through a plug of Celite, washing through with ether, the biphasic filtrate was separated and the organic phase evaporated under reduced pressure. The residue was purified using the Biotage purification system (ether-hexane gradient, 0:100 rising to 100:0 and holding) to give **111** (84 mg, 0.16 mmol, 72% yield) as a solid. Purity 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.42 (s, 9H, tBu), 2.51 (s, 3H, azaindole 6-Me), 3.57 (s, 2H, CH_2CO_2), 3.64 (s, 3H, MeO), 5.66 (s, 2H, CH_2Ph), 6.38 (d, *J*=2.3 Hz, 1H, Bn H-3), 6.88 (dd, *J*=2.5, 8.8 Hz, 1H, Bn H-4), 6.92 (d, *J*=7.8 Hz, 1H, azaindole H-4), 6.92

(s, 1H, azaindole H-2), 7.19 (t, *J*=8.4 Hz, 2H, SO_2PhF meta), 7.78 (d, *J*=7.8 Hz, 1H, azaindole H-5), 7.93 (dd, *J*=4.9, 8.8 Hz, 2H, SO_2PhF ortho), 8.16 (d, *J*=8.6 Hz, 1H, Bn H-3). UPLC/MS (3 min) retention time 2.12 min. LRMS: *m*/*z* 525 (M+1).

16.4. *(1-{2-[(4-Fluorophenyl)sulfonyl]-5-methoxybenzyl}-6-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)acetic acid (**112**)*

tert-Butyl ester **111** (84 mg, 0.16 mmol) was dissolved in 2 ml dichloromethane. 1 ml Trifluoroacetic acid was added and the mixture was stirred for 1 h. The mixture was evaporated under reduced pressure and the residue was re-dissolved in ethyl acetate. The organics were washed twice with water, twice with brine, dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to give **112** (46 mg, 0.095 mmol, 60% yield) as a solid. Purity 94%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.51 (s, 3H, azaindole 2-Me), 3.62 (s, 3H, MeO), 3.67 (s, 2H, CH_2CO_2), 5.66 (s, 2H, CH_2Ph), 6.41 (d, *J*=2.3 Hz, 1H, Bn H-3), 6.88 (dd, *J*=2.5, 8.8 Hz, 1H, Bn H-4), 6.91 (s, 1H, azaindole H-2), 6.92 (d, *J*=7.8 Hz, 1H, azaindole H-4), 7.17 (t, *J*=8.4 Hz, 2H, SO_2PhF meta), 7.76 (d, *J*=7.8 Hz, 1H, azaindole H-5), 7.91 (dd, *J*=5.1, 9.0 Hz, 2H, SO_2PhF ortho), 8.15 (d, *J*=9.0 Hz, 1H, Bn H-3). UPLC/MS (5 min) retention time 2.80 min. LRMS: *m*/*z* 469 (M+1).

17. Biological Assays

17.1 CRTh2 GTPgS antagonism binding assay

The assay was performed by pre-incubating 4-8 mg of membranes (obtained from CHO.K1 cells stably overexpressing the CRTh2 receptor) per well with the compound to be tested for 1 h, followed by incubation with 50 nM PGD_2 and 0.1 nM [^{35}S]-GTPγS in incubation buffer (20 mM HEPES, 10 mM $MgCl_2$, 100 mM NaCl, 10 mM GDP, 10 mg/ml Saponine and 0.2% BSA) for 2 h at room temperature. The reaction was terminated by filtering in GF/C plates pre-treated with 20 mM HEPES, 10 mM $MgCl_2$, 100 mM NaCl and 0.1% BSA and washing 6 times with wash buffer (20 mM NaH_2PO4, 20 mM Na_2HPO_4). After washing, the plates were dried and scintillation buffer Optiphase was added. The radioactivity retained in the filter was counted using a Microbeta liquid scintillation counter. Compound IC_{50}s were determined using Excel XL-fit for calculations.

17.2 CRTh2 Dissociation assay

Briefly, for each time-point in the assay, membranes were incubated as for the GTPγS assay (*vide supra*) for 2h with the test compound at 5-10×IC_{50}. Dissociation was initiated at t=0 by adding 100 µM PGD_2 and 0.1 nM ^{35}S- GTPγS (therefore, once the test compound dissociated, re-binding was prevented by mass-action law). After the appropriate time, the reaction was terminated by filtration and washing as above. For each test compound, residual inhibition of GTPγS binding was measured at 5 min, 15 min, 30 min, 1h, 2h, 3h, 4h, 20h and 25 h. Inhibition vs time was plotted for each compound tested. Dissociation half-lives were calculated by fitting an exponential decay curve to the inhibition vs time plot.

Acknowledgements

The authors thank Miriam Andrés and Sílvia Petit for their valuable assistance in the experimental procedures and the determination of potencies and residence times.

References and Notes

1 (a) Nagata, K.; Tanaka, K.; Ogawa, K.; Kemmotsu, K.; Imai, T.; Yoshie, O.; Abe, H.; Tada, K.; Nakamura, M.; Sugamura, K.; Takano, S. *J. Immunol.* **1999**, *162*, 1278. (b) Powell, W. S. *Prostaglandins Leukot. Essent. Fatty Acids* **2003**, *69*, 179.

2 (a) Hirai, H.; Tanaka, K.; Yoshie, O,; Ogawa, K.; Kenmotsu, K.; Takamori, Y.; Ichimasa, M.; Sugamura, K.; Nakamura, M.; Takano, S.; Nagata, K. *J. Exp. Med*. **2001**, *193*, 255. (b) Shichijo, M.; Sugimoto, H.; Nagao, K.; Inbe, H.; Encinas, J. A.; Takeshita, K.; Bacon, K. B.; Gantner, F. *J. Pharmacol. Exp. Ther*. **2003**, *307*, 518.

3 Xue, L.; Barrow, A.; Pettipher, R. *J. Immunol*. **2009**, *182*, 7580.

4 Xue, L.; Gyles, S. L.; Wettey, F. R.; Gazi, L.; Townsend, E.; Hunter, M. G.; Pettipher, R. *J. Immunol*. **2005**, *175*, 6531.

5 Chen, J. J.; Budelsky, A. L. *Prog. Med. Chem*. **2011**, *50*, 49.

6 (a) Medina, J. C.; Liu, J. *Annu. Rep. Med. Chem.* **2006**, *41*, 221. (b) Ulven, T.; Kostenis, E. *Exp. Opin. Ther. Patents* **2010**, *20*, 1505. (c) Burgess, L. *Annu. Rep. Med. Chem.* **2011**, *46*, 119.

7 Norman, P. *Exp. Opin. Invest. Drugs* **2010**, *19*, 947.

8 Norman, P. *Exp. Opin. Invest. Drugs* **2014**, *23*, 55.

9 Andrés, M.; Bravo, M.; Buil, M. A.; Calbet, M.; Castro, J.; Domènech, T.; Eichhorn, P.; Ferrer, M.; Gómez, E.; Lehner, M. D.; Moreno, I.; Roberts, R. S.; Sevilla, S.; *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3349.

10 Andrés, M.; Bravo, M.; Buil, M. A.; Calbet, M.; Castillo, M.; Castro, M.; Eichhorn, P.; Ferrer, M.; Lehner, M. D.; Moreno, I.; Roberts, R. S.; Sevilla, S. *Eur. J. Med Chem.* **2014**, *71*, 168.

11 Pettipher, R.; Whittaker, M. *J. Med. Chem.* **2012**, *55*, 2915.

12 Andrés, M.; Buil, M. A.; Calbet, M.; Casado, O.; Castro, J.; Eastwood, P. R.; Eichhorn, P.; Ferrer, M.; Forns, P.; Moreno, I.; Petit, S; Roberts, R. S. *Bioorg. Med. Chem. Lett*. **2014**, *24*, 5111.

13 Alonso, J. A.; Andrés, M.; Bravo, M.; Buil, M. A.; Calbet, M.; Castro, J.; Eastwood, P. R.; Eichhorn, P.; Esteve, C.; Gómez, E.; González, J.; Mir, M.; Petit, S.; Roberts, R. S.; Vidal, B.; Vidal, L.; Vilaseca, P.; Zanuy. M. *Bioorg. Med. Chem. Lett*. **2014**, *24*, 5118-5122.

14 Alonso, J. A.; Andrés, M.; Bravo, M.; Calbet, M.; Eastwood, P. R.; Eichhorn, P.; Esteve, C.; Ferrer, M.; Gómez, E.; González, J.; Mir, M.; Moreno, I.; Petit, S.; Roberts, R. S.; Sevilla, S.; Vidal, B.; Vidal, L.; Vilaseca, P.; Zanuy. M. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 5123-5126.

15 Horning, E. C.; Koo, J.; Fish, M. S.; Walker, G. N. *Org. Synth.* **1951**, *31*, 56-58.

16 Bobowski, G.; Shavel Jr., J. *J. Heterocycl. Chem*. **1980**, *17*, 519-528.

17 Meduna, V.; Sawlewicz, P.; Vogt, R. *Synth. Commun*. **1989**, *19*, 1487-1491.

18 Duschinsky, R.; Dolan, L. A. *J. Am. Chem. Soc*, **1946**, *68*, 2350-2355.

19 Madding, G. D.; Smith, D. W.; Sheldon, R. I.; Lee, B. *J. Heterocycl. Chem*. **1985**, *22*, 1121-1126.

20 VandenBerg, G. E.; Harrison, J. B.; Carter, H. E.; Magerlein, B. J. *Org. Synth. Coll. Vol*. **1973**, *5*, 946.

21 Gordon, T. D.; Singh, J.; Hansen, P. E.; Morgan, B. A. *Tetrahedron Lett*. **1993**, *34*, 1901-1904.

22 Eisenbraun, E. J. *Org. Synth*. **1965**, *45*, 28.

23 Filler, A.; Leipold, H. A. *J. Org. Chem*. **1962**, *27*, 4440-4443.

24 Wermuth, C. G.; Schlewer, G.; Bourguignon, J. J.; Maghioros, G.; Bouchet, M. J.; Moire, C.; Kan, J. P.; Worms, P.; Biziere, K. *J. Med. Chem.* 1989, 32, 528-537.

25 Shevchuk, M. I.; Shpak, S. T.; Tolochko, A. F. *Zhurnal Obshchei Khimii*, **1987**, *57*, 799-803.

26 Islam, A. M.; Hannout, I. B.; Souka, L. M.; Islam, I. E. *Egypt. J. Chem*. **1974**, *17*, 275-83.

27 Colyer, D. E.; Nortcliffe, A.; Wheeler, S. *Tetrahedron Lett*. **2010**, *51*, 5306-5308.

28 Lee, J, H.; Choi, B. S.; Chang, J. H.; Lee, H. B.; Yoon, J.-Y.; Lee, J.; Shin, H. *J. Org. Chem*. **2007**, *72*, 10261-10263.

29 Pijper, P. J.; Van der Goot, H.; Timmerman, H.; Nauta, W. T. *Eur. J. Med. Chem*. **1984**, *19*, 393-397.

30 Saikachi, H.; Kitagawa, T.; Sasaki, H.; Van Leusen, A. M. *Chem. Pharm. Bull*. **1979**, *27*, 793-796.

31 Minguez, J. M.; Vaquero, J. J.; Alvarez-Builla, J.; Castano, O.; Andres, J. L. *J. Org. Chem.* **1999**, *64*, 7788-7801.

32 Roberts, R. S.; Forns Berenguel, M. P.; Eastwood, P. R.; Sevilla Gomez, S.; Buil Albero, M. A.; Moreno Mollo, I. M.; Matassa, V. G.; Casado Vilches, O. EP2526945, **2012**.

33 Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc*. **2001**, *123*, 2074-2075.

34 Hands, D.; Bishop, B.; Cameron, M.; Edwards, J. S.; Cottrell, I. F.; Wright, S. H. B. *Synthesis*, **1996**, 877-882.

35 Compound **98** (CAS: 824-51-1) was sourced from Anichem Inc., NJ.

36 Mouaddib, A. Joseph, B.; Hasnaoui, A.; Merour, J.-Y. *Tetrahedron Lett*., **1999**, *40*, 5853-5854.

37 Other authors have also noted some of these SAR features: (a) Stearns, B. A.; Baccei, C.; Bain, G.; Broadhead, A.; Clark, R. C.; Coate, H.; Evans, J. F.; Fagan, P.; Hutchinson, J. H.; King, C.; Lee, C.; Lorrain, D. S.; Prasit, P.; Prodanovich, P.; Santini, A.; Scott, J. M.; Stock, N. S.; Truong, Y. P. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 4647-4651. (b) Luker, T.; Bonnert, R.; Brough, S.; Cook, A. R.; Dickinson, M. R.; Dougall, I.; Logan, C.; Mohammeda, R. T.; Paine, S.; Sanganee, H. J.; Sargent, C.; Schmidt, J. A.; Teague, S.; Thom, S. *Bioorg. Med. Chem. Lett*. **2011**, *21*, 6288-6292. (c) Simard, D.; Leblanc, Y.; Berthelette, C.; Zaghdane, M. H.; Molinaro, C.; Wang, Z.; Gallant, M.; Lau, S.; Thao, T.; Hamel, M.; Stocco, R.; Sawyer, N.; Sillaots, S.; Gervais, F.; Houle, R.; Lévesque, J.-F. *Bioorg. Med. Chem. Lett*. **2011**, *21*, 841-845.

Highlights

- Synthesis of sulphone-containing heteraromatic acetic acids as CRTh2 antagonists
- A multitude of synthetic routes are given
- Structure-activity relationships (SAR) discussed
- Structure-kinetic relationships (SKR) discussed
- Potent and long resident compounds are identified