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Identification of [4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)-2-pyrimidinyl] amines and ethers as potent and selective cyclooxygenase-2 inhibitors

Martin E. Swarbrick [§§], Paul J. Beswick [†], Robert J. Gleave [*], Richard H. Green, Sharon Bingham, Chas Bountra [†], Malcolm C. Carter [‡], Laura J. Chambers, Iain P. Chessell [§], Nick M. Clayton, Sue D. Collins, John A. Corfield, C. David Hartley [¶], Savvas Kleanthous, Paul F. Lambeth, Fiona S. Lucas, Neil Mathews [‡], Alan Naylor, Lee W. Page, Jeremy J. Payne, Neil A. Pegg [||], Helen S. Price, John Skidmore, Alexander J. Stevens, Richard Stocker, Sharon C. Stratton, Alastair J. Stuart [††], Joanne O. Wiseman

Pain and Neuroexcitability Discovery Performance Unit, Neurosciences Centre of Excellence for Drug Discovery, GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK

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ABSTRACT

A novel series of [4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)-2-pyrimidine-based cyclooxygenase-2 (COX-2) inhibitors, which have a different arrangement of substituents compared to the more common 1,2-diarylheterocycle based molecules, have been discovered. For example, 2-(butyloxy)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine (**47**), a member of the 2-pyrimidinyl ether series, has been shown to be a potent and selective inhibitor with a favourable pharmacokinetic profile, high brain penetration and good efficacy in rat models of hypersensitivity.

The demonstration that early selective inhibitors of cyclooxygenase-2 (COX-2), such as DuP697 (**1**)[1] and SC 58125 (**2**, Fig. 1),[2] could produce analgesic effects in preclinical models that was not accompanied by the typical gastrointestinal toxicity associated with nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin and indomethacin provoked intense interest in the area, and several groups have since reported potent and selective COX-2 inhibitors. The clinical promise of this class has been fulfilled by

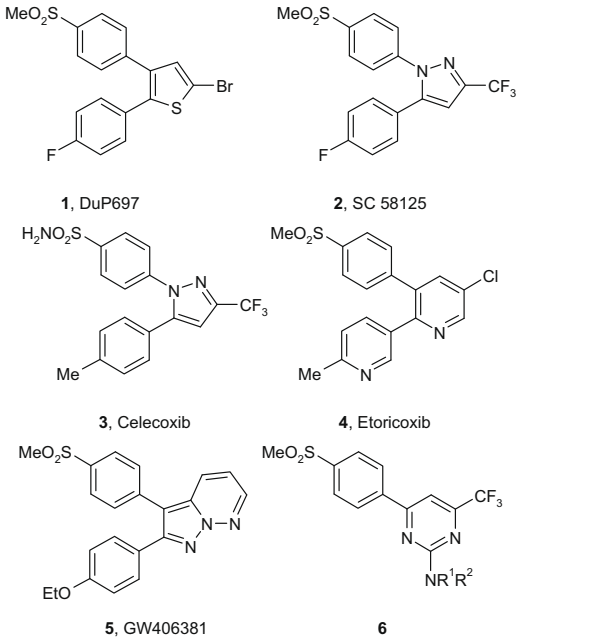

Figure 1.

* Corresponding author. Tel.: +44 1279 643079.
E-mail address: robert.j.gleave@gsk.com (R.J. Gleave).
† Present address: Structural Genomics Consortium (SGC), University of Oxford, Old Road Campus Research Building, Old Road Campus, Roosevelt Drive, Headington, Oxford OX3 7DQ, UK.
‡ Present address: Arrow Therapeutics, Britannia House, 7 Trinity Street, London SE1 1DA, UK.
§ Present address: MedImmune, Milstein Building, Granta Park, Cambridge CB21 6GH, UK.
¶ Present address: BioFocus DPI, Chesterford Research Park, Saffron Walden, Essex CB10 1XL, UK.
|| Present address: CellCentric Ltd, Chesterford Research Park, Little Chesterford, Cambridge CB10 1XL, UK.
†† Present address: Takeda Global Research and Development Centre Europe Ltd., 61 Aldwych, London WC2B 4AE, UK.
§§ Discovery Laboratory, Cancer Research Technology Ltd., 12 Rosemary Lane, Cambridge CB1 3LQ, UK.

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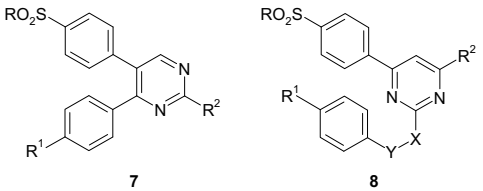
the marketed inhibitors (for example, celecoxib (**3**) and etoricoxib (**4**), Fig. 1) which demonstrate clinical efficacy equivalent to NSAIDs in the treatment of inflammatory and musculoskeletal pain, but with an improved gastric safety profile. Despite concerns about the safety of selective COX-2 inhibitors, raised since the withdrawal of rofecoxib due to evidence of increased cardiovascular risk, their potential therapeutic utility has now been extended into the areas of neurodegenerative disorders[3] and cancer.[4]

At the outset of our work in the area, all of the reported potent and selective COX-2 inhibitors featured a 1,2-diaryl substituted heterocyclic ring which represents the typical core template associated with this class, and we have recently reported the identification of GW406381 (**5**)[5] as well as demonstrating that a series of 4,5-diarylpyrimidines showed good activity against COX-2 with selectivity over COX-1.[6] We report here our discovery and investigation of a novel 4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)-2-pyrimidine-based series of COX-2 inhibitors,[7] introducing for the first time a 1,3,5-arrangement of substituents around a 6-membered heterocyclic ring **6**. Recently, the identification of an isomeric series of pyrimidine COX-2 inhibitors has also been reported.[8]

As part of an exercise to identify novel templates we studied the structural requirements for potency and selectivity within the 1,2-diaryl-heterocyclic series and concluded that there were three fundamental requirements, illustrated by the pyrimidine **7**. A phenylsulfonyl group appears critical for both potency and selectivity, adjacent to this a lipophilic aryl group often bearing a substituent R^1 is preferred and a small hydrophobic moiety on the heterocycle R^2 commonly confers additional potency. We proposed that a 2,4,6-trisubstituted heterocycle **8** would be capable of adopting a similar conformation to the 1,2 diaryl template **7** if a linker (*X*–*Y*) were introduced between the core ring and the second aryl group. This proposal was supported by molecular modelling studies (Fig. 2) which showed a good overlay of the minimum energy conformations of **7** (black) and **8** (magenta).

To test the hypothesis we initially prepared a series of 2,4,6-trisubstituted pyrimidines **13**–**18** as shown in Scheme 1.[9] The commercially available chloropyrimidine **9** underwent Suzuki coupling in good yield to give the sulfinylphenylpyrimidine **10**. A double oxidation using Oxone® efficiently converted both sulfide groups to sulfones and the resulting 2-sulfonyl pyrimidine **11** reacted readily with a number of amines to give the desired products **13**–**18**. The amines chosen were aniline, benzylamine and derivatives substituted in the 4-position with either fluorine or methyl, groups known to confer potency in the 1,2 diaryl series. The 6-trifluoromethyl substituent was chosen as molecular modeling



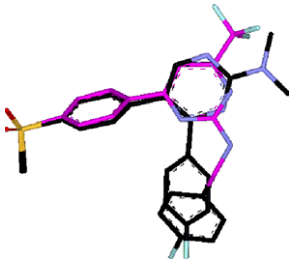
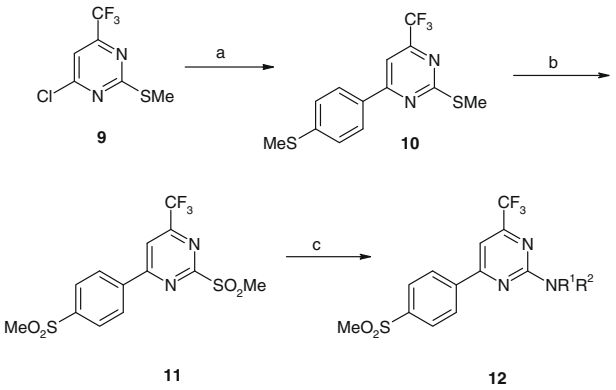


Figure 2. Overlay of minimal energy conformations of **7** and **8**.



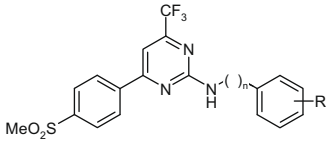
Scheme 1. Reagents: (a) 4(methylthio)phenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, DME, H_2O, 82%; (b) oxone, H_2O, MeOH, 91%; (c) R_1R_2NH, MeCN.

suggested this should bind in a similar area of the enzyme to the trifluoromethyl group in celecoxib (**3**) where it has been shown to be optimal for the small hydrophobic pocket in which it is believed to bind.[10]

Preliminary results are shown in Table 1. Encouragingly both the aniline and benzylamine derived compounds showed high levels of both potency and selectivity. The benzylamine derivatives demonstrated the greater potency, possibly due to the length of the linker allowing the aromatic ring to better fit the binding site.

Given the encouraging profiles of the compounds in Table 1 we were keen to further explore structure activity relationships within this novel series of COX-2 inhibitors and prepared a number of analogues in which the nature of the groups (R^1 and R^2, compound **12**) attached to the 2-amino group were varied. Investigation of the synthetic route used to prepare these molecules identified an optimized procedure for formation of the key intermediate **11** which is shown in Scheme 2.[9] 4-(Methylthio)acetophenone **19** is condensed with ethyl trifluoroacetate in the presence of base, giving the diketone **20** which is condensed with *S*-methylisothiourea without isolation to give the pyrimidine **10** in quantitative yield for the two steps. Oxidation using Oxone® again efficiently produces **11**. Compounds **21**–**33** were prepared from compound **11** in good yield and results are shown in Table 2.

Table 1
COX-2 inhibition and selectivity data for an initial set of compounds **13**–**18**



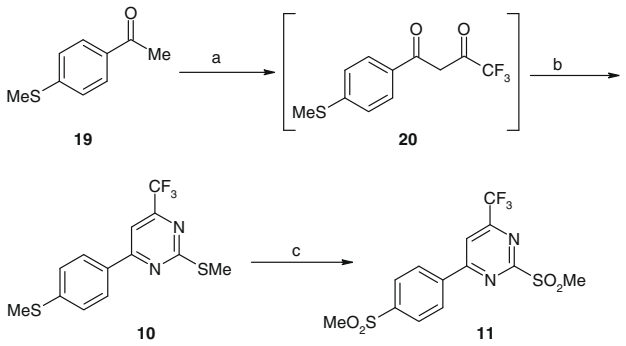
13-18

Compound	R	n	IC_{50} COX-2[a] (nM)	IC_{50} COX-1[b] (nM)	Selectivity[c]
13	H	0	5.6	>1,00,000	>17,857
14	4-Me	0	11	>1,00,000	>9090
15	4-F	0	7.2	>65,800	>9138
16	H	1	0.25	>1,00,000	>4,00,000
17	4-Me	1	<10	>1,00,000	>10,000
18	4-F	1	0.28	>1,00,000	>3,57,142
Celecoxib (**3**)	—	—	68	1689	4
Rofecoxib	—	—	32	>1,00,000	>3125
Valdecoxib	—	—	183	>1,00,000	>546
Etoricoxib (**4**)	—	—	347	>1,00,000	>288

[a] IC_{50} values for inhibition of PGE_2 produced by arachidonic acid stimulated COS cells stably expressing human COX-2 as described in Ref. 14 are an average of two determinations.

[b] IC_{50} values for inhibition of PGE_2 produced by arachidonic acid stimulated COS cells stably expressing human COX-1 as described in Ref. 14 are an average of two determinations.

[c] IC_{50} value for COX-1 divided by IC_{50} value against COX-2.



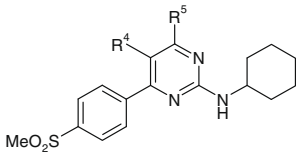
Scheme 2. Reagents: (a) Ethyl trifluoroacetate, NaH, DMF; (b) S-methylisothiourea, CH_3CN, ~100% for two steps; (c) oxone, H_2O, MeOH, 91%.

Interestingly a number of highly potent, selective molecules were produced, with analogues containing alkyl groups retaining the potency of the corresponding phenyl and benzyl derivatives. Potency was optimal when alkyl and cycloakyl groups (**22**–**27**) were present and the primary amino derivative **21** showed some activity. As reported with other series of COX-2 inhibitors the sulfone could be replaced by a sulfonamide group with retention of activity but accompanied by a drop in selectivity (**24**, **27**). Acyclic tertiary amines were tolerated (e.g., **31**), however cyclic tertiary amines were not (**32**). Introduction of any degree of polarity also resulted in a loss of activity (e.g., **33**).

We next investigated SAR around the 5 and 6 positions of the pyrimidine ring. Results are shown in Table 3 for the *N*-cyclohexyl series (R^1 = cyclohexyl, R^2 = H), and similar trends were observed for other active R^2 groups.

The compounds shown in Table 3 were prepared by the synthetic route illustrated in Scheme 3, a modification of that used to prepare the initial analogues as shown in Scheme 1. Commercial 2,4-dichloropyrimidines (**34**) underwent a selective Suzuki coupling, followed by oxidation to introduce the (methylsulfonyl)phenyl group in the 4-position. The 2-amino groups were then introduced by displacement of chloride. This route was used to prepare all of the compounds shown in Table 3 with the exception of compound **39** which was prepared as shown in Scheme 2.

Table 3
COX-2 inhibition and selectivity data for compounds **26** and **38**–**45**

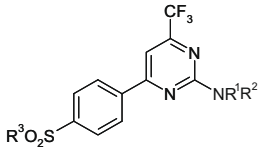


Compound	R^4	R^5	IC_{50} COX-2[a] (nM)	IC_{50} COX-1[b] (nM)	Selectivity[c]
26	H	CF_3	0.5	>58,400	>11,6800
38	H	OCH_2CF_3	16	6321	395
39	Me	CF_3	>10,000	>1,00,000	—
40	H	Me	1683	>1,00,000	>59
41	Me	H	>10,000	>1,00,000	—
42	H	H	>10,000	>1,00,000	—
43	H	NH_2	>10,000	>1,00,000	—
44	H	CO_2H	>10,000	>1,00,000	—
45	H	$CONH_2$	>10,000	>1,00,000	—

[a] IC_{50} values for inhibition of PGE2 produced by arachidonic acid stimulated COS cells stably expressing human COX-2 as described in Ref. 14 are an average of two determinations.
[b] IC_{50} values for inhibition of PGE2 produced by arachidonic acid stimulated COS cells stably expressing human COX-1 as described in Ref. 14 are an average of two determinations.
[c] IC_{50} value for COX-1 divided by IC_{50} value against COX-2.

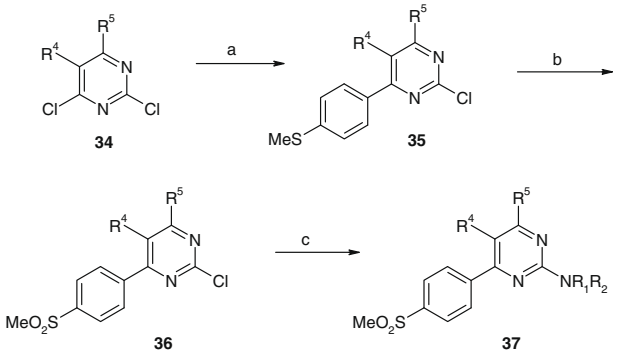
As discussed earlier, the trifluoromethyl group had been initially chosen following molecular modeling studies which suggested that this substituent should bind in a similar area of the enzyme to the trifluoromethyl group in celecoxib (**3**) where it has been shown to be optimal for the small hydrophobic pocket in which it is believed to bind,[10] and the data in Table 3 suggests that our hypothesis was correct. Increasing or reducing the size and lipophilicity of R^5 results in decreased activity (e.g., **38** and **40**), and polar functionality does not appear to be tolerated (**43**–**45**). Introduction of a methyl group on the carbon adjacent to the phenyl group also results in a loss of activity (**39** and **41**); we

Table 2
COX2 inhibition and selectivity data for compounds **21**–**33**



Compound	R^1	R^2	R^3	IC_{50} COX-2[a] (nM)	IC_{50} COX-1[b] (nM)	Selectivity[c]
21	H	H	Me	272	>1,00,000	>368
22	nPr	H	Me	5	>1,00,000	>2000
23	*n*Bu	H	Me	1.3	>1,00,000	>76,923
24	*n*Bu	H	NH_2	<1.4	700	>500
25	*i*Bu	H	Me	2	>66,200	>33,100
26	Cyclohexyl	H	Me	0.5	>58,400	>1,16,800
27	Cyclohexyl	H	NH_2	2.4	167	69.5
28	Cyclohexylmethyl	H	Me	29	>1,00,000	>3448
29	4-Tetrahydropyranyl	H	Me	18	>91,629	>5090
30	4-Tetrahydropyranylmethyl	H	Me	5	100,000	20,000
31	4-Methylphenyl	Me	Me	3	>74,175	>24,725
32		$-(CH_2)_5-$		>10,000	>1,00,000	—
33	4-Piperidinyl	H	Me	>10,000	>1,00,000	—

[a] IC_{50} values for inhibition of PGE_2 produced by arachidonic acid stimulated COS cells stably expressing human COX-2 as described in Ref. 14 are an average of two determinations.
[b] IC_{50} values for inhibition of PGE_2 produced by arachidonic acid stimulated COS cells stably expressing human COX-1 as described in Ref. 14 are an average of two determinations.
[c] IC_{50} value for COX-1 divided by IC_{50} value against COX-2.



Scheme 3. Reagents: (a) 4(methylthio)phenyl boronic acid, $Pd(PPh_3)_4$, Na_2CO_3, DME, H_2O, 82%; (b) oxone, H_2O, MeOH, 91%; (c) R_1R_2NH, MeCN.

suspect this loss of activity is due to the adjacent phenyl ring twisting further out of plane into a less favourable conformation.

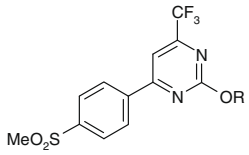
Encouraged by the good levels of COX-2 potency and selectivity observed in many examples of the [4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)-2-pyrimidinyl]amine series, we also sought to explore alternative linkers such as oxygen in the pyrimidine 2-position. Ether analogues **47**–**59** were readily prepared by the treatment of compound **11** with 1 equiv of the sodium anion of the requisite alcohol, or by treatment with an excess of the alcohol (as solvent) in the presence of 1.1 equiv of potassium carbonate, as shown in Scheme 4.[11]

COX-1 and COX-2 inhibition data for the ether series are summarised in Table 4. It should be noted that, for this series, screening was carried out using microsomal preparations of the COX enzymes, and the analogous data for celecoxib (**3**), rofecoxib (not shown) and compound **25** have been included for comparison. For further comparison, compound **47** gave IC_{50} values for COX-2 and COX-1 inhibition of 58 nM and >1,00,000 nM respectively when tested in the cellular assay used for Tables 1–3. It can be seen that a range of alkoxy, phenoxy and cycloalkoxy substituents (e.g., **47**–**56**) are well tolerated at the 2-position of the pyrimidine ring. While cyclopentylmethoxy (**57**) and cyclohexylmethoxy (**58**) substituents are also well tolerated, potency is somewhat eroded with the larger cycloheptylmethoxy group (**59**). In general, compounds from the ether series **47**–**58** display high levels of selectivity with respect to COX-1 inhibition, although this is slightly reduced with phenoxy and larger cycloalkyl substituents.

It has been suggested that COX-2 activity in a human whole blood assay is representative of clinical efficacy and that relative selectivity over COX-1 correlates with therapeutic index with respect to gastro-intestinal toxicity.[12,13] We tested representatives of the new 4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)-2-pyrimidine class of COX-2 inhibitor in a whole blood assay and results are shown in Table 5.[20] The five inhibitors tested were highly potent COX-2 inhibitors in this assay, at least as potent as marketed drugs and compound **16** was much more potent. High levels of selectivity over COX-1 were also observed.

Scheme 4. Reagents and conditions: $RO^-\ Na^+$ (1 equiv), THF, room temperature, or ROH (excess, as solvent), K_2CO_3 (1.1 equiv), 50 °C.

Table 4
Microsomal COX-2 inhibition and selectivity data for [4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)-2-pyrimidinyl] ethers

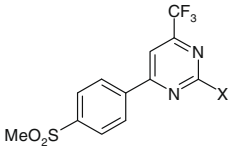


Compound	R	IC_{50} COX-2[a] (nM)	IC_{50} COX-1[b] (nM)	Selectivity[c]
Celecoxib (**3**)	—	63	>1000	>16
Rofecoxib	—	107	ND	—
25	—	12	>1,00,000	>8333
47	*n*Bu	21.5	>30,000	>1395
48	*i*Pr	63	52,556	834
49	*t*Bu	33	52,000	1576
50	4-Me–C_6H_4	<10	3752	>375
51	3-Me–C_6H_4	<10	4357	>436
52	Cyclobutyl	<10	19,000	>1900
53	Cyclopentyl	<10	4038	>404
54	Cyclohexyl	<10	1860	>186
55	Cycloheptyl	<10	1921	>192
56	Cyclooctyl	<10	3000	>300
57	Cyclopentylmethyl	22	69,000	3136
58	Cyclohexylmethyl	45	>1,00,000	>2222
59	Cycloheptylmethyl	1034	ND	—

[a] IC_{50} values for inhibition of PGE_2 produced by arachidonic acid stimulation of a COX-2 microsomal preparation from baculovirus-infected SF9 cells as described in Ref. 11 are an average of two determinations.
[b] IC_{50} values for inhibition of PGE_2 produced by arachidonic acid stimulation of a COX-1 microsomal preparation from baculovirus-infected SF9 cells as described in Ref. 11 are an average of two determinations.
[c] IC_{50} value for COX-1 inhibition divided by IC_{50} for COX-2 inhibition.

To determine their suitability for in vivo testing we investigated the pharmacokinetic properties of a number of the compounds described above, and several demonstrated excellent profiles, as exemplified by compounds **25** (also known elsewhere as GW637185X) and **47**. Following administration at a dose of 1 mg/kg to male rats as a 1 h intravenous infusion **25** demonstrated low blood clearance (10 ml/min/kg) with a steady-state volume of distribution indicative of tissue distribution of 6.0 L/kg

Table 5
COX-2 inhibition and selectivity data for representative compounds in a human whole blood assay[20]



Compound	R	IC_{50} COX-2[a] (nM)	IC_{50} COX-1[b] (nM)	Selectivity[c]
16	Benzylamino	8	39,300	4913
23	*n*Butylamino	70	>96,150	>1374
25	*i*Butylamino	206	62,000	301
26	Cyclohexylamino	62	11,600	187
47	*n*Butyloxy	158	17,410	110
Celecoxib (**3**)	—	336	10,194	30
Rofecoxib	—	260	15,500	60
Etoricoxib (**4**)	—	554	>100,000	>180

[a] IC_{50} values for inhibition of PGE_2 produced in lipoplysaccharide-stimulated human whole blood as described in Ref. 14.
[b] IC_{50} values for inhibition of TxB_2 produced in lipoplysaccharide-stimulated human whole blood as described in Ref. 14.
[c] IC_{50} value for COX-1 divided by IC_{50} value against COX-2.

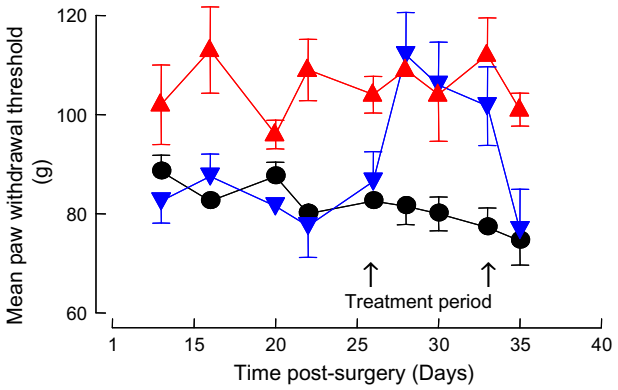


Figure 3. Reversal of the decrease in paw withdrawal threshold to mechanical stimulus by compound **47** in the CCI model of nerve injury-induced hyperalgesia. ●, Vehicle p.o.; ▼, **47** (5 mg/kg p.o. b.i.d.); ▲, Vehicle (sham) p.o.

and a terminal half-life of 9.0 h. When administered by oral gavage at a dose of 5 mg/kg as a suspension in 1% methylcellulose/water in a separate study, oral bioavailability was estimated to be 107%. Following administration at a dose of 1 mg/kg to male rats as a 1 h intravenous infusion, compound **47** demonstrated low blood clearance (24 mL/min/kg) with a steady-state volume of distribution indicative of tissue distribution of 5.7 L/kg and a terminal half-life of 4.2 h. When administered by oral gavage at a dose of 1 mg/kg as a suspension in 1% methylcellulose/water, oral bioavailability was approximately 84%.

Several of the compounds described above were found to be efficacious in the complete Freund's adjuvant rat model of acute inflammatory pain;[15] for example, compounds **25** and **47** were found to have ED_{50} values (dose that would give 50% reversal of hypersensitivity) of 0.5 and 2.1 mg/kg, showing a good correlation between in vitro and in vivo potency.

There is increasing interest in the important roles played by COX-2 and prostaglandins in the central nervous system (CNS).[16] We have determined the extent to which compounds **25**, **47**, celecoxib (**3**) and rofecoxib, cross the blood-brain barrier in rats. Compounds **25** (3.4:1) and **47** (3.2:1) were found to have relatively high brain:blood concentration ratios compared to rofecoxib (0.8:1) and celecoxib (0.1:1), suggesting that the new 4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)-2-pyrimidine class of COX-2 inhibitors may be useful to explore the role of COX-2 in the CNS. For example, compound **25** has been shown to protect against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced injury of nigrostriatal dopaminergic (DA) neurons in the mouse.[17] We chose to investigate the potential of compound **47** in the rat Chronic Constriction Injury (CCI) model[18] of nerve injury-induced hyperalgesia. In this model, hyperalgesia and allodynia are present for several weeks following loose ligation of the sciatic nerve with chromic gut suture. Mechanical hyperalgesia develops during the animals' post surgery recovery time. Central sensitisation is a component of this model, although peripheral mechanisms cannot be discounted. One group of animals (sham operated), which undergo an identical surgical procedure with the exception of the ligation, act as a positive control for reversal of the hypersensitivity. The sensitivity of this model to various clinically-validated and experimental drugs has been reported.[19] Mechanical hypersensitivity was quantified by measuring the reversal of the decrease in paw withdrawal threshold (in response to a mechanical stimulus) which is present in the ligated animals. Compound **47** was administered at 5 mg/kg po bid for 10 days and rats were tested on days 1 (after 1st dose), 3, 7 and 10 after dosing. Compound **47** fully reversed mechanical hypersensitivity to the level present in sham-operated animals by day 3 of dosing and this effect was maintained during the dosing period (Fig. 3).

In summary, we have identified a novel series of 4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)-2-pyrimidines as highly potent and selective COX-2 inhibitors. Several examples, illustrated by compounds **25** and **47**, have favourable pharmacokinetic profiles, with high levels of brain penetration in the rat. Compounds **25** and **47** also show good efficacy in a rat model of acute inflammatory pain, and **47** has been shown to reverse hypersensitivity in a rat model of nerve injury-induced hyperalgesia.

References and notes

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