European Journal of Medicinal Chemistry 71 (2014) 168–184

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

2-(1*H*-Pyrazol-1-yl)acetic acids as chemoattractant receptor-homologous molecule expressed on Th2 lymphocytes (CRTh2) antagonists

Miriam Andrés [a], Mónica Bravo [a], Maria Antonia Buil [a], Marta Calbet [a], Marcos Castillo [b], Jordi Castro [a], Peter Eichhorn [a], Manel Ferrer [a], Martin D. Lehner [a], Imma Moreno [a], Richard S. Roberts [a,*], Sara Sevilla [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, Baldiri Reixac 10, 08028 Barcelona, Spain

ARTICLE INFO

Article history:
Received 18 February 2013
Received in revised form
28 October 2013
Accepted 29 October 2013
Available online 9 November 2013

Keywords:
Pyrazole
CRTh2 antagonists
Structure–activity relationship (SAR)

ABSTRACT

In this manuscript, the synthesis and biological activity of a series of pyrazole acetic acid derivatives as CRTh2 antagonists is presented. Biological evaluation *in vitro* revealed that the pyrazole core showed in several cases a different structure–activity relationship (SAR) to that of related indole acetic acid. A potent series of ortho-sulfonyl benzyl substituents was found, from which compounds **27** and **63** were advanced to *in vivo* profiling.

1. Introduction

Prostaglandin D_2 (PGD_2) is derived from the metabolism of arachidonic acid by cyclooxygenases and downstream PGD_2 synthases. In the immune system, PGD_2 is mainly produced by mast cells [1] but also although at lower levels, by macrophages and Th2 lymphocytes [2]. PGD_2 binds to three different receptors, the thromboxane type prostanoid receptor (TP) [3], the PGD_2 receptor (DP, also known as DP1) [4] and the chemoattractant receptor homologous molecule expressed on Th2 lymphocytes (CRTh2, also known as DP2) [5]. CRTh2 is a G_i coupling GPCR, signalling through reduction of intracellular cyclic adenosine monophosphate (cAMP) and calcium mobilization and it is involved in the chemotaxis of Th2 lymphocytes, eosinophils and basophils [6]. CRTh2 also inhibits the apoptosis of Th2 lymphocytes [7] and stimulates the production of IL4, IL5, and IL13 [8], cytokines involved in important biological responses such as eosinophil recruitment and survival, mucus secretion, airway hyper-responsiveness and immunoglobulin E (IgE) production among others. Therefore, molecules that antagonize the pro-inflammatory PGD_2 effects mediated by CRTh2 on key cell types associated with allergic inflammation (basophils, eosinophils and Th2 lymphocytes) should have a potential benefit in related pathologies.

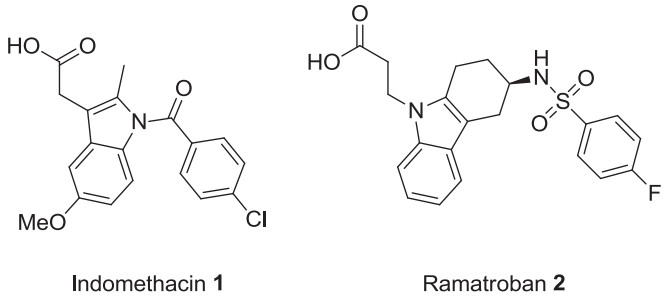
The search for CRTh2 antagonists is an active field with over 150 articles relating to chemistry and/or biology and around 200 patents published to date. Many companies are active in this area and several recent reviews have highlighted the progress and most advanced series [9–14]. A large proportion of the published chemical series owe their origins to the observations that the indole acetic acid indomethacin **1** inhibited the binding of labelled prostaglandin PGD_2 to CRTh2 (although **1** is in fact a partial agonist of the receptor) [15], and that the thromboxane inhibitor, the indole propionic acid Ramatroban **2** was also a fairly potent antagonist of CRTh2 [16] (Fig. 1).

While robust structural information on the receptor remains elusive, a clear preference for the arylacetic acid pharmacophore has emerged. Furthermore, these structures may be conceptually broken into three areas (Fig. 2) [14]:

1. The acetic acid “head” group. The chain length affects binding affinity, with acetic acid chains generally best. Alpha-substitution tends to lose potency and common bioisosteres of

* Corresponding author. 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 address: rick.roberts@almirall.com (R.S. Roberts).

0223-5234/$ – see front matter © 2013 Elsevier Masson SAS. All rights reserved.
http://dx.doi.org/10.1016/j.ejmech.2013.10.072



Indomethacin **1** Ramatroban **2**

Fig. 1. Chemical structures of Indomethacin **1** and Ramatroban **2**.

carboxylic acids (for example tetrazoles, acyl sulfonamides) are not well tolerated.

2. The "core" ring. This may be monocyclic or bicyclic and but for a few exceptions where activity is lost, no clear preference has emerged in this portion.
3. The "tail" group. This position seems to be the most free in terms of SAR and a great number of variations in chain length, directionality and polarity have been published.

We sought to take advantage of known SAR around the indole acetic acid pharmacophore by applying a conceptual ring expansion of the indole core, revealing a substituted pyrazole (Fig. 2). Two possible ring-openings were considered: this article addresses our work on pyrazole-1-acetic acids **4**, while the work on pyrazole-4-acetic acids **3** has been described elsewhere [17].

2. Chemistry

The first compounds **9** and **10** were synthesized from a common intermediate **6** (Scheme 1). Initially, condensation of 1-phenylbutane-1,3-dione with ethyl 2-hydrazinylacetate gave an almost quantitative yield of cyclised material, but as a 95:5 mixture pyrazoles with the undesired pyrazole **5** as the major product, as confirmed by NOE experiments (see Supplementary information).

Regioisomer formation in pyrazole condensation is a well-known problem which is influenced by the substitution of both the hydrazine and the 1,3-dicarbonyl (Fig. 3). Steric influence will try and place the large group of the 1,3-dicarbonlyl (R^{large}) in the 3-position of the newly formed pyrazole. Electronically, the more nucleophilic nitrogen of the hydrazine reacts first. This is inevitably the un-substituted NH_2 group when R^{hydr} is aromatic, however it is more evenly balanced when R^{hydr} is alkyl and often favouring the substituted nitrogen. Finally, the electronic preference of the 1,3-dicarbonyl is for the more reactive carbonyl to be attacked first. In the case of 1,3-diketones, this is the carbonyl group as drawn in the preferred enol tautomer form, but this preference is not easily estimated and less so measured [18].

To this end, we therefore first condensed 1-phenylbutane-1,3-dione with hydrazine and alkylated the resulting pyrazole with ethyl bromoacetate to give a 90:10 mixture of regioisomers, with the desired pyrazole **6** as the major product. Again, the electronic component defining which pyrazole tautomer is deprotonated is poorly defined, but the steric bulk of the 3-phenyl ring almost certainly dictated the regiochemistry of the alkylation (Fig. 3) [19]. The two regioisomers **5** and **6** were separable, but required laborious chromatography due to their similar polarities. This separation of regioisomers was a recurring hindrance throughout much of the chemistry.

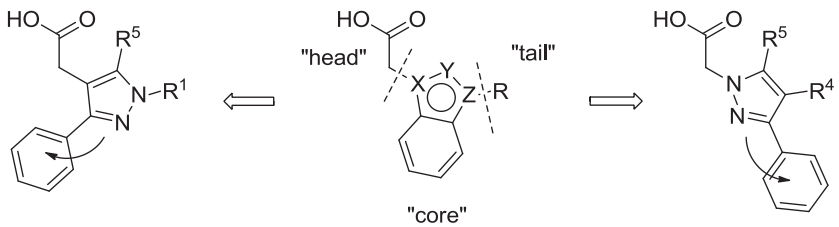
Sulphur containing analogues **9** and **10** were synthesized from **6** first by a sulfenylation reaction (**7**), followed by oxone-mediated oxidation as required (**8**), prior to basic hydrolysis (Scheme 1).

The bicyclic pyrazole compound **16** was synthesized as outlined in Scheme 2. The pyrazolopiperidine core (**12**) was synthesized from N-Boc piperidone using the methodology of Heller and Natarajan [20]. Using routine methodologies, pyrazole alkylation (**13**), de-protection of the Boc group (**14**) followed by capping with the desired acid chloride (**15**) and ester hydrolysis gave **16**.

The pyrazole acetic acid examples **27** and **28**, containing a functionalized benzyl tail group, were synthesized according to the route shown in Scheme 3, exemplified for the case of compound **27**. Further analogues of **27** were synthesized by the choice of appropriate, readily available starting materials. The sulfone tail-portions were synthesized from ortho-fluoro aldehydes **17** which were smoothly reacted with a range of thiols **18**. Complete oxidation to the sulfone (**19** → **20**) was achieved with meta-chloroperbenzoic acid (mCPBA). In this route, we then converted the aldehyde first to the alcohol **21** and then to the bromide **22**. Bromides of structure **22** were then alkylated with the appropriate 1,3-dicarbonyl compound **23** ("Method A"). The alkylation reaction was generally not purified as the products **24** tended to be oils and existed in a mixture of keto and enol tautomers. Subsequent condensation with hydrazine did give solid products **25** which could be purified adequately. Finally, alkylation with ethyl bromoacetate (**25** → **26**) ("Method E") and basic hydrolysis of the ester gave the desired pyrazole acetic acid **27**.

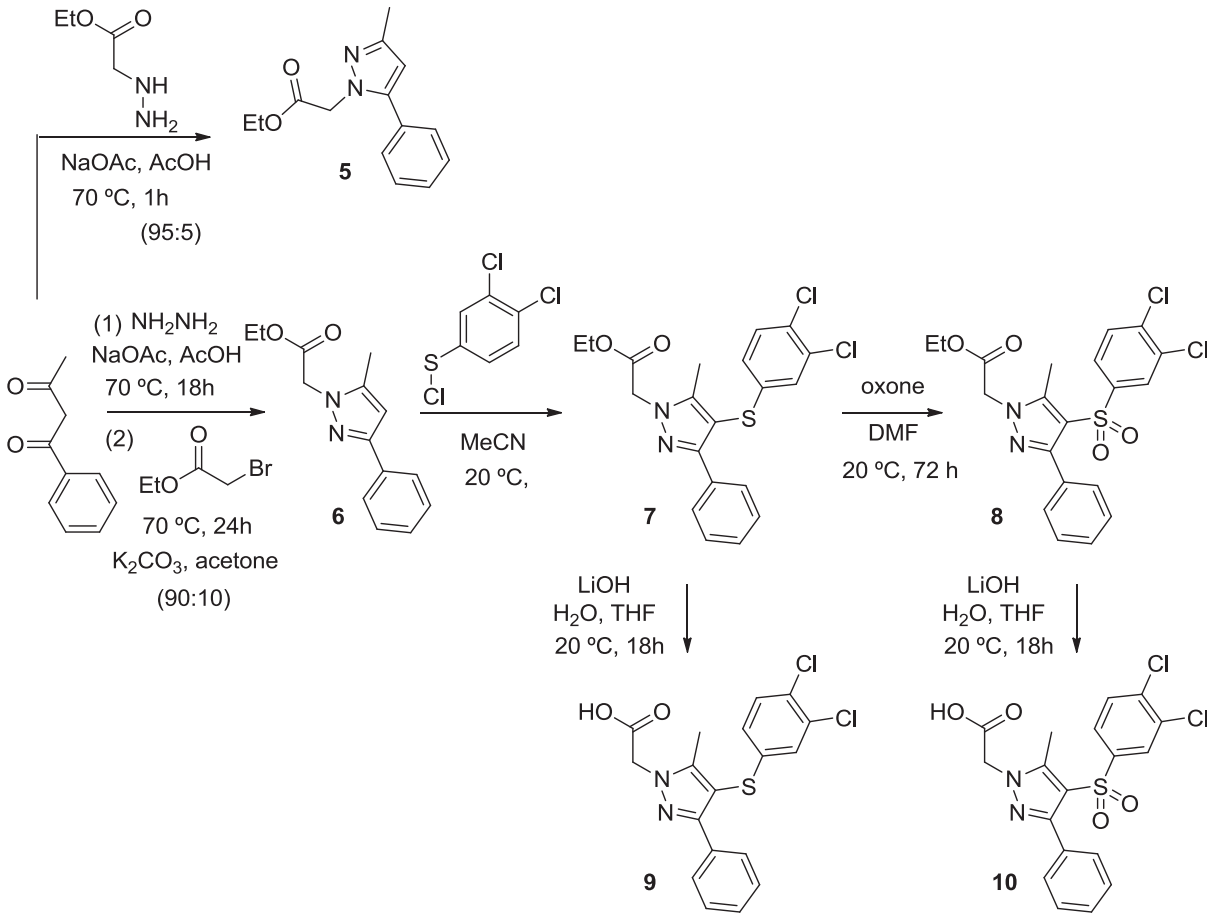
The route to compound **28** was followed the same steps of Scheme 3, replacing the alkylating agent of "Method A" (**22**) with commercial 2-(bromomethyl)quinoline.

Again, the *N*-alkylated pyrazoles **26** always required careful chromatography to separate the other minor regioisomer, typically formed in about 10% yield [21]. The structures of the desired major regioisomers were initially all confirmed by weak NOE enhancements observed between the methylene group of the acetate chain and the methyl group of the pyrazole (see Supplementary information). In addition, the ortho protons of the pyrazole 3-phenyl group were typically assigned as a downfield doublet between 7.5 and 8.0 ppm whereas in the minor, undesired products, the ortho protons were shifted upfield (see Experimental section



3 Described elsewhere **4** This work

Fig. 2. Conceptual opening of the indole core to reveal the pyrazole acetic acids.



Scheme 1. Synthetic routes to compounds **9** and **10**.

and Supplementary information). Ultimately, we were guided by the fact that the desired regioisomer of the alkylations was clearly the major product in the reaction and that it was also the first-eluting compound by silica.

We next expanded the chemistry of route, exemplified for the case of compound **35** (Scheme 4). Several 1,3-dicarbonyl compounds were synthesized to test the SAR of the 3-position of the pyrazole. Also, we had found that the alkylation step of Scheme 3 ("Method A") was difficult to purify adequately or to achieve in high yield. In addition, each aldehyde **20** required reduction and bromination. As an alternative route, we used a Knoevenagel condensation ("Method K") between the aldehydes **20** and the 1,3-dicarbonyls **30**. Subsequent reduction was achieved by one of two methods, according to the functional groups present in **31**. In the

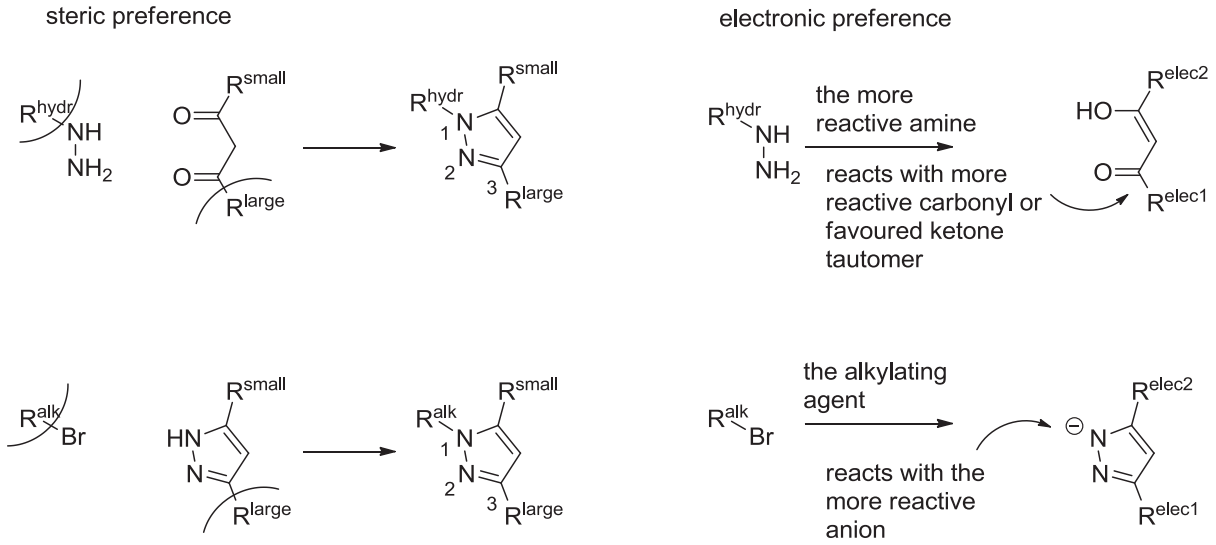
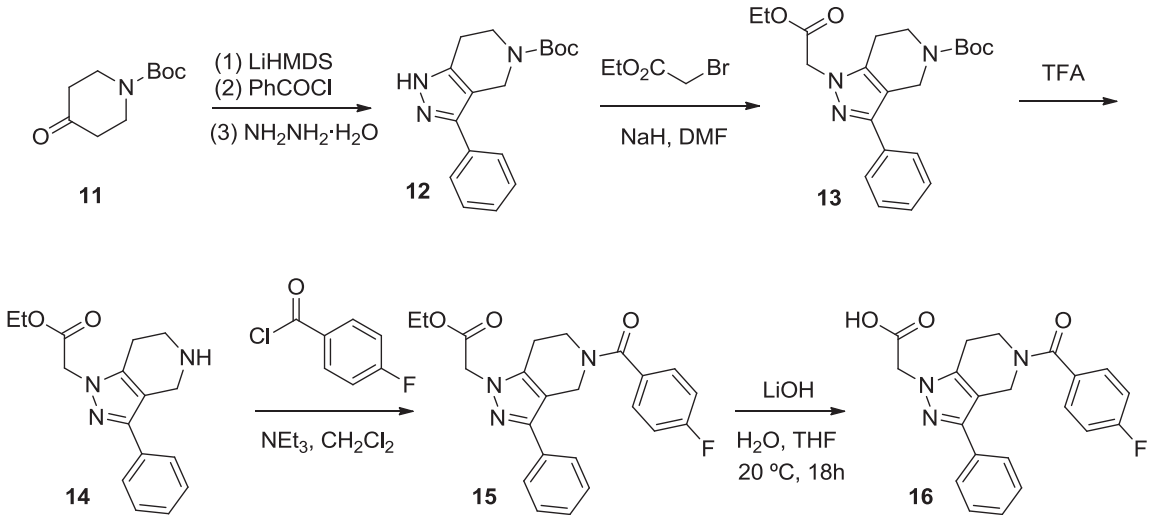
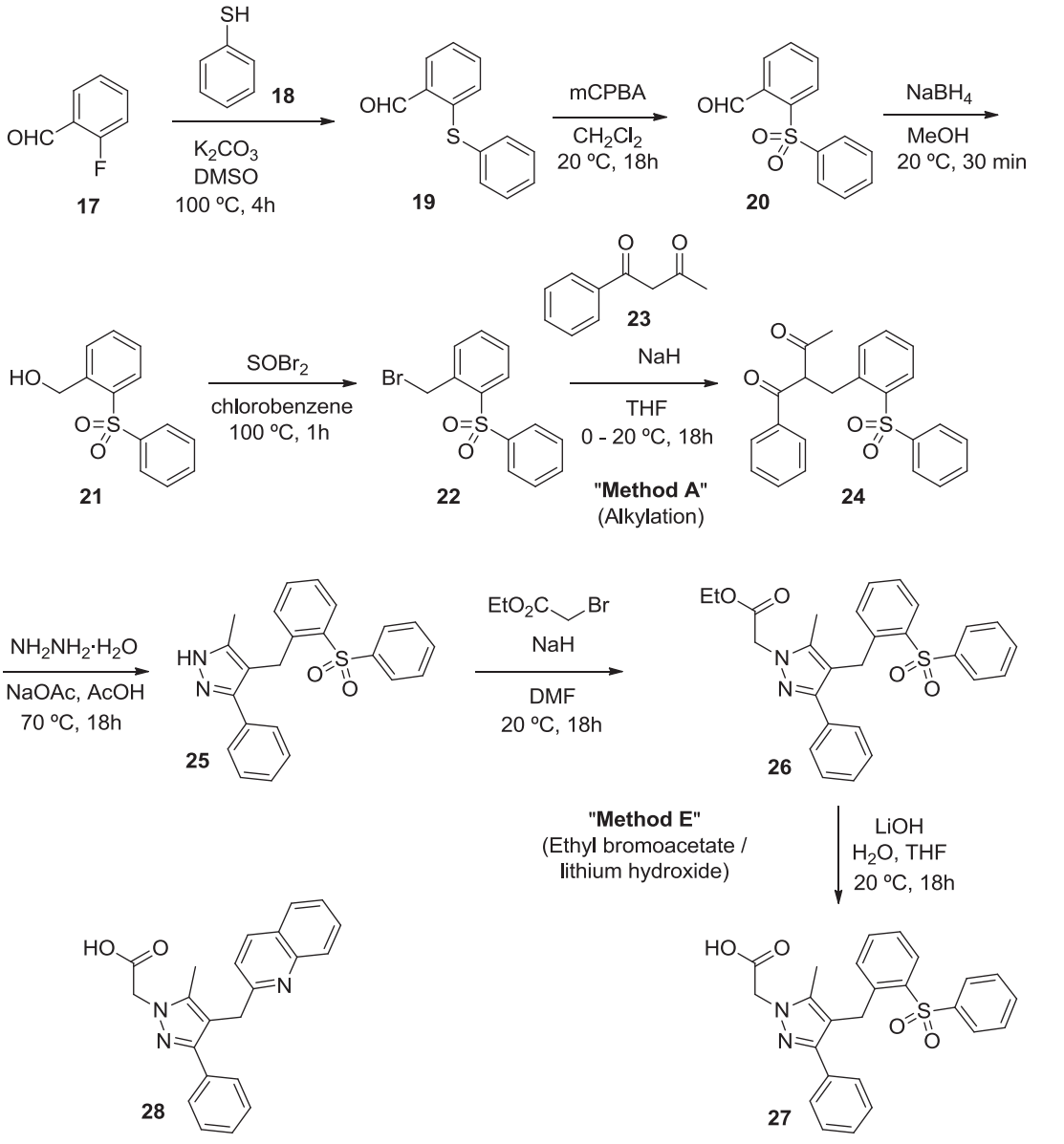


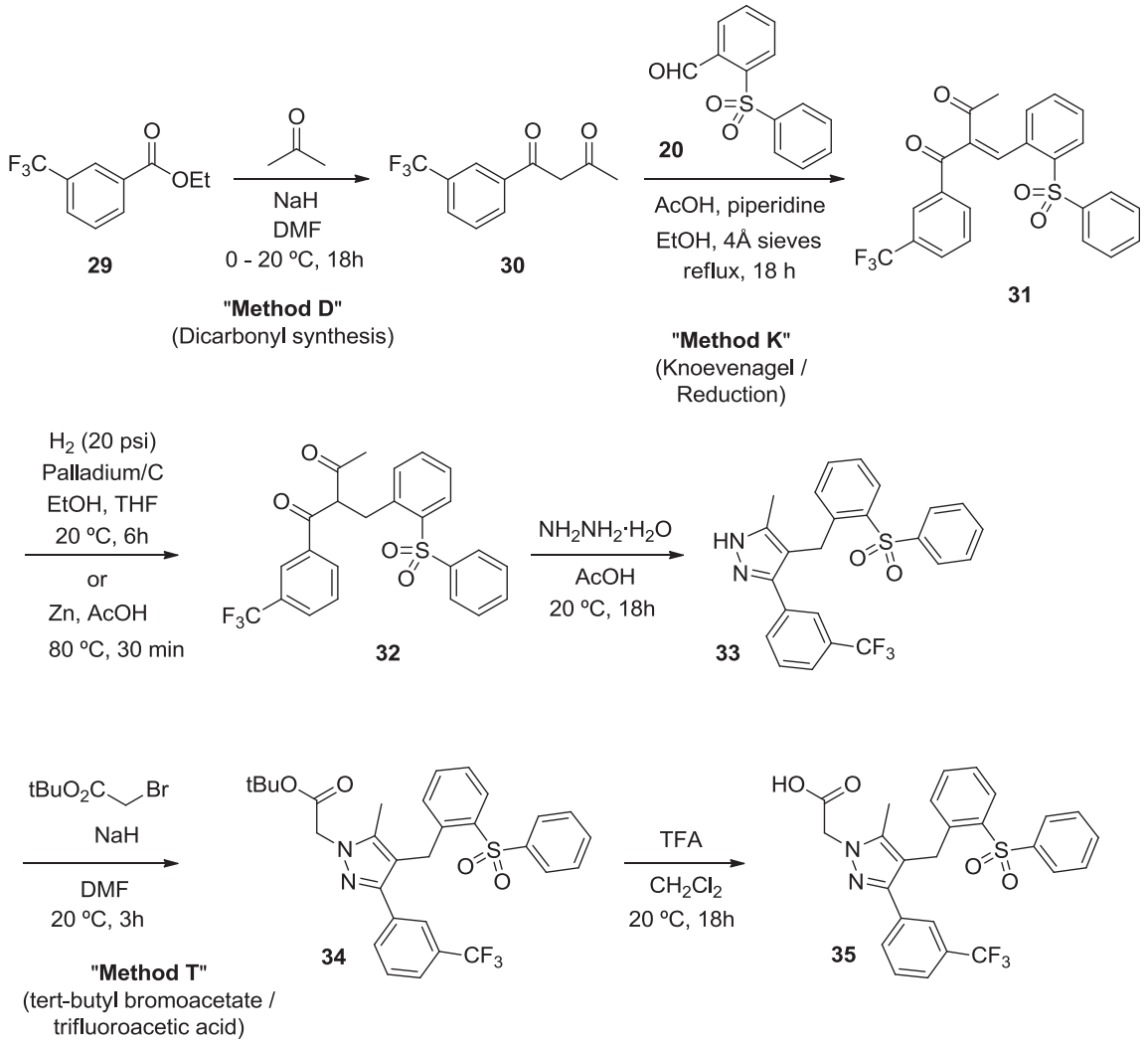
Fig. 3. Selectivity considerations in pyrazole condensations and alkylations.



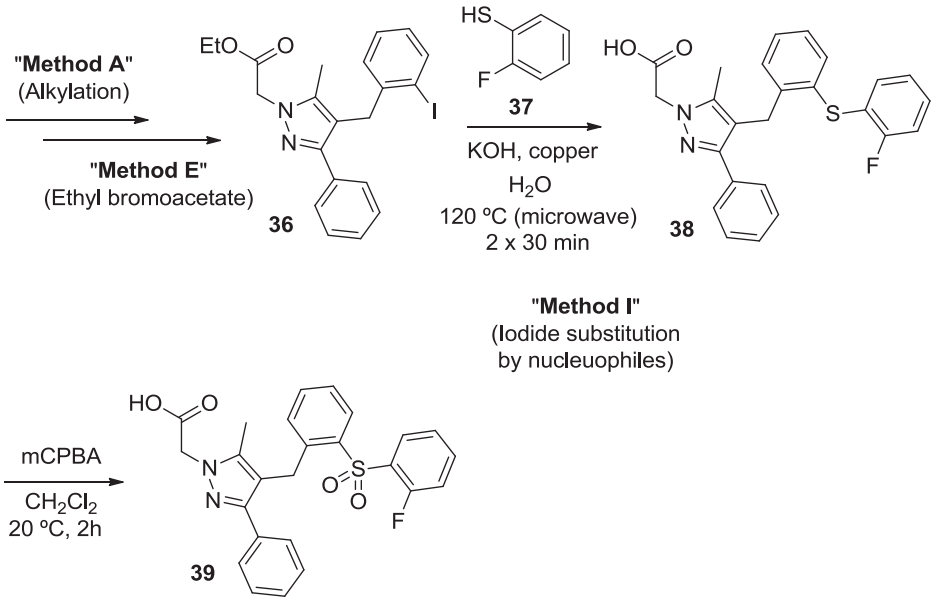
Scheme 2. Synthesis of compound **16**.



Scheme 3. Synthesis of compounds **27** and **28**.

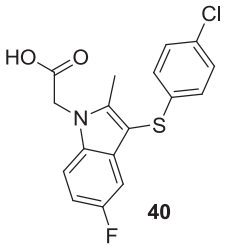
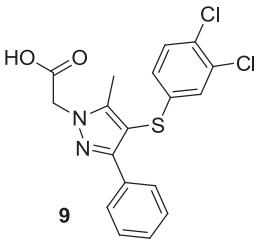
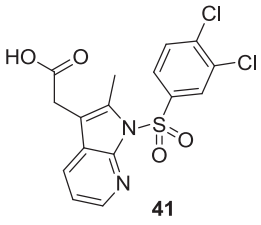
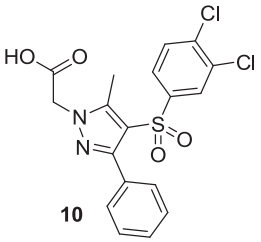
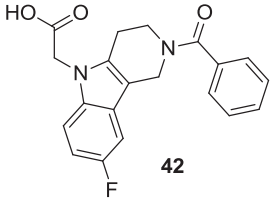
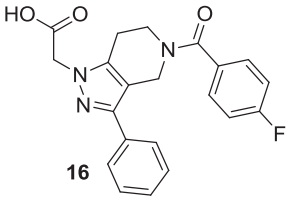
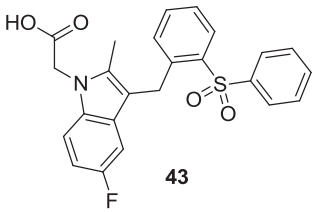
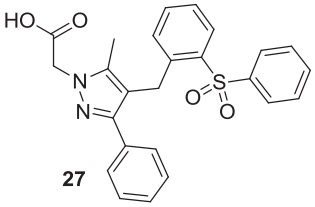
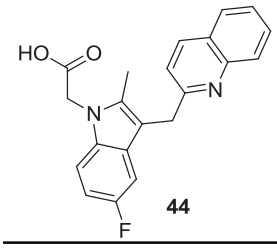
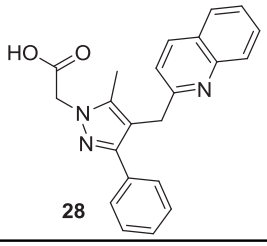


Scheme 4. Alternative route to pyrazoles (e.g **35**).



Scheme 5. Synthesis of pyrazoles (e.g. **39**) from common intermediate **36**.

Table 1
Lack of broad tail group SAR in the pyrazole series.

Reference compound	Company/reported potency	Pyrazole analogue	GTPγ binding
 **40**	Oxagen K_i 5 nM[a]	 **9**	34% @ 5 μM
 **41**	Novartis K_i 52 nM[a]	 **10**	38% @ 5 μM
 **42**	Actelion IC_{50} 1 nM[a]	 **16**	23% @ 5 μM
 **43**	Oxagen ESC hWB[b] IC_{50} 5 nM	 **27**	IC_{50} 35 nM
 **44**	Oxagen K_i 13 nM[a]	 **28**	37% @ 5 μM

[a] Data taken from Ref. [14] and references therein.
[b] Eosinophil shape change in human whole blood. Data taken from Ref. [13] and references therein.

absence of labile halogens, hydrogenation over palladium gave the desired compounds **32**. Alternatively, reduction with zinc metal in acetic acid also rapidly gave the same products and permitted the incorporation of halogen substituents which hydrogenation may have removed.

In this case, we also incorporated an alternative ester ("Method T"), the tert-butyl ester (**34**) allowing us the flexibility of either acid or basic conditions in the final hydrolysis.

Finally, to rapidly expand the SAR of the terminal portion of the tail, we synthesized common intermediate **36** from 2-iodobenzyl bromide using methods already described (Scheme 5). This gave us the advantage of only having to carry out a single purification of pyrazole regioisomers. The presence of the iodide then allowed us to introduce thioether, sulfoxide and sulfone groups, first through a copper catalysed insertion reaction carried our under microwave irradiation (**38**) ("Method I"). Under the basic reaction conditions,

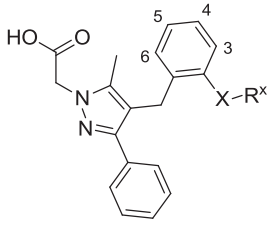
the ester was also hydrolysed in situ. Appropriate oxidation then gave the sulfone **39**. The iodide **36** could also be functionalized by other transition metal coupling reactions.

3. Results and discussion

All potency data was determined by a [^{35}S]GTPγS binding assay [22]. Our first impression was that the tail group of the pyrazoles would tolerate a wide range of substituents, however this turned out not to be the case (Table 1) [23]. The first set of pyrazoles synthesized took advantage of tail groups reportedly used to success with corresponding (aza)indole cores. In almost all cases, the pyrazole analogues were either weakly active or completely inactive. Only in the case of the ortho-sulfonyl benzyl tail **27** did we see activities in the same range as those reported for the corresponding bicyclic cores.

The reasons for this discrepancy are not obvious. The indole cores are all planar, whereas the 3-phenyl ring of the pyrazole compounds will be twisted with respect to the pyrazole due to the adjacent tail group in the 4-position. However, this twist should occur in all of the pyrazole analogues, **27** included.

Table 2
SAR around the sulphone tail.



Compound	Synthetic methods[a]	Proximal ring (benzylic)	X	R^x substitution (R^x = Ph unless stated)	GTPγS IC$_{50}$ (μM)
27	A, E	–	SO_2	–	0.04
39	I	–	SO_2	2-F	0.11
45	K, T	4-CF_3	SO_2	–	0.45
46	K, T	4-OMe	SO_2	–	0.07
47	K, T	4-CO_2H	SO_2	–	0.40
48	K, T	4-CO_2Me	SO_2	–	2.5
49	K, T	4-(N)	SO_2	–	2
50	K, T	5-F	SO_2	–	0.16
51	K, T	5-OMe	SO_2	–	0.06
52	I	–	SO_2	2-Me	0.22
53	I	–	SO_2	2,6-diMe	0.07
54	K, T	–	SO_2	3-F	0.20
55	K, T	–	SO_2	3-Cl	0.23
56	I	–	SO_2	3-CF_3	1.1
57	I	–	S	3-OMe	5
58	I	–	SO_2	3-OMe	0.52
59	I	–	SO_2	3-$CONMe_2$	5
60	I	–	S	3,4-diMe	2.3
61	I	–	SO	3,4-diMe	0.72
62	I	–	SO_2	3,4-diMe	0.38
63	K, T	–	SO_2	4-F	0.03
64	K, T	–	SO_2	4-Cl	0.11
65	K, E	–	SO_2	4-OMe	0.20
66	I	–	SO_2	4-OCF_3	0.47
67	I	–	SO_2	4-NMe_2	0.45
68	K, E	–	SO_2	4-SO_2Me	4
69	I	–	SO_2	R^x = Benzyl	0.11
70	I	–	SO_2	R^x = 8-Quinolinyl	0.27
71	I	–	–	R^x = 1-Naphthyl	Inactive

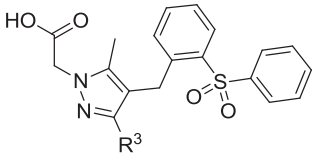
[a] Synthetic Methods: A = alkylation of 1–3 diketone (Scheme 3). D = 1,3-Dicarbonyl synthesized (Scheme 4). E = Ethyl bromoacetate/lithium hydroxide route (Scheme 3). I = iodide displacement with nucleophiles (Scheme 5). K = Knoevenagel/reduction method (Scheme 4). T = tert-butyl bromoacetate/trifluoroacetic acid method (Scheme 4).

With compound **27** identified, we then set about a structure–activity relationship (SAR) expansion of the tail group of both the proximal and the terminal aromatic rings (Table 2).

For the proximal (benzylic) ring, we observed that both the 4- and 5-methoxy (**46** and **51** respectively) maintained potency, while other changes generally resulted in loss of potency. Of note is the 4-carboxy group (**47**). While the potency loss of introduction of this group was around 10-fold, it should be taken into account however that the desolvation energy penalty of a carboxylic acid is generally very high. The only slight loss of potency is indicative that either the acid is compensating for the desolvation penalty by making an interaction with the receptor, or that this acid group is free of the receptor binding site and remains solvated in the bulk water environment. Both blocking the acid as an ester (**48**) and replacement of the proximal phenyl ring with a 4-pyridyl (**49**) lost considerable potency which overall may indicate a sensitive point of interaction with the receptor.

For the linker atom, we quickly determined that the sulfone was optimal, and that a 10-fold loss of potency was observed going from sulfone to sulphide (**57** to **58**, and **60**–**62**), showing a contribution to binding of the S=O bonds. Interestingly, the sulfoxide **61** only lost 2-fold potency relative to the sulfone **62**. Sulfoxides exist as a mixture of two enantiomers. The 2-fold drop in activity could indicate that only one of the two enantiomers is active and this in turn would imply that only one of the sulphone S=O bonds is

Table 3
SAR around the pyrazol-3-position.



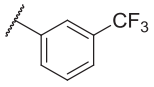
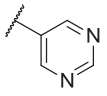
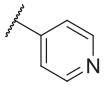
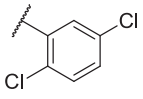
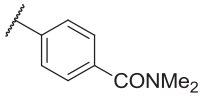
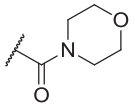
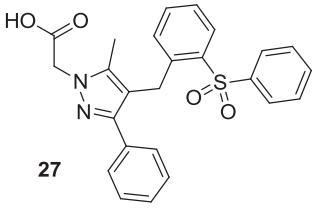
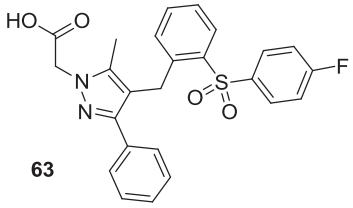
Compound	Synthetic methods	R^3	GTPγS IC$_{50}$ (μM)
27	A, E	Ph	0.035
35	D, K, T		0.05
72	K, E	Me	1.6
73	K, T	OH	Inactive
74	K, T	OMe	Inactive
75	D, A, T		0.087
76	D, A, T		0.3
77	D, K, T		5
78	D, K, T		inactive
79	K, E		0.44

Table 4
Profile of pyrazoles **27** and **63**.



27



63

Property	**27**	**63**
Potency		
GTPγ IC_{50} (μM)	0.04	0. 03
GTPγ IC_{50} + 1% HSA[a] (μM)	0.52	0.07
ESC[b] IC_{50} (isolated cells, μM)	0.05	0.004
ESC[b] IC_{50} (whole blood, μM)	0.24	0.05
Physical chemistry		
Caco AB/BA ($P_{app} \times 10^{-6}$ cm/s)	2/2	2/6
Solubility (pH1/7.4, mg/ml)	0.03/0.95	0.03/0.68
pKa[c]/log$D_{7.4}$[d]	3.5/0.4	nd/0.5
human plasma protein binding	99.3%	nd
Oral pharmacokinetics[e]		
C_{max} (ng/ml)	2340	4045
$AUC_{0\text{-inf}}$ (ng*h/ml)	2238	3198
Cl/F (ml/min/kg)	75	56
*t*½ (h)	5.1	4.0
F_{oral}	40%	50%

[a] Human serum albumin.
[b] Eosinophil shape change.
[c] Potentiometric method.
[d] Shake-flask method.
[e] 10 mg/kg, Wistar rat.

involved in binding. Chiral separation of the racemic sulfoxide would allow us to confirm this, but it was not carried out due to the modest activity of these compounds.

For the terminal aromatic ring R^x, we saw that almost every change we made resulted in a loss of activity, with only 4-fluorophenyl analogue **63** showing improved potency. Very large groups (3-$CONMe_2$ in **59** and 4-SO_2Me in **68**) were clearly too big. Finally, we replaced the sulphone linker with a rigid structure of the 1-naphthyl **71**. Even though the terminal phenyl ring was conserved, the compound was totally inactive, showing that either the sulfone linker was again necessary, that the orientation of the rings was different, or a combination of both.

In parallel, we also carried out a SAR expansion of the 3-position of the pyrazole (Table 3).

Small substituents were not well tolerated in the R^3 position (**72**–**74**). Of the other aromatic rings, ortho-substitution was not well tolerated (**77**). The dihedral angle of the pyrazole-aromatic bond will be greatly increased in these cases and it is possible that the CRTh2 receptor prefers a planar ring. Again, a very bulk substitution (**78**) was completely inactive.

Of all the analogues, we chose to further profile **27** and fluoro-analogue **63** (Table 4).

Both compounds were of similar potency as measured in the *in vitro* binding assay. In the presence of plasma proteins, notably albumin, **27** lost an order of magnitude of potency whereas **63** showed little shift, if any. The plasma protein binding (PPB) for **27** was measured at 99.3%, confirming the role of albumin in this shift. The pros and cons of plasma protein binding is a topic of active discussion [24]. The cells that express the CRTh2 receptor are found predominantly circulating in the blood and the receptor is expressed on the cell membranes, so the concentration of antagonist available to bind to the receptor should equal the calculated free concentration. However the whole blood potency data should not be considered in isolation, but in conjunction with the pharmacokinetic (PK) profile. Just as high PPB can attenuate the potency of a compound, so it can also attenuate the clearance of that compound resulting in a larger exposure, and the two effects effectively cancel each other out.

To this end, the oral PK profiles were measured in rat. Membrane permeability and solubility at physiological pH were acceptable for **27** and **63**, and as expected both compounds had acceptable oral bioavailabilities. Clearance was quite high but encouragingly, both compounds had long terminal half-lives, which is a requisite for a once-a-day chronic dosing regime. Between the two compounds, **63** showed a greater exposure, and combined with the higher potency in the shape change assay, made this the preferred compound.

4. Conclusions

The SAR around the pyrazole nucleus showed clear differences to that reported for the corresponding indole cores. Extensive SAR investigation showed this pyrazole template to be generally moderate potency. The subset of ortho-substituted benzyl tail groups led to the identification and characterization of **63** as the lead compound of the series. CRTh2 has been extensively investigated since its identification and a number of compounds have been progressed to clinical trials. In the context of the whole panorama of CRTh2 antagonists, compounds **63** did not achieve the levels of potency demonstrated by these clinical candidates, many of which display low nanomolar potencies. As such, the pyrazole series was not advanced for further studies, in favour of other more promising chemical series.

5. Experimental section

5.1. Chemistry

5.1.1. General

Reaction products were purified, when necessary, by flash chromatography on silica gel (40–63 μm) with the solvent system indicated. Purifications in reverse phase were made in a Biotage SP1® 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.

The chromatographic separations were obtained using a Waters 2795 system equipped with a Symmetry C18 (2.1 × 50 mm, 3.5 μM) column for methods 1, 2, 3 and 5 and a Symmetry C18 (2.1 × 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; 0–95% B, over 3 min; 95% B, 0.8 min.

Method 2 (9 min): 0% B, 0.5 min; 0–95% B, over 6.5 min; 95% B, 1 min.

Method 3 (15 min): 0–95% B, over 10.5 min; 95% B, 1.5 min.

Method 4 (30 min): 0–95% B, over 20 min; 95% B, 4 min.

Method 5 (6 min): 0–100% B, over 4.5 min; 100% B, 1.5 min.

^{1}H Nuclear Magnetic Resonance Spectra were recorded on a Varian Mercury plus operating at a frequency of 400 MHz. 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). Mass Spectra (*m*/*z*) were recorded on a Micromass ZMD or in a Waters ZQ mass spectrometer using ESI ionization.

5.1.2. Ethyl [(3-methyl-5-phenyl)-1H-pyrazol-1-yl]acetate (**5**)

1-Phenylbutane-1,3-dione (7.6 g, 47 mmol) was dissolved in 100 ml acetic acid. Ethyl 2-hydrazinylacetate hydrochloride (5.0 g, 31 mmol) and sodium acetate (12.9 g, 157 mmol) were added and the mixture was stirred at 70 °C for 1 h. The mixture was partitioned between ethyl acetate and water. The aqueous was extracted three times with ethyl acetate. The organic layer was washed sequentially three times with 4% w/v sodium bicarbonate solution and then with brine. The organics were dried over magnesium sulphate, filtered and evaporated under reduced pressure. The residue was purified using the SP1 Purification System (ethyl acetate–hexane gradient, 0:100 rising to 40:60) to give a 95:5 mixture of **5** and **6** (7.4 g, 30 mmol, 97%) as a yellow oil. **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.34–7.45 (m, 5H, ArH), 6.14 (s, 1H, pyrazole H-4), 4.81 (s, 2H, CH_2CO), 4.19 (q, 2H, J = 7.3 Hz, OCH_2CH_3), 2.32 (s, 3H, Me), 1.23 (t, 3H, J = 7.0 Hz, OCH_2CH_3). NOE experiments: Irradiation at 7.4 ppm (ArH) shows enhancement at 4.81 ppm (CH_2CO) only. Irradiation at 6.14 ppm (pyrazole H(4)) shows enhancement at 2.32 ppm (Me) only. HPLC/MS (9 min) retention time 5.98 min. LRMS: *m*/*z* 245 (M + 1).

5.1.3. Ethyl [(5-methyl-3-phenyl)-1H-pyrazol-1-yl]acetate (**6**)

1-Phenylbutane-1,3-dione (4.76 g, 29.4 mmol) was dissolved in 20 ml acetic acid. Hydrazine monohydrate (1.0 g, 19.6 mmol) and sodium acetate (8.0 g, 98 mmol) were added and the mixture was stirred at 70 °C overnight. The mixture was partitioned between ethyl acetate and water. The aqueous was extracted three times with ethyl acetate. The organic layer was washed sequentially three times with dilute potassium carbonate solution and then with brine. The organics were dried over magnesium sulphate, filtered and evaporated under reduced pressure. The residue was purified using the SP1 Purification System (ethyl acetate–hexane gradient, 0:100 rising to 30:70) to give 5-methyl-3-phenyl-1*H*-pyrazole (2.86 g, 18 mmol, 92%) as a pale yellow solid. Purity 98%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.27 (s, 3H, Me), 6.34 (s, 1H, pyrazole H(4)), 7.26–7.32 (m, 1H, para H), 7.33–7.39 (m, 2H, meta H) 7.71 (d, 2H, J = 7.42 Hz, ortho H). HPLC/MS (9 min) retention time 5.25 min. LRMS: *m*/*z*. 159 (M + 1).

3-Methyl-5-phenyl-1*H*-pyrazole (1.0 g, 6.3 mmol) and potassium carbonate (1.92 g, 13.9 mmol) were suspended in 20 ml acetone. Ethyl bromoacetate (1.44 ml, 13.9 mmol) was added and the mixture was stirred at reflux for 24 h. The mixture evaporated under reduced pressure and the residue was partitioned between ethyl acetate and water. The aqueous was extracted three times with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulphate, filtered and evaporated under reduced pressure. The residue was purified using the SP1 Purification System (ethyl acetate–hexane gradient, 0:100 rising to 20:80) to give **6** (0.85 g, 3.5 mmol, 55%). Purity 98%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.76 (d, 2H, J = 7.0 Hz, Ph ortho H), 7.37 (t, 2H, J = 7.6 Hz, Ph meta H), 7.28 (t, 1H, J = 7.4 Hz, Ph para H), 6.39 (s, 1H, pyrazole H(4)), 4.88 (s, 2H, CH_2CO), 4.23 (q, 2H, J = 7.3 Hz, OCH_2CH_3), 2.28 (s, 3H, Me), 1.28 (t, 3H, J = 7.2 Hz, OCH_2CH_3). NOE experiments: Irradiation at 2.28 ppm (Me) shows enhancement at 4.88 ppm (CH_2CO) only. Irradiation at 4.88 ppm (CH_2CO) shows enhancement at 2.28 ppm (Me) only. HPLC/MS (9 min) retention time 6.00 min. LRMS: *m*/*z* 245 (M + 1).

5.1.4. 2-(4-(3,4-Dichlorophenylthio)-5-methyl-3-phenyl-1H-pyrazol-1-yl)acetic acid (**9**)

N-Chlorosuccinimide (0.52 g, 4.0 mmol) was dissolved in 12 ml toluene and was cooled in an ice-bath. 3,4-Dichlorobenzene thiol (0.50 g, 4.0 mmol) was added drop-wise and the mixture was stirred at room temperature overnight, turning bright yellow. The solution was filtered and the filtrate was added slowly to a solution of **6** (0.50 g, 2.1 mmol) in 4 ml acetonitrile at 5 °C and the mixture was stirred at room temperature overnight. The mixture was evaporated under reduced pressure and was partially purified using the SP1 Purification System (ethyl acetate–hexane gradient, 0:100 rising to 30:70). The crude product obtained was further purified by reverse-phase chromatography to give ethyl 2-(4-(3,4-dichlorophenylthio)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl) acetate **7** (0.31 g, 0.75 mmol, 36%) as a pale yellow solid. Purity 99%. HPLC/MS (9 min) retention time 7.68 min. LRMS: *m*/*z* 421 (M + 1).

The ester **7** (75 mg, 0.18 mmol) was dissolved in 2 ml tetrahydrofuran and 1 ml water. Lithium hydroxide monohydrate (37 mg, 0.89 mmol) was added and the mixture was stirred overnight at room temperature. The mixture was diluted with dilute hydrochloric acid, forming a white precipitate. The solid was collected by filtration, was washed sequentially with water and ether and was dried under vacuum to give **9** (61 mg, 0.15 mmol, 87%) as a white solid. Purity 100%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.22 (s, 3H, Me), 4.71–4.77 (m, 2H, CH_2CO), 6.96 (dd, 1H, J = 8.40, 2.15 Hz, SPh H(6)), 7.22 (d, 1H, J = 1.95 Hz, SPh H(2)), 7.29–7.33 (m, 1H, Ph para H), 7.36 (t, 2H, J = 7.42 Hz, Ph meta H), 7.50 (d, 1H, J = 8.60 Hz, SPh H(5)), 7.73–7.79 (m, 2H, Ph ortho H). HPLC/MS (30 min) retention time 17.52 min. LRMS: *m*/*z* 393 (M + 1).

5.1.5. 2-(4-(3,4-Dichlorophenylsulfonyl)-5-methyl-3-phenyl-1H-pyrazol-1-yl)acetic acid (**10**)

Ethyl 2-(4-(3,4-dichlorophenylthio)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl) acetate **7** (0.20 g, 0.47 mmol) was dissolved in 5 ml

dimethylformamide and the mixture was cooled in an ice-bath. Oxone (1.05 g, 1.7 mmol) was added portion-wise and the mixture was stirred at room temperature for 3 d. The mixture was partitioned between 40% w/v sodium bisulfite solution and ether. The aqueous phase was extracted three times with ether. The combined organics were washed with brine, dried over magnesium 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 ethyl 2-(4-(3,4-dichlorophenylsulfonyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl) acetate **8** (0.18 g, 0.40 mmol, 83%) as a colourless oil. Purity 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.30 (t, 3H, $J = 7.23$ Hz, CH_2CH_3), 2.66 (s, 3H, Me), 4.26 (q, 2H, $J = 7.16$ Hz, CH_2CH_3), 4.92 (s, 2H, CH_2CO), 7.15–7.20 (m, 1H, ArH), 7.23–7.30 (m, 2H, ArH), 7.33–7.44 (m, 5H, ArH). HPLC/MS (9 min) retention time 7.07 min. LRMS: *m*/*z* 453 (M + 1).

The ester **8** (0.18 g, 0.40 mmol) was dissolved in 3 ml tetrahydrofuran and 1 ml water. Lithium hydroxide monohydrate (83 mg, 2.0 mmol) was added and the mixture was stirred overnight at room temperature. The mixture was diluted with dilute hydrochloric acid, forming a white precipitate. The solid was collected by filtration, was washed sequentially with water and ether and was dried under vacuum to give **10** (124 mg, 0.29 mmol, 74%) as a white solid. Purity 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.63 (s, 3H, Me), 4.94 (s, 2H, CH_2CO), 7.24–7.28 (m, 2H, ArH), 7.32–7.40 (m, 4H, ArH), 7.41–7.45 (m, 1H, ArH), 7.47 (d, 1H, $J = 1.95$ Hz, SPh H(3)). HPLC/MS (30 min) retention time 15.03 min. LRMS: *m*/*z* 425 (M + 1).

5.1.6. 2-(5-(4-Fluorobenzoyl)-3-phenyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridin-1-yl)acetic acid (**16**)

tert-Butyl 4-oxopiperidine-1-carboxylate (1.0 g, 5.0 mmol) was dissolved in 10 ml toluene and was cooled to 0 °C under argon. Lithium hexamethyldisilazide (1 M in THF, 5.3 ml, 5.3 mmol) was added and he mixture was stirred for 1 min. Benzoyl chloride (0.29 ml, 2.5 mmol) was added ad the mixture was stirred at room temperature for 1 h. The mixture was diluted with 5 ml acetic acid, 20 ml ethanol and 10 ml tetrahydrofuran. Hydrazine hydrate (4.1 ml, 84 mmol) was added and the mixture was stirred for 15 min. The mixture was basified with 1 N sodium hydroxide and was extracted five times with ethyl acetate. The organics were dried over magnesium sulphate, filtered and evaporated. The residue was purified by column chromatography (ethyl acetate–hexane gradient, 0:100 rising to 100:0) to give *tert*-butyl 3-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*c*]pyridine-5(4*H*)-carboxylate **12** (0.65 g, 2.17 mmol, 82%) as a white solid. Purity 92%. HPLC/MS (6 min) retention time 4.18 min. LRMS: *m*/*z* 300 (M + 1).

12 (0.55 g, 1.83 mmol), caesium carbonate (0.90 g, 2.75 mmol) and ethyl bromoacetate (2.0 mmoL) were suspended in 5 ml dimethylformamide and the mixture was stirred for 30 min. The mixture was partitioned between water and ethyl acetate. The organics were washed with brine, dried over magnesium sulphate, filtered and evaporated. The residue was purified by column chromatography (ethyl acetate–hexane gradient, 0:100 rising to 80:20) to give *tert*-butyl 1-(2-ethoxy-2-oxoethyl)-3-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-c]pyridine-5(4*H*)-carboxylate **13** (0.50 g, 1.3 mmol, 60%) as a colourless oil. Purity 98%. HPLC/MS (6 min) retention time 4.23 min. LRMS: *m*/*z* 386 (M + 1).

13 (495 mg, 1.28 mmol) was dissolved in 4 ml dichloromethane. 1.5 ml Trifluoroacetic acid was added and the mixture was stirred at room temperature for 90 min. The mixture was evaporated and the residue partitioned between saturated sodium carbonate solution and dichloromethane. The aqueous was extracted four times with dichloromethane and the combined organics were dried over magnesium sulphate, filtered and evaporated under reduced pressure to give ethyl 2-(3-phenyl-4,5,6,7-tetrahydro-1*H*-pyrazolo [4,3-*c*]pyridin-1-yl)acetate **14** (338 mg, 1.19 mmol, 93%) as a colourless oil. Purity 98%. HPLC/MS (6 min) retention time 2.50 min. LRMS: *m*/*z* 286 (M + 1).

14 (70 mg, 0.24 mmol) was dissolved in 0.5 ml dichloromethane. Triethylamine (85 μl, 0.35 mmol) and 4-fluorobenzoyl chloride (42 μl, 0.35 mmol) were added and the mixture stirred for 20 min. The mixture diluted with saturated sodium carbonate solution and was extracted three time with dichloromethane. The combined organics were washed with brine, dried over magnesium sulphate, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (ethyl acetate–hexane gradient, 30:70 rising to 40:60) to give ethyl 2-(5-(4-fluorobenzoyl)-3-phenyl-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*c*] pyridin-1-yl)acetate **15** (59 mg, 0.14 mmol, 59%) as a white solid. Purity 100%. HPLC/MS (6 min) retention time 4.04 min. LRMS: *m*/*z* 408 (M + 1).

15 (59 mg, 0.14 mmol) was dissolved in 3 ml of tetrahydrofuran and 1.5 ml of water. Lithium hydroxide (17 mg, 0.42 mmol) was added and the mixture was stirred at room temperature for min. The organics were concentrated under reduced pressure and the aqueous solution was acidified to pH 1 with 1 N hydrochloric acid. The aqueous was extracted several times with dichloromethane, the combined organics were dried over magnesium sulphate, filtered and evaporated under reduced pressure to give **16** (37 mg, 0.10 mmol, 70%) as a white solid. Purity 99%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.16 (br. s. 1H, OH), 7.56–7.71 (m, 2H, Ph ortho H), 7.51 (dd, 2H $J = 8.4$, 5.7 Hz, PhF H-2 and H-6), 7.44 (m, 2H, ArH), 7.18–7.38 (m, 3H, ArH), 4.92 (s, 2H, CH_2CO), 4.79 (m, 1H, C(4)H_AH_B), 4.56–4.74 (m, 1H, C(4)H_AH_B), 3.91 (m, 1H, C(6)H_AH_B), 3.61 (m, 1H, C(6)H_AH_B), 2.74 (m, 2H, C(7)H_2). HPLC/MS (30 min) retention time 13.65 min. LRMS: *m*/*z* 380 (M + 1).

5.1.7. 2-(Phenylthio)benzaldehyde (**19**)

2-Fluorobenzaldehyde **17** (9 ml, 90 mmol) and benzenethiol **18** (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 100 °C 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 give **19** (18.5 g, 78 mmol, 95%) 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, ArH), 7.29–7.46 (m, 7H, ArH), 7.88 (dd, $J = 7.42$, 1.56 Hz, 1H, ArH), 10.40 (s, 1H, CHO). HPLC/MS (9 min) retention time 6.53 min. LRMS: *m*/*z* 215 (M + 1).

5.1.8. 2-(Phenylsulfonyl)benzaldehyde (**20**)

2-(Phenylthio)benzaldehyde (**19**) (3.5 g, 16.3 mmol) was dissolved in 50 ml dichloromethane. 3-Chloroperoxybenzoic acid (77% max purity, 11 g, 49 mmol) was added in portions and the mixture was stirred at room temperature overnight. The mixture was washed sequentially 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 **20** (1.9 g, 7.7 mmol, 47%) as a white solid. Purity 100%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.67 (t, 2H, $J = 7.62$ Hz, $PhSO_2$ meta H), 7.75 (t, 1H, $J = 7.42$ Hz, $PhSO_2$ para H), 7.88–7.99 (m, 3H, ArH), 8.02 (d, 2H, $J = 7.42$ Hz, $PhSO_2$ ortho H), 8.20 (d, 1H, $J = 7.82$ Hz, ArH), 10.68 (s, 1H, CHO). HPLC/MS (9 min) retention time 5.47 min. LRMS: *m*/*z* 247 (M + 1).

5.1.9. [2-(Phenylsulfonyl)phenyl]methanol (**21**)

2-(Phenylsulfonyl)benzaldehyde (**20**) (2.0 g, 7.74 mmol) was dissolved in 16 ml methanol. Sodium borohydride (150 mg, 3.86 mmol) was added portion-wise and the mixture was agitated

at room temperature for 30 min. Dilute hydrochloric acid (5% v/v solution) was added and the mixture was concentrated under reduced pressure. The residue was taken up with water and the aqueous was extracted with dichloromethane. The combined organics were washed with brine and were dried over sodium sulphate. Filtration and evaporation gave **21** (1.90 g, 7.66 mmol, 98%) as a yellow solid. Used as such without further purification. Purity 96%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.14 (br. s., 1H, OH), 4.74 (s, 2H, CH_2), 7.48–7.58 (m, 4H, ArH), 7.61 (d, 1H, J = 7.42 Hz, 1H), 7.65 (d, 1H, J = 7.42 Hz, ArH), 7.90 (d, 2H, J = 7.42 Hz, $PhSO_2$ ortho H), 8.15 (d, 1H, J = 7.82 Hz, 1H). HPLC/MS (9 min) retention time 4.97 min. LRMS: m/z 249 (M + 1).

5.1.10. 1-(Bromomethyl)-2-(phenylsulfonyl)benzene (**22**)

[2-(Phenylsulfonyl)phenyl]methanol (**21**) (1.9 g, 7.66 mmol) was dissolved in 20 ml chlorobenzene. Thionyl bromide (1.46 ml, 18.3 mmol) was slowly added and the mixture was heated at 100 °C for 1 h. The mixture was concentrated under reduced pressure and the residue was partitioned between dichloromethane and water. 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. The residue was purified using the SP1 Purification System (ethyl acetate–hexane gradient, 0:100 rising to 8:92) to give **22** (1.95 g, 6.27 mmol, 82%) as an oil. Purity 94%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.89 (s, 2H, CH_2), 7.47–7.67 (m, 6H, ArH), 7.92 (d, 2H, J = 7.42 Hz, $PhSO_2$ ortho H), 8.19 (d, 1H, J = 8.21 Hz). HPLC/MS (9 min) retention time 6.03 min. LRMS: m/z 311, 313 (M + 1).

5.2. General "Method A"

5.2.1. 1-Phenyl-2-[2-(phenylsulfonyl)benzyl]butane-1,3-dione (**24**)

Sodium hydride (60% dispersion in oil, 118 mg, 2.95 mmol) was first washed with hexanes to remove the oil and was then suspended in 10 ml tetrahydrofuran and cooled to 0 °C in an ice-bath. A solution of 1-phenylbutane-1,3-dione **23** (300 mg, 1.85 mmol) dissolved in 2 ml tetrahydrofuran was added drop-wise and with stirring. Upon addition, the mixture was stirred for 1 h at room temperature. A solution of 1-(bromomethyl)-2-(phenylsulfonyl) benzene (**22**) (690 mg, 2.22 mmol) in 3 ml tetrahydrofuran was added drop-wise with stirring and the mixture was stirred overnight at room temperature. The organics were concentrated under reduced pressure and the residue was re-suspended in aqueous ammonium chloride solution. The solution was extracted three times with ether and the combined organics were washed with brine, dried over sodium sulphate and evaporated under reduced pressure. The residue was purified by reverse-phase chromatography using the SP1 Purification System to give **24** (256 mg, 0.65 mmol, 35%) as a colourless oil. Purity 94%. ^{1}H NMR spectrum complicated by mixtures of tautomers. HPLC/MS (9 min) retention time 6.47 min. LRMS: m/z 393 (M + 1).

5.2.2. 5-Methyl-3-phenyl-4-[2-(phenylsulfonyl)benzyl]-1H-pyrazole (**25**)

1-Phenyl-2-[2-(phenylsulfonyl)benzyl]butane-1,3-dione (**24**) (254 mg, 0.65 mmol) was dissolved in 5 ml acetic acid. Hydrazine monohydrate (27 mg, 0.54 mmol) and sodium acetate (221 mg, 2.7 mmol) were added and the mixture was stirred at 70 °C overnight. The mixture was partitioned between ethyl acetate and water. The aqueous was extracted three times with ethyl acetate. The organic layer was washed sequentially with brine, dilute potassium carbonate solution and brine and was dried over sodium sulphate and evaporated under reduced pressure. The residue was purified using the SP1 Purification System (ethyl acetate–hexane gradient, 0:100 rising to 40:60) to give **25** (178 mg, 0.46 mmol, 85%) as a white solid. Purity 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.81 (s, 3H, Me), 4.12 (s, 2H, CH_2), 7.00–7.04 (m, 1H, ArH), 7.15–7.24 (m, 5H, ArH), 7.42–7.51 (m, 4H, ArH), 7.53–7.59 (m, 1H, ArH), 7.85–7.91 (m, 2H, ArH), 8.29–8.34 (m, 1H, ArH). HPLC/MS (9 min) retention time 6.27 min. LRMS: m/z 389 (M + 1).

5.3. General "Method E"

5.3.1. Ethyl {5-methyl-3-phenyl-4-[2-(phenylsulfonyl)benzyl]-1H-pyrazol-1-yl}acetate (**26**)

5-Methyl-3-phenyl-4-[2-(phenylsulfonyl)benzyl]-1*H*-pyrazole (**25**) (300 mg, 0.77 mmol) was dissolved in 8 ml dimethylformamide. Sodium hydride (60% dispersion in oil, 40 mg, 1 mmol) previously washed with pentane was added in portions and the mixture was stirred for 30 min at room temperature. Ethyl 2-bromoacetate (0.11 ml, 0.95 mmol) dissolved in 2 ml dimethylformamide was added and the mixture was agitated overnight. The mixture was poured into water and the solution was extracted three times with ethyl acetate. The combined organics were washed with brine, dried over sodium sulphate and evaporated under reduced pressure. The residue was purified using the SP1 Purification System (ethyl acetate–hexane gradient, 0:100 rising to 50:50) to give **26** (230 mg, 0.48 mmol, 63%) as a white solid. Purity 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.29 (t, 3H, J = 7.03 Hz, CH_2*Me*), 1.87 (s, 3H, ArMe), 4.14 (s, 2H, Ar*CH*$_2$Ar), 4.24 (q, 2H, J = 7.03 Hz, *CH*$_2$Me), 4.90 (s, 2H, $COCH_2$), 7.02–7.22 (m, 6H, ArH), 7.40–7.51 (m, 4H, ArH), 7.52–7.59 (m, 1H, ArH), 7.89 (d, 2H, J = 7.82 Hz, $PhSO_2$ ortho H), 8.29–8.35 (m, 1H, Ar). HPLC/MS (9 min) retention time 6.70 min. LRMS: m/z 475 (M + 1).

5.3.2. {5-Methyl-3-phenyl-4-[2-(phenylsulfonyl)benzyl]-1H-pyrazol-1-yl}acetic acid (**27**)

Ethyl {5-methyl-3-phenyl-4-[2-(phenylsulfonyl)benzyl]-1*H*-pyrazol-1-yl}acetate (**26**) (114 mg, 0.24 mmol) was dissolved in 4 ml of tetrahydrofuran and 4 ml of water. Lithium hydroxide (50 mg, 1.2 mmol) was added and the mixture was agitated at room temperature overnight. The mixture was concentrated under reduced pressure and the residue was acidified with 5 N hydrochloric acid to give a white precipitate. The precipitate was filtered and washed with water. The solid was dried under reduced pressure to give **27** (98 mg, 0.22 mmol, 91%) as a white solid. Purity 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.79 (s, 3H, Me), 4.11 (s, 2H, Ar*CH*$_2$Ar), 4.88 (s, 2H, $COCH_2$), 6.95–7.00 (m, 1H, ArH), 7.08–7.14 (m, 2H, ArH), 7.15–7.21 (m, 3H, ArH), 7.39–7.49 (m, 4H, ArH), 7.52–7.58 (m, 1H, ArH), 7.84–7.88 (m, 2H, ArH), 8.27–8.32 (m, 1H, ArH). HPLC/MS (30 min) retention time 15.39 min. LRMS: m/z 447 (M + 1).

5.3.3. 2-(5-Methyl-3-phenyl-4-(quinolin-2-ylmethyl)-1H-pyrazol-1-yl)acetic acid (**28**)

Following general methods A, *E*: White solid. Purity 98%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.20 (s, 3H, Me), 4.25 (s, 2H, $ArCH_2Ar$), 4.96 (s, 2H, CH_2CO), 7.17 (d, 1H, J = 8.60 Hz, quinoline H(3)), 7.23–7.29 (m, 1H quinoline H(6)), 7.33 (t, 2H, J = 7.62 Hz, Ph meta), 7.54 (t, 1H, J = 7.62 Hz, Ph para), 7.64 (d, 2H, J = 7.03 Hz, Ph ortho), 7.72 (t, 1H, J = 7.62 Hz, quinoline H(7)), 7.89 (d, 1H, J = 7.82 Hz, quinoline H(5)), 7.95 (d, 1H, J = 8.21 Hz, quinoline H(8)), 8.22 (d, 1H, J = 8.60 Hz, quinoline H(4)). HPLC/MS (30 min) retention time 8.98 min. LRMS: m/z 358 (M + 1).

5.4. General "Method D"

5.4.1. 1-[3-(Trifluoromethyl)phenyl]butane-1,3-dione (**30**)

Sodium hydride (60% dispersion in oil, 390 mg, 9.75 mmol) was first washed with hexanes to remove the oil and was then

suspended in 7 ml dimethylformamide. A solution of methyl 3-(trifluoromethyl)benzoate **29** (1.0 g, 4.9 mmol) in 2 ml dimethylformamide was added drop-wise and with stirring. Upon addition, the mixture was stirred for 1 h at room temperature. Acetone (400 μl, 5.44 mmol) was added drop-wise and the mixture was stirred overnight at room temperature. The mixture was poured into water and the aqueous layer was extracted four times with ether. The aqueous layer was acidified with 2 N hydrochloric acid and was extracted three times with ether. The combined organics were dried over sodium sulphate and evaporated under reduced pressure. The residue was purified using the SP1 Purification System (ethyl acetate–hexane gradient, 0:100 rising to 10:90) to give **30** (640 mg, 2.78 mmol, 56%) as an oil. Purity 100%. ^{1}H NMR spectrum complicated by mixtures of tautomers. HPLC/MS (15 min) retention time 8.53 min. LRMS: *m*/*z* 229 (M − 1).

5.5. General "Method K"

5.5.1. 2-[2-(Phenylsulfonyl)benzylidene]-1-[3-(trifluoromethyl) phenyl]butane-1,3-dione (*31*)

1-[3-(Trifluoromethyl)phenyl]butane-1,3-dione (**30**) (635 mg, 2.76 mmol) and 2-(phenylsulfonyl)benzaldehyde (**20**) (680 mg, 2.76 mmol) were dissolved in 8 ml ethanol. Piperidine (44 μl, 0.44 mmol), acetic acid (210 μl, 3.67 mmol) and a spoonful of 4 Å molecular sieves were added and the mixture was heated at 80 °C overnight. The mixture was filtered and was concentrated under reduced pressure. The resulting residue was purified using the SP1 Purification System (ethyl acetate–hexane gradient, 0:100 rising to 20:80) to give **31** (759 mg, 1.65 mmol, 60%) as a solid. Purity 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.37 (s, 1H, C=CH), 8.15 (s, 1H, ArH), 8.10 (d, 1H, J = 7.8 Hz, ArH), 7.96 (d, 2H, J = 7.4 Hz, $PhSO_2$ ortho H), 7.66–7.72 (m, 2H, ArH), 7.58–7.66 (m, 3H, ArH), 7.44 (t, 1H, J = 7.4 Hz, $PhSO_2$ para H), 7.37–7.41 (m, 1H, ArH), 7.30–7.37 (m, 1H, ArH), 7.23–7.30 (m, 1H, ArH), 2.47 (s, 3H, Me). HPLC/MS (9 min) retention time 6.83 min. LRMS: *m*/*z* 459 (M + 1).

5.5.2. 2-[2-(Phenylsulfonyl)benzyl]-1-[3-(trifluoromethyl)phenyl] butane-1,3-dione (*32*)

2-[2-(Phenylsulfonyl)benzylidene]-1-[3-(trifluoromethyl) phenyl]butane-1,3-dione (**31**) (759 mg, 1.66 mmol) was dissolved in 15 ml acetic acid. Zinc dust (670 mg, 10.3 mmol)) was added and the mixture was stirred at 80 °C for 30 min. The mixture was allowed to cool and was filtered. The solid was washed with ethyl acetate and the combined organics were concentrated under reduced pressure to give **32** (762 mg, 1.66 mmol, 100%) as a solid. Used without further purification. Purity 100%. ^{1}H NMR (400 MHz, $CDCl_3$) keto tautomer δ ppm 8.11–8.16 (m, 1H, ArH), 8.09 (s, 1H, CF_3Ph-H-2), 8.04 (d, 1H, J = 7.8 Hz, CF_3Ph-H-6), 7.82 (d, 2H, J = 7.4 Hz, $PhSO_2$ ortho H), 7.77 (dd, 1H, J = 13.0, 7.4 Hz, ArH), 7.49–7.63 (m, 4H, ArH), 7.32–7.40 (m, 2H, ArH), 7.14–7.19 (m, 1H, ArH), 5.29 (dd, 1H, J = 8.2, 5.9 Hz, COCHCO), 3.56 (dd, 1H, J = 13.9, 5.7 Hz, CH_AH_B), 3.32 (dd, 1H, J = 13.7, 8.6 Hz, CH_AH_B), 2.15 (s, 3H, Me). HPLC/MS (9 min) retention time 6.97 min. LRMS: *m*/*z* 461 (M + 1).

5.5.3. 5-Methyl-4-[2-(phenylsulfonyl)benzyl]-3-[3-(trifluoromethyl)phenyl]-1H-pyrazole (*33*)

2-[2-(Phenylsulfonyl)benzyl]-1-[3-(trifluoromethyl)phenyl] butane-1,3-dione (**32**) (762 mg, 1.6 mmol) was dissolved in 6 ml acetic acid. Hydrazine monohydrate (0.13 ml, 2.68 mmol) was added and the mixture was stirred at room temperature overnight. The mixture was evaporated under reduced pressure and the residue was partitioned between dichloromethane and water. The aqueous was extracted twice with dichloromethane. The combined organics were washed with brine, dried over sodium sulphate, filtered and evaporated under reduced pressure to give **33** (755 mg, 1.66 mmol, 100%) as a solid. Used as such without further purification. Purity 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.26–8.33 (m, 1H, ArH), (d, 2H, J = 7.42 Hz, $PhSO_2$ ortho H), 7.63 (s, 1H, ArH), 7.56 (t, 1H, J = 7.2 Hz, $PhSO_2$ para H), 7.40–7.52 (m, 5H, ArH), 7.19–7.27 (m, 2H, ArH), 6.97–7.04 (m, 1H, ArH), 4.13 (s, 2H, CH_2), 1.93 (s, 3H, Me). HPLC/MS (9 min) retention time 6.82 min. LRMS: *m*/*z* 457 (M + 1).

5.6. General "Method T"

5.6.1. tert-Butyl {5-methyl-4-[2-(phenylsulfonyl)benzyl]-3-[3-(trifluoromethyl)phenyl]-1H-pyrazol-1-yl}acetate (*34*)

5-Methyl-4-[2-(phenylsulfonyl)benzyl]-3-[3-(trifluoromethyl) phenyl]-1*H*-pyrazole (**33**) (300 mg, 0.66 mmol) was dissolved in 10 ml dimethylformamide under nitrogen. Sodium hydride (60% dispersion in oil, 33 mg, 0.86 mmol) previously washed with pentane was added in portions and the mixture was stirred for 1 h at room temperature. *tert*-Butyl 2-bromoacetate (0.12 ml, 0.79 mmol) dissolved in 2 ml dimethylformamide was added and the mixture was stirred at room temperature for 3 h. The mixture was poured into water and the solution was extracted three times with ether. The combined organics were washed with water and brine. The organic layer was dried over sodium sulphate and evaporated under reduced pressure. The residue was purified using the SP1 Purification System (ethyl acetate–hexane gradient, 0:100 rising to 20:80) to give **34** (228 mg, 0.40 mmol, 61%) of the title compound. Purity 100%. HPLC/MS (9 min) retention time 7.52 min. LRMS: *m*/*z* 571 (M + 1).

5.6.2. {5-Methyl-4-[2-(phenylsulfonyl)benzyl]-3-[3-(trifluoromethyl)phenyl]-1H-pyrazol-1-yl}acetic acid (*35*)

tert-Butyl {5-methyl-4-[2-(phenylsulfonyl)benzyl]-3-[3-(trifluoromethyl)phenyl]-1*H*-pyrazol-1-yl}acetate (**34**) (228 mg, 0.40 mmol) was dissolved in 5 ml dichloromethane. Trifluoroacetic acid (2.15 ml, 28 mmol) was added and the mixture was stirred at room temperature overnight. The mixture was concentrated under reduced pressure. The residue was taken up in a little water, the mixture frozen and lyophilized overnight to give **35** (146 mg, 0.27 mmol, 67%) as a white solid. Purity 97%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.94 (s, 3H, Me), 4.18 (s, 2H, $ArCH_2Ar$), 4.88 (s, 2H, $COCH_2$), 6.97 (d, 1H, J = 2.3 Hz, ArH), 7.24–7.28 (m, 1H, ArH), 7.29–7.45 (m, 6H, ArH), 7.52 (t, 1H, J = 7.42 Hz, $PhSO_2$ para H), 7.64 (br s. 1H, ArH), 7.84 (d, 2H, J = 7.82 Hz, $PhSO_2$ ortho H), 8.20 (br. s, 1H, ArH). HPLC/MS (30 min) retention time 17.27 min. LRMS: *m*/*z* 515 (M + 1).

5.6.3. Ethyl [4-(2-iodobenzyl)-5-methyl-3-phenyl-1H-pyrazol-1-yl] acetate (*36*)

Following general methods A, E: White solid. Purity 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.29 (t, 3H, J = 7.2 Hz, CH_2Me), 2.09 (s, 3H, ArMe), 3.90 (s, 2H, $ArCH_2Ar$), 4.26 (q, 2H, J = 7.23 Hz, CH_2Me), 4.95 (s, 2H, $COCH_2$), 6.88–6.95 (m, 2H, ArH), 7.22 (t, 1H, J = 7.52 Hz, ArH), 7.25–7.34 (m, 3H, ArH), 7.42–7.46 (m, 2H, ArH), 7.88 (dd, 1H, J = 7.72, 1.27 Hz, Ar). HPLC/MS (6 min) retention time 4.57 min. LRMS: *m*/*z* 461 (M + 1).

5.7. General "Method I"

5.7.1. (4-{2-[(2-Fluorophenyl)thio]benzyl}-5-methyl-3-phenyl-1H-pyrazol-1-yl)acetic acid (*38*)

Ethyl [4-(2-iodobenzyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl] acetate (**36**) (91 mg, 0.20 mmol) potassium hydroxide (22 mg, 0.39 mmol), copper (13 mg, 0.20 mmol) and 2-fluorobenzenethiol **37** (25 μl, 0.20 mmol) were suspended in 1 ml water. The mixture was heated at 120 °C under microwave irradiation (CEM Discover) for two cycles of 30 min each. The solution was allowed to cool and was partitioned between 2 N hydrochloric acid and ethyl acetate. The aqueous layer was extracted twice with ethyl acetate. The

combined organics were dried over magnesium sulphate and evaporated. The resulting residue was purified by reverse-phase chromatography (formic acid buffer) using the SP1 Purification system to give **38** (45 mg, 0.10 mmol, 52%) as a white solid. Purity 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.97 (s, 3H, Me), 4.01 (s, 2H, $ArCH_2Ar$), 4.91 (s, 2H, $COCH_2$), 6.94–6.98 (m, 1H, ArH), 7.00–7.04 (m, 2H, ArH), 7.04–7.10 (m, 1H, ArH), 7.14–7.18 (m, 2H, ArH), 7.18–7.24 (m, 1H, ArH), 7.25–7.29 (m, 3H, ArH), 7.31–7.34 (m, 1H, ArH), 7.37–7.42 (m, 2H, ArH), 9.03 (s, 1H, OH). HPLC/MS (6 min) retention time 4.65 min. LRMS: *m/z* 433 (M + 1).

5.7.2. (4-{2-[(2-Fluorophenyl)sulfonyl]benzyl}-5-methyl-3-phenyl-1H-pyrazol-1-yl)acetic acid (**39**)

(4-{2-[(2-Fluorophenyl)thio]benzyl}-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)acetic acid (**38**) (65 mg, 0.13 mmol) was dissolved in 2 ml dichloromethane and the mixture was cooled in an ice-bath. 3-Chloroperoxybenzoic acid (50% max purity, 90 mg, 0.26 mmol) was added and the mixture was stirred at room temperature for 2 h. The mixture was evaporated under reduced pressure. The resulting residue was purified by reverse-phase chromatography (formic acid buffer) using the SP1 Purification system to give **39** (15 mg, 0.032 mmol, 32%) as a white solid. Purity 94%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.32–8.38 (m, 1H, ArH), 8.11 (td, 1H, J = 7.3, 1.2 Hz, terminal Ph H(3)), 7.51–7.59 (m, 1H, ArH), 7.45 (dd, 2H, J = 5.0, 3.9 Hz, ArH), 7.20–7.27 (m, 1H, ArH), 7.14–7.19 (m, 3H, ArH), 7.06–7.14 (m, 3H, ArH), 7.00 (d, 1H, J = 3.3 Hz, ArH), 4.90 (s, 2H, $COCH_2$), 4.07 (s, 2H, $ArCH_2Ar$), 1.83 (s, 3H, Me). HPLC/MS (30 min) retention time 15.54 min. LRMS: *m/z* 465 (M + 1).

5.7.3. {5-Methyl-3-phenyl-4-[2-(phenylsulfonyl)-4-(trifluoromethyl)benzyl]-1H-pyrazol-1-yl}acetic acid (**45**)

Following general methods K, T: White solid. Purity 99%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.80 (s, 3H, Me), 4.08 (s, 2H, $ArCH_2Ar$), 4.97 (s, 2H, $COCH_2$), 7.01–7.24 (m, 6H, ArH), 7.67 (t, 2H, J = 7.62 Hz, $PhSO_2$ meta H), 7.77 (t, 1H, J = 7.42 Hz, $PhSO_2$ para H), 7.96–8.08 (m, 3H, ArH), 8.48 (s, 1H, proximal Ph H(3)), 13.14 (br. s., 1H, OH). HPLC/MS (30 min) retention time 17.47 min. LRMS: *m/z* 515 (M + 1).

5.7.4. {4-[4-Methoxy-2-(phenylsulfonyl)benzyl]-5-methyl-3-phenyl-1H-pyrazol-1-yl}acetic acid (**46**)

Following general methods K, T: Yellow solid. Purity 96%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.77 (s, 3H, ArMe), 3.85 (s, 3H, OMe), 3.92 (s, 2H, $ArCH_2Ar$), 4.95 (s, 2H, $COCH_2$), 6.82 (d, 1H, J = 8.60 Hz, proximal Ph H(5)), 7.04–7.23 (m, 6H, ArH), 7.64 (t, 2H, J = 7.42 Hz, $PhSO_2$ meta H), 7.68–7.84 (m, 2H, ArH), 7.95 (d, 2H, J = 7.42 Hz, $PhSO_2$ ortho H), 13.10 (br. s., 1H, OH). HPLC/MS (30 min) retention time 15.57 min. LRMS: *m/z* 477 (M + 1).

5.7.5. 4-{[1-(Carboxymethyl)-5-methyl-3-phenyl-1H-pyrazol-4-yl]methyl}-3-(phenylsulfonyl)benzoic acid (**47**)

Following general methods K, T: White solid. Purity 93%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.79 (s, 3H, Me), 4.06 (s, 2H, $ArCH_2Ar$), 4.96 (s, 2H, $COCH_2$), 7.05 (d, 1H, J = 8.21 Hz, ArH), 7.08–7.22 (m, 5H, ArH), 7.65 (t, 2H, J = 7.62 Hz, $PhSO_2$ meta H), 7.74 (t, 1H, J = 7.42 Hz, $PhSO_2$ para H), 7.96 (d, 2H, J = 7.82 Hz, $PhSO_2$ ortho H), 8.09 (d, 1H, J = 7.82 Hz, proximal Ph H(5)), 8.75 (s, 1H, proximal Ph H(3)). HPLC/MS (30 min) retention time 14.53 min. LRMS: *m/z* 491 (M + 1).

5.7.6. {4-[4-(Methoxycarbonyl)-2-(phenylsulfonyl)benzyl]-5-methyl-3-phenyl-1H-pyrazol-1-yl}acetic acid (**48**)

Following general methods K, T: White solid. Purity 90%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.79 (s, 3H, ArMe), 3.91 (s, 3H, OMe), 4.06 (br. s., 2H, $ArCH_2Ar$), 4.97 (s, 2H, $COCH_2$), 7.01–7.15 (m, 6H, ArH), 7.65 (t, 2H, J = 7.42 Hz, $PhSO_2$ meta H), 7.75 (t, 1H, J = 7.03 Hz, $PhSO_2$ para H), 7.97 (d, 2H, J = 7.42 Hz, $PhSO_2$ ortho H), 8.12 (d, 1H, J = 7.82 Hz, proximal Ph H(5)), 8.77 (s, 1H, proximal Ph H(3)). HPLC/MS (30 min) retention time 16.10 min. LRMS: *m/z* 505 (M + 1).

5.7.7. (5-Methyl-3-phenyl-4-{[3-(phenylsulfonyl)pyridin-4-yl]methyl}-1H-pyrazol-1-yl)acetic acid (**49**)

Following general methods K, T: White solid. Purity 99%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.85 (s, 3H, Me), 4.06 (s, 2H, $ArCH_2Ar$), 4.98 (s, 2H, $COCH_2$), 6.89 (d, 1H, J = 5.08 Hz, Pyr H(5)), 7.02–7.14 (m, 4H, ArH), 7.14–7.21 (m, 1H, ArH), 7.67 (t, 2H, J = 7.82 Hz, $PhSO_2$ meta H), 7.77 (t, 1H, J = 7.42 Hz, $PhSO_2$ para H), 8.04 (d, 2H, J = 7.42 Hz, $PhSO_2$ ortho H), 8.70 (d, 1H, J = 5.08 Hz, Pyr H(6)), 9.26 (s, 1H, Pyr H(2)), 13.15 (br. s., 1H, OH). HPLC/MS (30 min) retention time 14.26 min. LRMS: *m/z* 448 (M + 1).

5.7.8. {4-[5-Fluoro-2-(phenylsulfonyl)benzyl]-5-methyl-3-phenyl-1H-pyrazol-1-yl}acetic acid (**50**)

Following general methods K, T: White solid. Purity 94%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.85 (s, 3H, Me), 4.09 (s, 2H, $ArCH_2Ar$), 4.88 (s, 2H, $COCH_2$), 6.67 (d, 1H, J = 10.16 Hz, proximal Ph H(6)), 7.03–7.22 (m, 5H, ArH), 7.42–7.51 (m, 3H, ArH), 7.56 (t, 1H, J = 6.90 Hz, proximal Ph H(4)), 7.85 (d, 2H, J = 7.42 Hz, $PhSO_2$ ortho H), 8.33 (dd, 1H, J = 8.79, 5.67 Hz, proximal Ph H(3)). HPLC/MS (30 min) retention time 15.85 min. LRMS: *m/z* 465 (M + 1).

5.7.9. {4-[5-Methoxy-2-(phenylsulfonyl)benzyl]-5-methyl-3-phenyl-1H-pyrazol-1-yl}acetic acid (**51**)

Following general methods K, T: Pale yellow solid. Purity 98%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.81 (s, 3H, ArMe), 3.68 (s, 3H, OMe), 3.96 (s, 2H, $ArCH_2Ar$), 4.97 (s, 2H, $COCH_2$), 6.38 (d, 1H, J = 1.95 Hz, proximal Ph H(6)), 7.01–7.25 (m, 6H, ArH), 7.63 (t, 2H, J = 7.82 Hz, $PhSO_2$ meta H), 7.69 (t, 1H, J = 7.42 Hz, $PhSO_2$ para H), 7.88 (d, 2H, J = 7.42 Hz, $PhSO_2$ ortho H), 8.21 (d, 1H J = 8.99 Hz, proximal Ph H(3)). HPLC/MS (30 min) retention time 15.35 min. LRMS: *m/z* 477 (M + 1).

5.7.10. (5-Methyl-4-{2-[(2-methylphenyl)sulfonyl]benzyl}-3-phenyl-1H-pyrazol-1-yl)acetic acid (**52**)

Following general method I: Yellow solid. Purity 90%. ^{1}H NMR (400 MHz, CDCl3) δ ppm 1.79 (s, 3H, pyrazole Me), 2.36 (s, 3H, PhMe), 3.99 (s, 2H, $ArCH_2Ar$), 4.87 (s, 2H, $COCH_2$), 6.94–6.99 (m, 1H, ArH), 7.09–7.19 (m, 5H, ArH), 7.20–7.24 (m, 1H, ArH), 7.31 (t, 1H, J = 7.52 Hz, ArH), 7.37 - 7.46 (m, 3H, ArH), 8.18 (dd, 1H, J = 7.91, 1.07 Hz, ArH), 8.23–8.28 (m, 1H, ArH). HPLC/MS (30 min) retention time 16.38 min. LRMS: *m/z* 461 (M + 1).

5.7.11. (4-{2-[(2,6-Dimethylphenyl)sulfonyl]benzyl}-5-methyl-3-phenyl-1H-pyrazol-1-yl)acetic acid (**53**)

Following general method I: White solid. Purity 94%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.80 (s, 3H, pyrazole Me), 2.52 (s, 6H, 2× PhMe), 3.93 (s, 2H, $ArCH_2Ar$), 4.89 (s, 2H, $COCH_2$), 6.94–6.98 (m, 1H, ArH), 7.07 (d, 2H, J = 7.62 Hz, $PhSO_2$ meta H), 7.15–7.23 (m, 5H, ArH), 7.24 (d, 1H, J = 7.42 Hz, $PhSO_2$ para H), 7.34–7.39 (m, 2H, ArH), 8.06–8.11 (m, 1H, ArH). HPLC/MS (30 min) retention time 17.05 min. LRMS: *m/z* 475 (M + 1).

5.7.12. (4-{2-[(3-Fluorophenyl)sulfonyl]benzyl}-5-methyl-3-phenyl-1H-pyrazol-1-yl)acetic acid (**54**)

Following general methods K, T: White solid. Purity 99%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.84 (s, 3H, Me), 4.05 (s, 2H, $ArCH_2Ar$), 4.91 (s, 2H, $COCH_2$), 6.97 (d, 1H, J = 7.42 Hz, proximal Ph H(6)), 7.04–7.23 (m, 5H, ArH), 7.52–7.63 (m, 3H, ArH), 7.63–7.80 (m, 3H, ArH), 8.23 (d, 1H, J = 7.42 Hz, terminal Ph H(2)). HPLC/MS (30 min) retention time 16.05 min. LRMS: *m/z* 465 (M + 1).

*5.7.13. (4-{2-[(3-Chlorophenyl)sulfonyl]benzyl}-5-methyl-3-phenyl-1H-pyrazol-1-yl)acetic acid (**55**)*

Following general methods K, T: White solid. Purity 99%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.85 (s, 3H, Me), 4.04 (s, 2H, $ArCH_2Ar$), 4.96 (s, 2H, $COCH_2$), 6.96 (d, 1H, $J = 7.03$ Hz, ArH), 7.07–7.15 (m, 4H, ArH), 7.14–7.22 (m, 1H, ArH), 7.53–7.72 (m, 3H, ArH), 7.81 (d, 1H, $J = 7.82$ Hz, terminal Ph H(6)), 7.87–7.95 (m, 2H, ArH), 8.26 (d, 1H, $J = 1.56$ Hz, terminal Ph H(2)). HPLC/MS (30 min) retention time 16.79 min. LRMS: m/z 481 (M + 1).

*5.7.14. [5-Methyl-3-phenyl-4-(2-{[3-(trifluoromethyl)phenyl] sulfonyl}benzyl)-1H-pyrazol-1-yl]acetic acid (**56**)*

Following general method I: Purity 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.32 (dd, 1H, $J = 7.5$, 1.7 Hz, terminal Ph H(6)), 8.11 (s, 1H, terminal Ph H(2)), 8.07 (d, 1H, $J = 8.2$ Hz, ArH), 7.80 (d, 1H, $J = 7.8$ Hz, ArH), 7.60 (t, 1H, $J = 7.8$ Hz, ArH), 7.50 (td, 1H, $J = 7.6$, 1.5 Hz, ArH), 7.47 (t, 1H, $J = 7.6$ Hz, ArH), 7.03–7.18 (m, 6H, ArH), 4.88 (s, 2H, $COCH_2$), 4.10 (s, 2H, $ArCH_2Ar$), 1.92 (s, 3H, Me). HPLC/MS (30 min) retention time 17.04 min. LRMS: m/z 515 (M + 1).

*5.7.15. (4-{2-[(3-Methoxyphenyl)thio]benzyl}-5-methyl-3-phenyl-1H-pyrazol-1-yl)acetic acid (**57**)*

Following general method I: White solid. Purity 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.14 (br. s. 1H, OH), 7.40–7.44 (m, 1H, ArH), 7.34–7.40 (m, 2H, ArH), 7.22–7.28 (m, 3H, ArH), 7.09–7.20 (m, 3H, ArH), 6.96 (d, 1H, $J = 4.1$ Hz, ArH), 6.74 (d, 2H, $J = 7.0$ Hz, ArH), 6.70 (s, 1H, terminal Ph H(2)), 4.89 (s, 2H, $COCH_2$), 3.97 (s, 2H, $ArCH_2Ar$), 3.72 (s, 3H, OMe), 1.93 (s, 3H, ArMe). HPLC/MS (6 min) retention time 4.66 min. LRMS: m/z 445 (M + 1).

*5.7.16. (4-{2-[(3-Methoxyphenyl)sulfonyl]benzyl}-5-methyl-3-phenyl-1H-pyrazol-1-yl)acetic acid (**58**)*

Following general method I: White solid. Purity 100%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.25–8.32 (m, 1H, ArH), 7.39–7.45 (m, 3H, ArH), 7.33–7.38 (m, 2H, ArH), 7.20 (t, 1H, $J = 7.0$ Hz, ArH), 7.18 (d, 2H, $J = 7.0$ Hz, ArH), 7.12 (m, 2H, ArH), 7.06 (dd, 1H, $J = 7.7$, 1.9 Hz), 7.00 (dd, 1H, $J = 5.0$, 4.0 Hz, ArH), 4.89 (s, 2H, s, $COCH_2$), 4.14 (s, 2H, $ArCH_2Ar$), 3.75 (s, 3H, OMe), 1.85 (s, 3H, ArMe). HPLC/MS (30 min) retention time 15.71 min. LRMS: m/z 477 (M + 1).

*5.7.17. {4-[2-({3-[(Dimethylamino)carbonyl]phenyl}sulfonyl) benzyl]-5-methyl-3-phenyl-1H-pyrazol-1-yl}acetic acid (**59**)*

Following general method I: Pale yellow solid. Purity 97%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.30 (dd, 1H, $J = 7.1$, 2.1 Hz, terminal Ph (H(6)), 7.91 (s, 1H, terminal Ph H(3)), 7.90 (d, 1H, $J = 7.5$ Hz, terminal Ph H(4)), 7.63 (d, 1H, d, $J = 7.6$ Hz, proximal Ph H(3)), 7.53 (t, 1H, $J = 7.8$ Hz, terminal Ph H(5)), 7.37–7.49 (m, 2H, ArH), 7.14–7.25 (m, 5H, ArH), 7.05 (d, 1H, $J = 2.0$ Hz ArH), 4.87 (s, 2H, $COCH_2$), 4.12 (s, 2H, $ArCH_2Ar$), 3.08 (s, 3H, NMe_AMe_B), 2.81 (s, 3H, NMe_AMe_B), 1.76 (s, 3H, ArMe). HPLC/MS (30 min) retention time 13.84 min. LRMS: m/z 518 (M + 1).

*5.7.18. (4-{2-[(3,4-Dimethylphenyl)thio]benzyl}-5-methyl-3-phenyl-1H-pyrazol-1-yl)acetic acid (**60**)*

Following general method I: White solid. Purity 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.42 (dd, 2H, $J = 6.3$, 2.8 Hz, ArH), 7.26–7.31 (m, 3H, ArH), 7.23–7.25 (m, 1H, ArH), 7.10–7.14 (m, 1H, ArH), 7.09 (s, 1H, terminal Ph H(2)), 7.06 (d, 1H, $J = 7.5$ Hz, terminal Ph H(5)), 7.00 (dd, 1H, $J = 7.7$, 1.5 Hz, terminal Ph H(6)), 6.91 (dd, 1H, $J = 5.0$, 4.0, Hz, proximal Ph H(6)), 6.01 (br. s., 1H, ArH), 4.91 (s, 2H, $COCH_2$), 3.99 (s, 2H, $ArCH_2Ar$), 2.24 (s, 3H, PhMe), 2.21 (s, 3H, PhMe), 2.01 (s, 3H, pyrazole Me). HPLC/MS (30 min) retention time 20.49 min. LRMS: m/z 443 (M + 1).

*5.7.19. (4-{2-[(3,4-Dimethylphenyl)sulfinyl]benzyl}-5-methyl-3-phenyl-1H-pyrazol-1-yl)acetic acid (**61**)*

Following general method I: Yellow solid. Purity 93%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.04 (d, 1H, $J = 7.2$ Hz, ArH), 8.01 (s, 1H, terminal Ph H(2)), 7.45 (t, 1H, $J = 7.4$ Hz, ArH), 7.32–7.36 (m, 1H, ArH), 7.26 (m, 6H, ArH), 7.14 (d, 1H, $J = 8.0$ Hz), 6.97 (d, 1H, $J = 7.6$ Hz, proximal Ph H(6)), 4.90 (s, 2H, $COCH_2$), 4.05 (d, 1H, $J = 17.4$ Hz, $ArCH_AH_BAr$), 3.76 (d, 1H, $J = 17.6$ Hz, $ArCH_AH_BAr$), 2.25 (s, 3H, PhMe), 2.20 (s, 3H, PhMe), 1.91 (s, 3H, pyrazole Me). HPLC/MS (30 min) retention time 15.81 min. LRMS: m/z 459 (M + 1).

*5.7.20. (4-{2-[(3,4-Dimethylphenyl)sulfonyl]benzyl}-5-methyl-3-phenyl-1H-pyrazol-1-yl)acetic acid (**62**)*

Following general method I: White solid. Purity 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.27 (dd, 1H, $J = 5.6$, 3.6 Hz, proximal Ph H(3)), 7.60 (s, 1H, terminal Ph H(2)), 7.57 (d, 1H, $J = 7.8$ Hz, terminal Ph H(6)), 7.41 (dd, 2H, $J = 5.7$, 3.5 Hz, ArH), 7.16–7.21 (m, 2H, ArH), 7.13 (d, 2H, $J = 7.5$ Hz, ArH), 7.06 (t, 2H, $J = 7.5$ Hz, pyrazole Ph meta H), 6.98 (dd, 1H, $J = 5.0$, 3.5 Hz, proximal Ph H(6)), 4.90 (2 H, s, $COCH_2$), 4.14 (2 H, s, $ArCH_2Ar$), 2.28 (s, 3H, PhMe), 2.21 (s, 3H, PhMe), 1.88 (s, 3H, pyrazole Me). HPLC/MS (30 min) retention time 16.81 min. LRMS: m/z 475 (M + 1).

*5.7.21. (4-{2-[(4-Fluorophenyl)sulfonyl]benzyl}-5-methyl-3-phenyl-1H-pyrazol-1-yl)acetic acid (**63**)*

Following general methods K, T: White solid. Purity 99%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.86 (s, 3H, ArMe), 4.01 (s, 2H, $ArCH_2Ar$), 4.97 (s, 2H, $COCH_2$), 6.95 (d, 1H, $J = 7.03$ Hz, proximal Ph H(6)), 7.01–7.16 (m, 4H, ArH), 7.15–7.25 (m, 1H, ArH), 7.45 (t, 2H, $J = 8.79$ Hz, terminal Ph H(3) and H(5)), 7.56 (t, 1H, $J = 7.42$ Hz, ArH), 7.60 (td, 1H, $J = 7.42$, 1.56 Hz, ArH), 8.00 (dd, 2H, $J = 8.60$, 5.08 Hz, terminal Ph H(2) and H(6)), 8.25 (d, 1H, $J = 7.42$ Hz, proximal Ph H(3)), 13.15 (br. s., 1H, OH). HPLC/MS (30 min) retention time 15.87 min. LRMS: m/z 465 (M + 1).

*5.7.22. (4-{2-[(4-Chlorophenyl)sulfonyl]benzyl}-5-methyl-3-phenyl-1H-pyrazol-1-yl)acetic acid (**64**)*

Following general methods K, T: White solid. Purity 99%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.87 (s, 3H, ArMe), 4.00 (s, 2H, $ArCH_2Ar$), 4.98 (s, 2H, $COCH_2$), 6.95 (d, 1H, $J = 7.42$ Hz, proximal Ph H(6)), 7.00–7.14 (m, 4H, ArH), 7.13–7.27 (m, 1H, ArH), 7.51–7.66 (m, 2H, ArH), 7.68 (d, 2H, $J = 8.60$ Hz, terminal Ph H(3) and H(5)), 7.92 (d, 2H, $J = 8.60$ Hz, terminal Ph H(2) and H(6)), 8.25 (dd, 1H, $J = 7.4$ and 1.3 Hz, proximal Ph H(3)), 13.13 (br. s., 1H, OH). HPLC/MS (30 min) retention time 16.89 min. LRMS: m/z 481 (M + 1).

*5.7.23. (4-{2-[(4-Methoxyphenyl)sulfonyl]benzyl}-5-methyl-3-phenyl-1H-pyrazol-1-yl)acetic acid (**65**)*

Following general methods K, E: White solid. Purity 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.26 (dd, 1H, $J = 5.5$, 3.5 Hz, ArH), 7.78 (d, 2H, $J = 8.6$ Hz terminal Ph H(2) and H(6)), 7.40 (dd, 2H, $J = 5.7$, 3.3 Hz, ArH), 7.04–7.23 (m, 5H, ArH), 6.97 (d, 1H, $J = 5.5$ Hz, proximal Ph H(6)), 6.89 (d, 2H, $J = 9.0$ Hz, terminal Ph H(3) and H(5)), 4.91 (s, 2H, $COCH_2$), 4.12 (s, 2H, $ArCH_2Ar$), 3.81 (s, 3H, OMe), 1.87 (s, 3H, ArMe). HPLC/MS (30 min) retention time 15.56 min. LRMS: m/z 477 (M + 1).

*5.7.24. [5-Methyl-3-phenyl-4-(2-{[4-(trifluoromethoxy)phenyl] sulfonyl}benzyl)-1H-pyrazol-1-yl]acetic acid (**66**)*

Following general method I: White solid. Purity 97%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.30 (dd, 1H, $J = 7.1$, 2.1 Hz, terminal Ph H(2) and H(6)), 7.91 (d, 2H, $J = 8.8$ Hz, terminal Ph H(3) and H(5)), 7.42–7.54 (m, 2H, ArH), 7.25–7.30 (m, 2H, ArH), 7.22 (t, 1H, $J = 7.1$ Hz, ArH), 7.09–7.19 (m, 4H, ArH), 7.03 (d, 1H, $J = 2.0$ Hz, proximal Ph H(6)), 4.92 (s, 2H, $COCH_2$), 4.11 (s, 2H, $ArCH_2Ar$), 1.89 (s,

3H, ArMe). HPLC/MS (30 min) retention time 17.42 min. LRMS: *m*/*z* 531 (M + 1).

5.7.25. [4-(2-{[4-(Dimethylamino)phenyl]sulfonyl}benzyl)-5-methyl-3-phenyl-1H-pyrazol-1-yl]acetic acid (**67**)

Following general method I gave, upon mCPBA oxidation, 64 mg of the crude N-oxide [4-(2-{[4-(dimethylnitroryl)phenyl]sulfonyl} benzyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl]acetic acid. HPLC/MS (6 min) retention time 3.68 min. LRMS: *m*/*z* 506 (M + 1).

The N-oxide was dissolved in 4 ml methanol. Palladium (10% on carbon, 50 mg) was added and the mixture was stirred at room temperature for 1 h under a hydrogen atmosphere at 50 psi. The mixture was filtered and evaporated under reduced pressure. The resulting residue was purified by reverse-phase chromatography (formic acid buffer) using the SP1 Purification system to give **67** (8 mg, 0.016 mmol, 12% over two steps) as a white solid. Purity 98%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.87 (s, 3H, ArMe), 3.00 (s, 6H, NMe_2), 4.18 (s, 2H, $ArCH_2Ar$), 4.86 (s, 2H, $COCH_2$), 6.57 (d, 2H, J = 9.18 Hz, terminal Ph H(3) and H(5)), 6.92–6.98 (m, 1H, proximal Ph H(6)), 7.05–7.11 (m, 2H, ArH), 7.11–7.20 (m, 3H, ArH), 7.32–7.36 (m, 2H, ArH), 7.66 (d, 2H, J = 8.99 Hz, terminal Ph H(2) and H(6)), 8.19–8.23 (m, 1H, proximal Ph H(3)). HPLC/MS (30 min) retention time 15.82 min. LRMS: *m*/*z* 490 (M+1).

5.7.26. [5-Methyl-4-(2-{[4-(methylsulfonyl)phenyl]sulfonyl} benzyl)-3-phenyl-1H-pyrazol-1-yl]acetic acid (**68**)

Following general methods K, E: white solid. Purity 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.33 (d, 1H, J = 7.0 Hz, proximal Ph H(3)), 8.03 (s, 4H, terminal Ph), 7.51 (br. s., 2H, ArH), 7.19–7.28 (m, 2H, ArH), 7.08–7.16 (m, 4H, ArH), 7.05 (d, 1H, J = 6.6 Hz, proximal Ph H(6)), 4.90 (s, 2H, $COCH_2$), 4.06 (s, 2H, $ArCH_2Ar$), 3.01 (s, 3H, SO_2Me), 1.91 (s, 3H, ArMe). HPLC/MS (30 min) retention time 14.35 min. LRMS: *m*/*z* 525 (M + 1).

5.7.27. {4-[2-(Benzylsulfonyl)benzyl]-5-methyl-3-phenyl-1H-pyrazol-1-yl}acetic acid (**69**)

Following general method I: White solid. Purity 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.73 (d, 1H, J = 7.8 Hz, proximal Ph H(3)), 7.37–7.45 (m, 3H, ArH), 7.28–7.34 (m, 3H, ArH), 7.20–7.28 (m, 4H, ArH), 7.05 (d, 1H, J = 7.8 Hz, proximal Ph H(6)), 7.02 (d, 2H, J = 7.0 Hz, terminal Ph ortho H), 4.94 (s, 2H, $COCH_2$), 4.30 (s, 2H, SO_2CH_2Ar), 4.20 (s, 2H, $ArCH_2Ar$), 1.99 (s, 3H, ArMe). HPLC/MS (30 min) retention time 15.64 min. LRMS: *m*/*z* 461 (M + 1).

5.7.28. {5-Methyl-3-phenyl-4-[2-(quinolin-8-ylsulfonyl)benzyl]-1H-pyrazol-1-yl}acetic acid (**70**)

Following general method I: White solid. Purity 94%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.82 (dd, 1H, J = 4.1, 1.6 Hz quinoline H(2)), 8.69 (dd, 1H, J = 7.4, 1.0 Hz, quinoline H(5)), 8.63 (d, 1H, J = 8.0 Hz, ArH), 8.19 (dd, 1H, J = 8.3, 1.5 Hz, quinoline H(4)), 8.01 (d, 1H, J = 7.4 Hz, ArH), 7.59 (t, 1H, J = 7.7 Hz, ArH), 7.45 (dd, 1H, J = 8.3, 4.1 Hz quinoline H(3)), 7.44 (d, 1H, J = 8.0 Hz, ArH), 7.36 (t, 1H, J = 7.0 Hz, ArH), 7.04 (t, 1H, J = 7.4 Hz, ArH), 7.00 (d, 2H, J = 7.4 Hz, Ph ortho), 6.89 (d, 1H, J = 7.6 Hz, proximal Ph H(6)), 6.79 (t, 2H, J = 7.7 Hz Ph meta), 4.82 (s, 2H, $COCH_2$), 4.10 (s, 2H, $ArCH_2Ar$), 1.74 (s, 3H, Me). HPLC/MS (30 min) retention time 14.49 min. LRMS: *m*/*z* 498 (M+1).

5.7.29. Ethyl 2-(5-methyl-4-(2-(naphthalen-1-yl)benzyl)-3-phenyl-1H-pyrazol-1-yl)acetate (**71**)

A mixture of **36** (78 mg, 0.17 mmol), naphthylen-1-ylboronic acid (44 mg, 0.26 mmol), [1,1′-bis(diphenylphosphino)ferrocene] palladium(II) dichloride (7 mg, 0.01 mmol) and caesium carbonate solution (2 M, 0.25 ml, 0.5 mmol) were suspended in 3.5 ml dioxane in a pressure tube. The solution was degassed, the tube sealed and the mixture stirred at 90 °C overnight. The mixture was filtered through Celite and the filtrate was evaporated under reduced pressure. The residue was partitioned between ethyl acetate and water. The organics were washed with brine, dried over magnesium sulphate, filtered and evaporated under reduced pressure. The residue was purified using the SP1 Purification System (ethyl acetate–hexane gradient, 0:100 rising to 20:80). to give ethyl 2-(5-methyl-4-(2-(naphthalen-1-yl)benzyl)-3-phenyl-1*H*-pyrazol-1-yl) acetate (54 mg, 0.12 mmol, 69%) as a pale yellow solid. HPLC/MS (9 min) retention time 7.68 min. LRMS: *m*/*z* 461 (M + 1).

The ester (52 mg, 0.11 mmol) was dissolved in 1 ml tetrahydrofuran and 1 ml water. Lithium hydroxide monohydrate (24 mg, 0.57 mmol) was added and the mixture was stirred for 2 h. The organics were evaporated under reduced pressure and the mixture was acidified to pH 4 with dilute hydrochloric acid, forming a white precipitate. The solid was collected by filtration, was washed with water and was dried under vacuum to give **71** (34 mg, 0.079 mmol, 70%) as a white solid. Purity 100%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.13 (br. s. 1H, OH), 8.00 (d, 1H, J = 7.4 Hz, ArH), 7.96 (d, 1H, J = 8.2 Hz, ArH), 7.60 (t, 1H, J = 7.6 Hz, ArH), 7.49–7.57 (m, 2H, ArH), 7.43–7.49 (m, 2H, ArH), 7.33–7.40 (m, 2H, ArH), 7.17–7.30 (m, 6H, ArH), 6.97–7.04 (m, 1H, ArH), 4.94 (s, 2H, CH_2CO), 3.55 (d, 1H, J = 17.0 Hz, $ArCH_ACH_BAr$), 3.37 (d, 1H, J = 17.0 Hz, $ArCH_ACH_BAr$), 2.02 (s, 3H, Me). HPLC/MS (30 min) retention time 19.65 min. LRMS: *m*/*z* 433 (M + 1).

5.7.30. {3,5-Dimethyl-4-[2-(phenylsulfonyl)benzyl]-1H-pyrazol-1-yl}acetic acid (**72**)

Following general methods K, E: White solid. Purity 98%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.25 (d, 1H, J = 7.4 Hz, proximal Ph H(3)), 7.88 (d, 2H, J = 7.8 Hz, $PhSO_2$ ortho H), 7.58 (t, 1H, J = 7.4 Hz, $PhSO_2$ para H), 7.51 (t, 2H, J = 7.6 Hz, $PhSO_2$ meta H), 7.44 (t, 1H, J = 7.4 Hz, proximal Ph H(5)), 7.40 (t, 1H, J = 7.4 Hz, proximal Ph H(4)), 6.89 (d, 1H, J = 7.4 Hz, proximal Ph H(6)), 4.73 (s, 2H, $COCH_2$), 3.94 (br. s., 2H, $ArCH_2Ar$), 1.86 (s, 3H, pyrazole-3-Me), 1.80 (s, 3H, pyrazole-5-Me). HPLC/MS (30 min) retention time 13.45 min. LRMS: *m*/*z* 385 (M + 1).

5.7.31. 2-(3-Hydroxy-5-methyl-4-(2-(phenylsulfonyl)benzyl)-1H-pyrazol-1-yl)acetic acid (**73**)

Following general methods K, T: White solid. Purity 100%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.62 (s, 3H, Me), 3.76 (s, 2H, $ArCH_2Ar$), 4.56 (s, 2H, CH_2CO), 7.17 (d, 1H, J = 6.64 Hz, proximal Ph H(6)), 7.48–7.54 (m, 1H, ArH), 7.55–7.60 (m, 1H, ArH), 7.61–7.67 (m, 2H, ArH), 7.70–7.75 (m, 1H, ArH), 7.86–7.91 (m, 2H, ArH), 8.15 (dd, 1H, J = 7.82, 1.56 Hz, proximal Ph H(3)), 11.52 (s, 1H, OH, possibly as NH tautomer). HPLC/MS (30 min) retention time 11.25 min. LRMS: *m*/*z* 387 (M + 1).

5.7.32. 2-(3-Methoxy-5-methyl-4-(2-(phenylsulfonyl)benzyl)-1H-pyrazol-1-yl)acetic acid (**74**)

Following general methods K, T: The methoxy group was introduced as follows:

Prior to deprotection to give **73**, *tert*-butyl 2-(3-hydroxy-5-methyl-4-(2-(phenylsulfonyl)benzyl)-1*H*-pyrazol-1-yl)acetate (36 mg, 0.08 mmol) was dissolved in 5 ml acetone. Potassium carbonate (23 mg, 0.16 mmol) and dimethyl sulphate (8 μl, 0.08 mmol) were added and the mixture was stirred at reflux overnight. The mixture evaporated under reduced pressure and the residue was partitioned between ethyl acetate and water. The organics were washed with brine, dried over magnesium sulphate, filtered and evaporated under reduced pressure. The residue was purified using the SP1 Purification System (ethyl acetate–hexane gradient, 0:100 rising to 100:0) to give tert-butyl 2-(3-methoxy-5-methyl-4-(2-(phenylsulfonyl)benzyl)-1*H*-pyrazol-1-yl)acetate

(15 mg, 0.03 mmol, 41%) as a colourless oil. HPLC/MS (9 min) retention time 6.77 min. LRMS: *m*/*z* 457 (M + 1).

Deprotection according to general method T gave **74**. White solid. Purity 98%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.84 (s, 3H, Me), 3.59 (s, 3H, OMe), 3.91 (s, 2H, $ArCH_2Ar$), 4.63 (s, 2H, CH_2CO), 7.18 (d, 1H, J = 7.42 Hz, proximal Ph H(6)), 7.35–7.42 (m, 1H, ArH), 7.43–7.54 (m, 3H, ArH), 7.54–7.62 (m, 1H, ArH), 7.83–7.90 (m, 2H, ArH), 8.13–8.26 (m, 1H, proximal Ph H(3)). HPLC/MS (30 min) retention time 11.95 min. LRMS: *m*/*z* 401 (M + 1).

5.7.33. {5-Methyl-4-[2-(phenylsulfonyl)benzyl]-3-pyrimidin-5-yl-1H-pyrazol-1-yl}acetic acid (**75**)

Following general methods D, A, T: White solid. Purity 95%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.84 (s, 3H, Me), 4.07 (s, 2H, $ArCH_2Ar$), 5.01 (s, 2H, $COCH_2$), 6.91–6.96 (m, 1H, proximal Ph H(6)), 7.55–7.60 (m, 2H, ArH), 7.60–7.65 (m, 2H, ArH), 7.68–7.74 (m, 1H, ArH), 7.88–7.92 (m, 2H, ArH), 8.20–8.24 (m, 1H, ArH), 8.53 (s, 2H, pyrimidine H(4) and H(6)), 9.01 (s, 1H, pyrimidine H(2)), 12.71–13.25 (br. s, 1H, OH). HPLC/MS (30 min) retention time 12.75 min. LRMS: *m*/*z* 449 (M + 1).

5.7.34. {5-Methyl-4-[2-(phenylsulfonyl)benzyl]-3-pyridin-4-yl-1H-pyrazol-1-yl}acetic acid (**76**)

Following general methods D, A, T: White solid. Purity 98%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.87 (s, 3H, Me), 4.08 (s, 2H, $ArCH_2Ar$), 5.01 (s, 2H, $COCH_2$), 6.85–6.89 (m, 1H, proximal Ph H(6)), 6.99–7.02 (m, 2H, ArH), 7.55–7.59 (m, 2H, ArH), 7.63–7.69 (m, 2H, ArH), 7.71–7.77 (m, 1H, ArH), 7.93–7.97 (m, 2H, ArH), 8.23–8.29 (m, 3H, ArH), 13.24 (s, 1H, OH). HPLC/MS (30 min) retention time 10.21 min. LRMS: *m*/*z* 448 (M + 1).

5.7.35. {3-(2,5-Dichlorophenyl)-5-methyl-4-[2-(phenylsulfonyl) benzyl]-1H-pyrazol-1-yl}acetic acid (**77**)

Following general methods D, K, T: White solid. Purity 97%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.19 (d, 1H, J = 7.4 Hz, proximal Ph H(3)), 7.78 (d, 2H, J = 7.4 Hz, terminal Ph ortho), 7.54 (t, 1H, J = 7.4 Hz, terminal Ph para), 7.44 (t, 2H, J = 7.8 Hz, terminal Ph meta), 7.33–7.43 (m, 2H, ArH), 7.22 (d, 1H, J = 8.4 Hz, Cl_2Ph H(3)), 7.17 (dd, 1H, J = 8.4, 2.5 Hz, Cl_2Ph H(4)), 7.04 (d, 1H, J = 2.3 Hz, Cl_2Ph H(6)), 6.96 (d, 1H, J = 7.4 Hz, proximal Ph H(6)), 4.89 (s, 2H, $COCH_2$), 3.97 (s, 2H, $ArCH_2Ar$), 1.94 (s, 3H, ArMe). HPLC/MS (30 min) retention time 16.71 min. LRMS: *m*/*z* 515 (M + 1).

5.7.36. 2-(3-(4-(Dimethylcarbamoyl)phenyl)-5-methyl-4-(2-(phenylsulfonyl)benzyl)-1H-pyrazol-1-yl)acetic acid (**78**)

Following general methods D, K, T: White solid. Purity 98%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.27–8.33 (m, 1H, proximal Ph H(3)), 7.87 (d, 2H, J = 7.8 Hz, terminal Ph ortho), 7.60 (t, 1H, J = 7.4 Hz, terminal Ph para), 7.50 (t, 2H, J = 7.6 Hz, terminal Ph meta), 7.42–7.46 (m, 2H, ArH), 7.24 (d, 2H, J = 7.0 Hz, PhCO H(3) and H(5)), 7.20 (d, 2H, J = 7.0 Hz, PhCO H(2) and H(6)), 6.93–7.01 (m, 1H, proximal Ph H(6)), 4.87 (s, 2H, CH_2CO), 4.13 (s, 2H, $ArCH_2Ar$), 3.11 (s, 3H, $CONMe_AMe_B$), 2.94 (s, 3H, $CONMe_AMe_B$), 1.86 (s, 3H, Me).). HPLC/MS (30 min) retention time 13.88 min. LRMS: *m*/*z* 518 (M + 1).

5.7.37. {5-Methyl-3-(morpholin-4-ylcarbonyl)-4-[2-(phenylsulfonyl)benzyl]-1H-pyrazol-1-yl}acetic acid (**79**)

Following general methods K, E: White solid. Purity 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.11 (d, 1H, J = 7.9 Hz, proximal Ph H(3)), 7.86 (d, 2H, J = 7.6 Hz, terminal Ph ortho), 7.63–7.54 (m, 1H, ArH), 7.51 (t, 2H, J = 7.3 Hz, terminal Ph meta), 7.47–7.39 (m, 1H, ArH), 7.34 (t, 1H, J = 7.4 Hz, ArH), 7.03 (d, 1H, J = 7.0 Hz, proximal Ph H(6)), 4.68 (s, 2H, $COCH_2$), 4.06 (s, 2H, $ArCH_2Ar$), 3.49 (s, 4H, NCH_2CH_2O), 3.33 (s, 4H, NCH_2CH_2O), 1.86 (s, 3H, Me). HPLC/MS (30 min) retention time 12.62 min. LRMS: *m*/*z* 484 (M + 1).

5.8. CRTh2 GTPγS antagonism binding assay

The assay was performed by pre-incubating 4–8 μg 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 μM GDP, 10 μg/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.

5.9. CRTh2 radioligand binding serum shift assay

The assay was performed as above, replacing 0.2% BSA of the incubation buffer with 1% HSA.

5.10. CRTh2 isolated cell eosinophil cell shape assay

Citrated whole blood was obtained from consenting donors and polymorphonuclear (OMN) leukocytes were obtained by gradient centrifugation on Polymorphprep for 40 min at 500G brake off. The PMN fraction was re-suspended in calcium free buffer (10 mM HEPES, 10 mM glucose, 0.1% BSA in calcium free PBS) and centrifuged for 10 min at 400G at room temperature. Red blood cells were lysed by adding 20 ml of 0.2% saline buffer (0.2% NaCl) for 40 s and stopped by adding 20 ml of 1.6% saline buffer (1.6% NaCl). For compound treatment, 90 μl of PMNs cells (re-suspended at a density of 5×10^6 cells/ml in 10 mM HEPES, 10 mM glucose, 0.1% BSA in calcium containing PBS) were incubated for 10 min with 10 μl of compound to be tested followed by incubation with 10 μl of 500 nM PGD_2 for exactly 4 min at 37 °C. Fixation was performed by addition of 0.2 ml of ice-cold 1:5 diluted CellFix (BD Biosciences) and samples were immediately analysed on a FACSCalibur (BD Biosciences). Eosinophils were gated on the basis of auto-fluorescence in the FL2 channels and shape change of 600 cells was assayed by forward scatter and side scatter analysis. Compound IC_{50}s were determined using Excel XL-fit for calculations.

5.10.1. CRTh2 whole blood eosinophil cell shape assay

Whole blood obtained from consenting donors was mixed with heparin and kept in rotation until use. For compound treatment, 90 μl of blood was mixed with 10 μl of compound to be tested and incubated for 10 min at room temperature followed by addition of 10 μl of 500 nM PGD_2 for exactly 4 min at 37 °C. The reaction was stopped by placing the tubes on ice and adding of 0.25 ml of ice-cold 1:5 diluted CellFix (BD Biosciences). Red blood cells were lysed in two steps by adding 2 ml of lysis solution (150 mM ammonium chloride, 10 mM potassium hydrogencarbonate), incubating for 20 and 10 min respectively and centrifuging at 300G for 5 min at 6 °C. The pellet was re-suspended in 0.2 ml fixative solution and immediately analysed on a FACSCalibur (BD Biosciences). Eosinophils were gated on the basis of auto-fluorescence in the FL2 channels and shape change of 600 cells was assayed by forward scatter and side scatter analysis. Compound IC_{50}s were determined using Excel XL-fit for calculations.

Acknowledgements

The authors thank the following for their valuable assistance in the experimental procedures: Manel de Luca, José Luís Gómez, Encarna Jiménez, Francisco Jiménez, Juan Navarro, Isabel Pagan and Sílvia Petit.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2013.10.072.

References

[1] R.A. Lewis, N.A. Soter, P.T. Diamond, K.F. Austen, J.A. Oates, L.J. Roberts II, J. Immunol. 129 (1982) 1627.
[2] Y. Urade, M. Ujihara, Y. Horiguchi, K. Ikai, O. Hayaishi, J. Immunol. 143 (1989) 2982;
K. Tanaka, K. Ogawa, K. Sugamura, M. Nakamura, S. Takano, K. Nagata, J. Immunol. 164 (2000) 2277.
[3] R.A. Coleman, R.L.G. Sheldrick, Br. J. Pharmacol. 96 (1989) 688;
H.P. Francis, S.J. Greenham, U.P. Patel, A.M. Thompson, P.J. Gardiner, Br. J. Pharmacol. 104 (1991) 596.
[4] Y. Boie, N. Saywer, D.M. Slipetz, K.M. Metters, M. Abramovitz, J. Biol. Chem. 270 (1995) 18910.
[5] K. Nagata, K. Tanaka, K. Ogawa, K. Kemmotsu, T. Imai, O. Yoshie, H. Abe, K. Tada, M. Nakamura, K. Sugamura, S. Takano, J. Immunol. 162 (1999) 1278;
W.S. Powell, Prostaglandins Leukot. Essent. Fatty Acids 69 (2003) 179.
[6] H. Hirai, K. Tanaka, O. Yoshie, K. Ogawa, K. Kenmotsu, Y. Takamori, M. Ichimasa, K. Sugamura, M. Nakamura, S. Takano, K. Nagata, J. Exp. Med. 193 (2001) 255;
M. Shichijo, H. Sugimoto, K. Nagao, H. Inbe, J.A. Encinas, K. Takeshita, K.B. Bacon, F. Gantner, J. Pharmacol. Exp. Ther. 307 (2003) 518.
[7] L. Xue, A. Barrow, R. Pettipher, J. Immunol. 182 (2009) 7580.
[8] L. Xue, S.L. Gyles, F.R. Wettey, L. Gazi, E. Townsend, M.G. Hunter, R. Pettipher, J. Immunol. 175 (2005) 6531.
[9] J.C. Medina, J. Liu, Annu. Rep. Med. Chem. 41 (2006) 221.
[10] T. Ulven, E. Kostenis, Expert Opin. Ther. Patents (2010) 1505.
[11] P. Norman, Expert Opin. Investig. Drugs 19 (2010) 947.
[12] L. Burgess, Annu. Rep. Med. Chem. 46 (2011) 119.
[13] J.J. Chen, A.L. Budelsky, Prog. Med. Chem. 50 (2011) 49.
[14] R. Pettipher, M. Whittaker, J. Med. Chem. 55 (2012) 2915.
[15] H. Hirai, K. Tanaka, S. Takano, M. Ichimasa, M. Nakamura, K. Nagata, J. Immunol. 168 (2002) 981.
[16] H. Sugimoto, M. Shichijo, T. Iino, Y. Manabe, A. Watanabe, M. Shimazaki, F. Gantner, K.B. Bacon, J. Pharmacol. Exp. Ther. 305 (2003) 347.
[17] M. Andrés, M. Bravo, M.A. Buil, M. Calbet, J. Castro, T. Domènech, P. Eichhorn, M. Ferrer, E. Gómez, M.D. Lehner, I. Moreno, R.S. Roberts, S. Sevilla, Bioorg. Med. Chem. Lett. 23 (2013) 3349.
[18] J. Elguero, in: A.R. Katritzky, C.W. Rees, E.F.V. Scriven (Eds.), Comprehensive Heterocyclic Chemistry II, Vol. 3, Pergamon Press, Oxford, 1996;
G. Coispeau, J. Elguero, Bull. Chim. Soc. Fr (1970) 2717;
G. Coispeau, J. Elguero, R. Jacquier, Bull. Chim. Soc. Fr (1970) 689;
R. Lazaro, D. Mathieu, R. Phan Tan Luu, J. Elguero, Bull. Chim. Soc. Fr (1977) 1163;
H. Garcia, S. Iborra, M.A. Miranda, I.M. Morera, J. Primo, Heterocycles 32 (1991) 1746.
[19] For similar examples of regioselective pyrazole alkylation, see: (a) R. Noël, Y. Shin, X. Song, Y. He, M. Koenig, W. Chen, Y.Y. Ling, L. Lin, C.H. Ruiz, P. LoGrasso, M.D. Cameron, D.R. Duckett, T.M. Kamenecka, Bioorg. Med. Chem. Lett. 21 (2011) 2732;
(b) P.A. Bradley, P.D. de Koning, K.R. Gibson, Y.C. Lecouturier, M.C. MacKenny, I. Morao, C. Poinsard, T.J. Underwood, Synlett (2010) 873;
(c) J.M. Ralph, T.H. Faitg, D.J. Silva, Y. Feng, C.W. Blackledge, J.L. Adams, Tetrahedron Lett. 50 (2009) 1377;
(d) T.I. Savchenko, O.V. Silin, S.M. Kovalenko, V.I. Musatov, V.M. Nikitchenko, A.V. Ivachtchenko, Synth. Commun. 37 (2007) 1321.
[20] S.T. Heller, S.R. Natarajan, Org. Lett. 8 (2006) 2675.
[21] All final compounds derived from these minor regioisomers were inactive (data not shown).
[22] Compound potencies were initially measured by both [^{35}S]-GTPγS binding assay and a [^{3}H]-PGD_2 displacement assay. As we saw a good correlation ($r^2 = 0.88$, $n = 27$), the GTPγS assay was chosen as the preferred method.
[23] Masood and co-workers have also highlighted a low hit rate for a CRTh2-focussed library of pyrazoles M.A. Masood, M. Gardner, K. Dack, D. Winpenny, G. Lunn, Bioorg. Med. Chem. Lett. 22 (2012) 3682.
[24] G.L. Trainor, Exp. Opin. Drug Discov. 2 (2007) 51;
D.A. Smith, L. Di, E.H. Kerns, Nat. Rev. Drug Discov. 9 (2010) 919;
X. Liu, C. Chen, C.E.C.A. Hop, Curr. Top. Med. Chem. 11 (2011) 450.