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Novel 2-(4-methylsulfonylphenyl)pyrimidine derivatives as highly potent and specific COX-2 inhibitors

Aurelio Orjales,* Ramón Mosquera, Beatriz López, Roberto Olivera, Luis Labeaga and M. Teresa Núñez

Department of Research, Faes Farma S.A., Máximo Aguirre 14, 48940 Leioa, Spain

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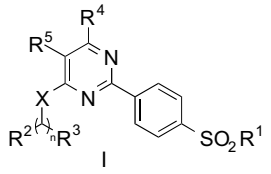
Abstract—New series of 2-(4-methylsulfonylphenyl) and 2-(4-sulfamoylphenyl)pyrimidines were synthesized and evaluated for their ability to inhibit cyclooxygenase-2 (COX-2). COX-1 and COX-2 inhibitory activity of these compounds was determined using purified enzyme (PE) and human whole blood (HWB) assays. Extensive structure–activity relationship (SAR) work was carried out within these series, and a wide number of potent and specific COX-2 inhibitors were identified (HWB COX-2 IC_{50} = 2.4–0.3 nM and 80- to 780-fold more selective than rofecoxib).

1. Introduction

The discovery and characterization of the cyclooxygenase-2 (COX-2) enzyme early in the 1990s[1] led to the hypothesis that selective inhibitors of this isoform would exhibit similar clinical efficacy but reduced ulcerogenicity than traditional nonsteroidal antiinflammatory drugs (NSAIDs), which were dual nonselective cyclooxygenase-1 (COX-1) and COX-2 inhibitors. Rofecoxib[2] and celecoxib[3] were the first COX-2 selective inhibitors to reach the market followed by valdecoxib[4] and etoricoxib.[5] The worldwide withdrawal of rofecoxib (Vioxx) because of evidence of increased cardiovascular risk[6] has raised concern about the safety of COX-2 selective inhibitors.[7] Research efforts[8] to clarify if the observed cardiovascular events are due to the mechanism of action of the entire class of compounds or to the particular structure of rofecoxib point out to the first reason as the most probable cause of aforementioned undesired adverse effects.[9] Additionally, it has recently been suggested that traditional NSAIDs are not devoid of toxicity on the cardiovascular system either.[10] Nevertheless, the potential therapeutic applications of selective COX-2 inhibitors have been expanded beyond the areas of analgesia and inflammation, as shown by recent studies on COX-2 that have been focused on cancer[11] and neurodegenerative disorders.[12]

Tricyclic molecules possessing as a common feature 1,2-diaryl substitution on a central heterocyclic or carbocyclic ring system represent a major class of selective COX-2 inhibitors and extensive work has been carried out in this area.[13] On the other hand, pyrimidine ring has scarcely been used as template for the synthesis of new selective COX-2 inhibitors.[13,14] Nevertheless, a group of pyrimidine derivatives have been described recently as a new class of potent and selective COX-2 inhibitors.[15] As part of our research programm aimed at the discovery of new selective COX-2 inhibitors, we describe herein the synthesis and biological evaluation of novel 2-(4-methylsulfonylphenyl) and 2-(4-sulfamoylphenyl)pyrimidines **I** (Fig. 1) as potential antiinflammatory agents. The substitution pattern of these compounds is substantially different from that of previously reported pyrimidine based COX-2 inhibitors[15] and



I

Figure 1. Pyrimidine based COX-2 inhibitors.

Keywords: 2-(4-Methylsulfonylphenyl)pyrimidines; 2-(4-Sulfamoylphenyl)pyrimidines; COX-2 inhibitors.
* Corresponding author. Tel.: +34 944818300; fax: +34 944818309; e-mail: aorjales@faes.es

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it has already been demonstrated that this is a crucial feature for significant activity.[16] In this paper, we report the synthesis and characterization of 2-(4-methylsulfonylphenyl)pyrimidines as a new series of potent COX-2 inhibitors with unprecedentedly high degree of selectivity for this enzyme.

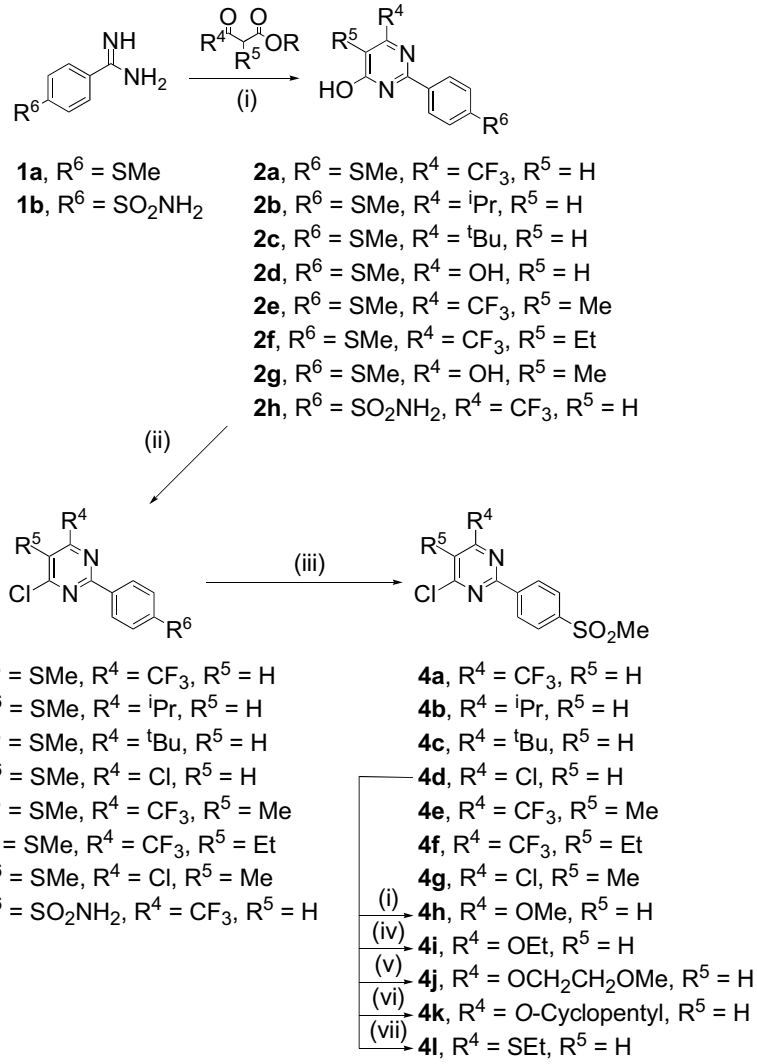
2. Results and discussion

2.1. Chemistry

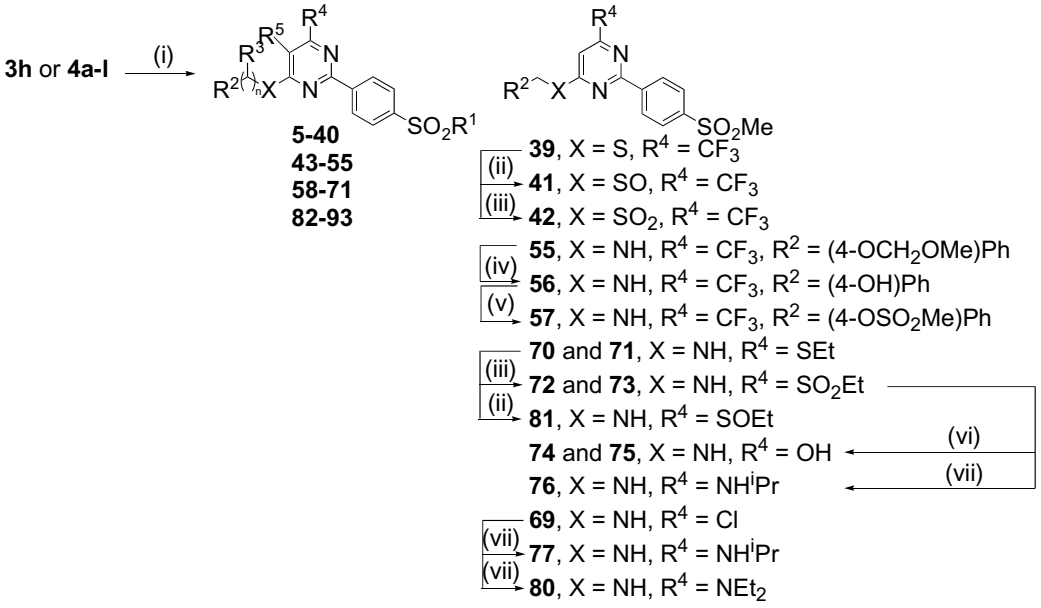
Synthetic methods employed to prepare pyrimidines of general formula **I** are outlined in Schemes 1–3. Target compounds were obtained from adequately substituted intermediates **3h** and **4a–l** which were synthesized as illustrated in Scheme 1. Starting amidines **1a** and **1b** were readily obtained from the corresponding commercially available nitriles by known methods.[17] Condensation of **1a** and **1b** with the appropriate acetoacetate or malonate derivative in the presence of a base afforded hydroxypyrimidines **2a–h**, which were treated with $POCl_3$ to give chloropyrimidines **3a–h**. Oxidation of derivatives **3a–g**, using an aqueous solution of OXONE (potassium peroxymonosulfate), afforded key intermediates **4a–g**, while precursors **4h–l** were obtained from **4d** by reaction with the adequate alkoxide or with sodium ethanethiolate.

Standard methods for aromatic nucleophilic substitution of 4-chloropyrimidines were employed to obtain target pyrimidines **5–40**, **43–55**, **58–71** and **82–93** from intermediates **3h** and **4a–l** (Scheme 2). Further synthetic transformations, such as oxidation, hydrolysis or a second nucleophilic displacement, of suitable final pyrimidines provided structures **41-42**, **56–57**, **72–77** and **80–81** (Scheme 2).

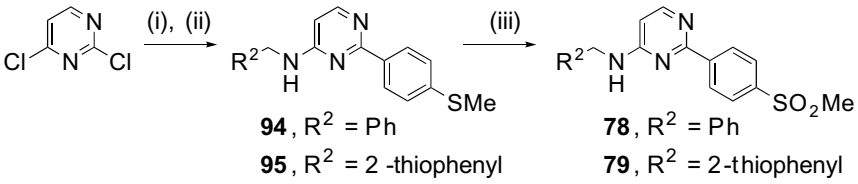
A more convenient alternative synthetic path was followed to prepare 6-unsubstituted derivatives **78** and **79** (Scheme 3). Treatment of commercially available 2,4-dichloropyrimidine with one equivalent of the adequate amine and subsequent Suzuki-Miyaura cross-coupling with 4-(methylthio)phenylboronic acid yielded 4-amino-



Scheme 1. General synthetic path for intermediates **4**. Reagents: (i) NaOMe, MeOH; (ii) $POCl_3$; (iii) OXONE, THF, H_2O; (iv) EtOH, NaH, THF; (v) $MeOCH_2CH_2OH$, NaH, THF; (vi) NaH, cyclopentanol, THF; (vii) NaSEt, THF.



Scheme 2. Synthesis of final products **5**–**77** and **80**–**93**. Reagents: (i) $R^2(CHR^3)_nXH$, base; (ii) PhI(OH)OTs, CH_2Cl_2; (iii) OXONE, THF, H_2O; (iv) HCl, EtOH; (v) MsCl, DMAP, py; (vi) NaOH aq; (vii) $^iPrNH_2$ or Et_2NH.



Scheme 3. Synthetic scheme for **78** and **79**. Reagents: (i) $R^2CH_2NH_2$, Et_3N, CH_2Cl_2; (ii) 4-(Methylthio)phenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, DME, H_2O; (iii) OXONE, THF, H_2O.

pyrimidine intermediates **94** and **95**. After oxidation of said compounds, pyrimidines **78** and **79** were isolated with high overall yield. Two-dimensional NMR experiments (HSQC, HMBC and NOESY) were performed to assess the chemical structure of **78** and **79**.

2.2. Biology

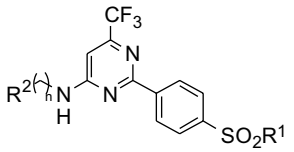
All compounds herein described were tested for their ability to inhibit COX-1 and COX-2 by using the in vitro purified enzyme (PE)[18] and human whole blood (HWB)[19] assays. In both assays, the compounds were tested at 10 μM in triplicate determinations. COX-1 and COX-2 IC_{50} values were calculated for compounds that showed a percentage of inhibition higher than 50% and were obtained by non-linear regression from three independent experiments with 8–10 different concentrations in triplicate. In all cases, the standard error mean (SEM) was less than 15%. For each assay Selectivity Index (SI) was calculated as the ratio IC_{50}s COX-1/COX-2.

IC_{50} and SI values obtained from the PE enzyme assay were useful for SAR studies. HWB assay is widely considered as the benchmark model[20] and values from this test were also employed as a selection criterion. In all cases, the ratio HWB COX-2 IC_{50}/PE COX-2 IC_{50} ($I_{HWB/PE}$) was used as an index to compare the data of both assays. It has been reported in the literature that potency of drugs is often significantly reduced in the HWB assay[5b,21] when compared with other in vitro tests, which is probably due to binding to plasma proteins, to the presence of endogenous arachidonic acid at the time of COX-2 induction and to possible low cellular permeability profile of the drugs. In consequence we expected $I_{HWB/PE}$ to be >1 as a general rule. In contrast, many of the studied compounds had better values of HWB COX-2 IC_{50} than PE COX-2 IC_{50} and consequently $I_{HWB/PE}$ were usually <1, which might be indicative of good cellular permeability or to low affinity for plasma proteins, interference of the compounds with the expression of COX-2[13e] as possible hypothesis. Tables 1–5 show biological data for compounds **5-93**. Tables 2–5 do not show PE data, but PE COX-2 IC_{50} in relation to HWB COX-2 IC_{50} are given as $I_{HWB/PE}$ indexes.

2.3. Structure–activity relationships

The study was initially focused on 6-trifluoromethyl substituted pyrimidines as this group is ubiquitously present in structures of previously reported pyrimidine based COX-2 inhibitors.[15] Extensive structure–activity relationship (SAR) studies for the diarylheterocycle class have shown that *para*-SO_2NH_2 or SO_2Me substitution at one of the aryl rings is required for optimum

Table 1. In vitro COX-2 inhibitory activities of compounds **5**–**34**



I ($R^3 = R^5 = H$, $R^4 = CF_3$)

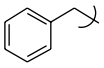
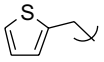
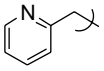
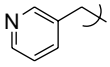
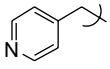
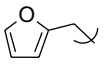
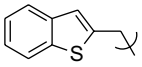
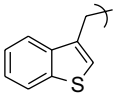
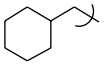
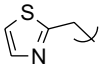
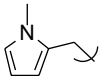
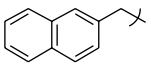
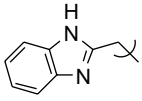
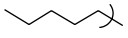
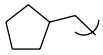
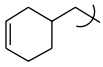
Compound	R^1	$R^2(CH_2)_n$	PE		HWB		$I_{HWB/PE}$
			IC_{50}[a]	SI	IC_{50}[a]	SI	
5	NH_2		3980	>25	>10,000	>5	5.2
6	Me		140	>71	71.0	1408	0.51
7	NH_2		22.3	3529	157.6	>634	5.50
8	Me		22.4	>4464	2.1	10,702	0.09
9	NH_2		72.0	1388	51.9	>193	0.70
10	Me		17.6	>5692	46.5	215	2.60
11	NH_2		3000	>33	>10,000	>10	>3
12	Me		>10,000	>1	>10,000	>1	—
13	NH_2		>10,000	>1	>10,000	>1	—
14	Me		>10,000	>1	>10,000	>1	—
15	NH_2		1890	>52	3330	>3	1.80
16	Me		2950	>34	298.5	>335	0.10
17	NH_2		14.4	>6920	2790	>3	193
18	Me		200.7	>498	140	>497	0.7
19	NH_2		15.2	6570	140.4	>71	8.20
20	Me		5.92	>10,000	293.4	341	49.60
21	NH_2		10,000	>10	>10,000	>1	—
22	Me		10,000	>1	>10,000	>1	—
23	NH_2		712	>140	803.5	>124	1.10
24	Me		>10,000	>3610	1480	>68	0.053
25	Me		459.7	>217	83.6	>1195	0.18
26	Me		177.8	>562	28.8	>3467	0.16
27	Me		>10,000	>1	>10,000	>1	—
28	Me		>10,000	>1	>10,000	>1	—
29	Me		>10,000	>10	728.6	137	0.07
30	Me		7760	>13	789.8	>127	0.10

Table 1 (*continued*)

Compound	R^1	$R^2(CH_2)_n$	PE		HWB		$I_{HWB/PE}$
			IC_{50}[a]	SI	IC_{50}[a]	SI	
31	Me		>10,000	>1	>10,000	>1	—
32	Me		191.6	>522	475.9	80	2.48
33	Me		252.6	>396	238.5	419	0.94
34	Me		43.1	>2317	32.9	>304	0.76
Rofecoxib	—	—	292.0	>342	211.0	104	0.72

[a] Data are indicated as IC_{50} (nM). SEM less than 15%.

COX-2 inhibitory potency and selectivity.[22] These polar groups are known to induce COX-2 selectivity by insertion into the secondary pocket of COX-2 binding site that is absent in COX-1.[22] To compare the ability of SO_2NH_2 and SO_2Me to induce COX-2 selective inhibition in pyrimidines **I** (Fig. 1), a representative group of 2-(4-sulfamoylphenyl) and the corresponding 2-(4-methylsulfonylphenyl)pyrimidines was prepared (compounds **5**–**24**, Table 1). Noticeable differences between PE and HWB assays were observed for sulfonamides **7**, **17** and **19**, which behaved as potent and selective COX-2 inhibitors in the PE assay (PE COX-2 IC_{50} 14.4–22.3 nM and SI >4000), but showed a sharp drop in potency in the HWB assay (HWB COX-2 IC_{50} 140.4–2790 nM). In fact, $I_{HWB/PE}$ indexes for sulfonamide derivatives were >1 (Table 1). Compound **9** was an exception to this observation. In contrast, it was found that the corresponding sulfonylmethyl analogues **8**, **18** and **20** were even more potent in the HWB assay than in the PE assay ($I_{HWB/PE}$ indexes were <1 as for rofecoxib). As the best potency and selectivity profile in the HWB assay was observed for methylsulfonyl derivatives (compare HWB COX-2 IC_{50} for **6**, **8**, **18** and **20** vs the corresponding analogues **5**, **7**, **17** and **19**), SO_2Me substituent was chosen as polar group to incorporate in new pyrimidines.

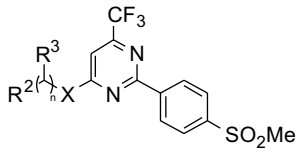
On the other hand, the nature of the ring present at R^2 was found to be crucial for activity. Compounds with best HWB COX-2 IC_{50} values (<100 nM) bear a phenyl (**6**) or thiophenyl (**8**–**10**) ring in this position. On the contrary, when that cycle was pyridine (**11**–**16**) or cyclohexyl (**23**–**24**) the resulting pyrimidines both sulfonamide and sulfonylmethyl derivatives were inactive. It is noteworthy that, in one case, even the presence at position R^2 of a different regioisomer caused a complete loss of activity (compare 2-benzo[*b*]thiophene containing pyrimidines **19** and **20** with the corresponding 3-benzo[*b*]thiophene isomers **21** and **22**). Nevertheless, the same effect was not observed for 2-thiophenyl derivatives **7** and **8** which show similar potency as the corresponding 3-thiophenyl regioisomers **9** and **10**. The slight differences in HWB COX-2 IC_{50} values observed for thiophene containing compounds **7**–**10** evidenced the fact that they might be promising lead structures for the synthesis of new COX-2 inhibitors. Moreover, given that 2-thiophenyl **7** and **8** derivatives were more selective than the corresponding 3-thiophenyl regioisomers **9** and **10**, **8** was selected as lead structure for chemical optimization. Sulfonylmethyl derivatives **25**–**34** were synthesized to further study the impact of R^2 substituent on activity of pyrimidines **I**. It was confirmed that the presence of alkyl or cycloalkyl radicals in this position leads to low activity products (compounds **29**–**33**). In contrast, compound **34**, bearing a partially unsaturated carbocycle at that position, showed a HWB COX-2 IC_{50} 45-fold lower than the corresponding saturated analogue **24**. Several other aromatic and heteroaromatic rings were introduced at R^2 (Table 1, compounds **25**–**28**) and it was finally concluded that best HWB COX-2 IC_{50} (2.1–71.0 nM) and SI (1400–10,202) values were obtained when R^2 was phenyl, thiophen-2-yl or 1*H*-pyrrol-2-yl (pyrimidines **6**, **8** and **26**, respectively). Thiazolyl containing derivative **25** was also a promising structure but synthetically it was less easily accessible.

To explore the effect of X, R^3 and *n* in COX-2 inhibitory potency and selectivity of pyrimidines **I**, sulfonylmethyl derivatives **35**–**45** were prepared and tested (Table 2).

A substantial decrease in inhibitory activity was found when X was a fully substituted nitrogen atom (compounds **35** and **36**), especially for *N*-ethyl substituted derivative **36**. On the other hand, sulfur containing derivatives **40** and **43** have promising COX-2 IC_{50} values while a complete loss of COX-2 inhibitory activity was recorded for compounds **41** and **42**, which are oxidized analogues of **40**. The discouraging preliminary studies aimed at testing **40** and **43** as leaders for the development of new coxibs[23] along with the aforementioned deleterious effect of *S*-oxidation in activity led us to discontinue studies on 4-thiopyrimidines.

In the case of product **37** (R^3 = Me) a noticeable decrease in potency and selectivity was observed when compared to the unsubstituted aminopyrimidine **6**. Analogues of compound **6** devoid of a methylene bridge in the 4-aminosubstituent ($n = 0$) such as pyrimidines **38** and **39** were completely inactive as COX-2 inhibitors. In the same way, the presence of an ethylene tether in

Table 2. In vitro COX-2 inhibitory activities of compounds **35–45** in HWB assay

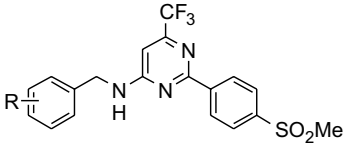


I (R^1 = Me, R^4 = CF_3, R^5 = H)

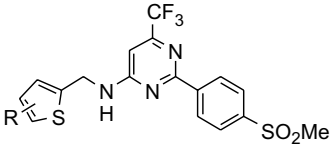
Compound	X	*n*	R^3	R^2	IC_{50}[a] (nM)	SI	$I_{HWB/PE}$
6[b]	NH	1	H	Ph	71.0	1408	0.51
35	NMe	1	H	Ph	454.5	22	0.50
36	NEt	1	H	Ph	>10,000	>1	—
37	NH	1	Me	Ph	521.8	74	18.95
38	NH	0	—	Ph	>10,000	>1	—
39	NH	0	—	4-^{i}Pr-Ph	>10,000	>1	—
40	S	1	H	Ph	527.8	>189	27.7
41	SO	1	H	Ph	>10,000	>1	—
42	SO_2	1	H	Ph	>10,000	>1	—
8[b]	NH	1	H	Thiophen-2-yl	2.1	10,702	0.09
43	S	1	H	Thiophen-2-yl	4.1	>24,450	0.58
44	NH	2	H	Thiophen-2-yl	1210	>83	<0.12
26[b]	NH	1	H	1-Methyl-1*H*-pyrrol-2-yl	28.8	>3467	0.16
45	NH	2	H	1-Methyl-1*H*-pyrrol-2-yl	3980	>25	<0.40

[a] SEM less than 15%.
[b] Included for comparison purposes.

Table 3. In vitro COX-2 inhibitory activities of compounds **46–61** in HWB assay



Ia (R^4 = CF_3, R^5 = H)



Ib (R^4= CF_3, R^5= H)

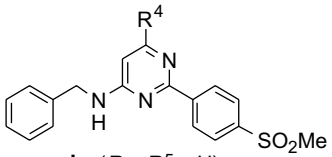
Compound	I	R	IC_{50}[a] (nM)	SI	$I_{HWB/PE}$
6[b]	**Ia**	H	71	1408	0.50
46	**Ia**	4-Me	48.4	>2065	0.20
47	**Ia**	4-F	77.2	1296	0.80
48	**Ia**	2-Me	5720	>17	0.90
49	**Ia**	3-Me	1930	>52	4.90
50	**Ia**	4-^{i}Pr	>10,000	>1	—
51	**Ia**	3,5-DiF	300.3	>333	3.50
52	**Ia**	4-CF_3	1920	>52	2.90
53	**Ia**	4-OCF_3	>10,000	>1	—
54	**Ia**	4-OMe	272.3	>367	<0.03
55	**Ia**	4-OCH_2OMe	>10,000	>1	—
56	**Ia**	4-OH	635	>158	2.10
57	**Ia**	4-OSO_2Me	>10,000	>1	—
58	**Ia**	4-NH_2	211.3	473	1.40
8[b]	**Ib**	H	2.1	10,702	0.10
59	**Ib**	3-Me	527.8	189	9.90
60	**Ib**	5-Me	11.7	>852	0.50
61	**Ib**	5-Cl	5.4	>18,622	0.34

[a] SEM less than 15%.
[b] Included for comparison purposes.

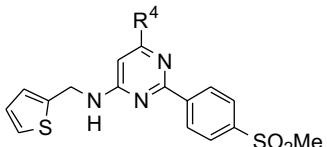
this substituent (*n* = 2) led to low activity compounds **44** and **45**. Thus, best potency and selectivity was accomplished when the group $X(CH(R^3))_nR^2$ in pyrimidines **I** was $NHCH_2Ar$, where Ar was phenyl or 2-thiophenyl (compounds **6** and **8**, respectively).

Accordingly, pyrimidines **Ia** and **Ib** (Fig. 2) arose as feasible templates for further optimization and in an effort to understand the effect of substituent R for both templates compounds **46–61** were synthesized (Table 3). In the case of pyrimidines **Ia**, when R was 4-fluoro

Table 4. In vitro COX-2 inhibitory activities of compounds **62–84** in HWB assay



Ia (R = R^5 = H)

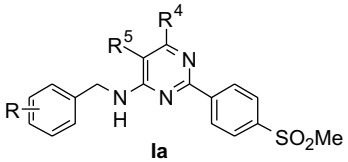


Ib (R = R^5 = H)

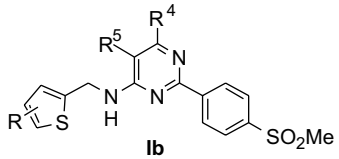
Compound	I	R^4	IC_{50}[a] (nM)	SI	$I_{HWB/PE}$
6[b]	**Ia**	CF_3	71.0	1408	0.51
8[b]	**Ib**	CF_3	2.1	10,702	0.09
62	**Ia**	^{i}Pr	25.3	>396	0.55
63	**Ib**	^{i}Pr	9.8	>1018	0.38
64	**Ia**	^{t}Bu	93.9	1065	1.63
65	**Ib**	^{t}Bu	31.1	>322	1.39
66	**Ia**	OMe	5.1	>19,646	0.15
67	**Ib**	OMe	0.4	>22,004	0.06
68	**Ia**	Cl	10.9	>9124	0.07
69	**Ib**	Cl	1.2	>81,300	0.09
70	**Ia**	SEt	24.1	414	1.56
71	**Ib**	SEt	1.2	>8403	0.20
72	**Ia**	SO_2Et	90.7	>110	0.40
73	**Ib**	SO_2Et	144.5	15	0.15
74	**Ia**	OH	49.3	>2030	0.07
75	**Ib**	OH	79.4	>1259	0.03
76	**Ia**	NH^iPr	273.8	>365	0.02
77	**Ib**	NH^iPr	10.3	>9718	0.05
78	**Ia**	H	>10,000	>1	—
79	**Ib**	H	9.2	>10,905	0.06
80	**Ib**	NEt_2	6.1	>1642	0.05
81	**Ib**	SOEt	37.6	>266	0.03
82	**Ib**	OEt	0.3	>33,333	0.02
83	**Ib**	$OCH_2CH_2OCH_3$	2.4	>41,841	0.02
84	**Ib**	*O*-Cyclopentyl	7.5	>13,351	0.21

[a] SEM less than 15%.
[b] Included for comparison purposes.

Table 5. In vitro COX-2 inhibitory activities of compounds **85–93** in HWB assay



Ia



Ib

Compound	I	R	R^4	R^5	IC_{50}[a] (nM)	SI	$I_{HWB/PE}$
6[b]	**Ia**	H	CF_3	H	71.0	1408	0.51
85	**Ia**	H	CF_3	Me	18.0	>556	0.27
8[b]	**Ib**	H	CF_3	H	2.1	10,702	0.09
86	**Ib**	H	CF_3	Me	38.2	>78	0.73
87	**Ib**	H	CF_3	Et	120.9	>83	0.86
88	**Ia**	4-Me	Cl	H	44.4	>2252	0.19
89	**Ia**	4-Me	Cl	Me	36.7	>2726	0.43
47[b]	**Ia**	4-F	CF_3	H	77.2	1296	0.82
90	**Ia**	4-F	CF_3	Me	22.4	>447	0.43
91	**Ia**	4-F	CF_3	Et	102.8	>972	0.67
92	**Ia**	4-F	Cl	H	33.7	2969	0.35
93	**Ia**	4-F	Cl	Me	68.8	>145	0.41

[a] SEM less than 15%.
[b] Included for comparison purposes.

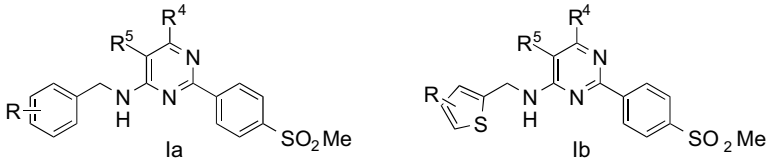


Figure 2. New pyrimidine based templates for the design of COX-2 inhibitors.

(product **47**) or 4-methyl (compound **46**) HWB COX-2 IC_{50} values were not affected but, shifting of methyl group from *para*- (as in derivative **46**) to *ortho*- (compound **48**) or *meta*-position (compound **49**) or presence of a *para*-high volume substituent such as ^{i}Pr, CF_3, OCF_3, OCH_2OMe, or OSO_2Me (products **50**, **52**, **53**, **55** and **57**) resulted in a complete loss of activity. On the other hand, for template **Ib** substitution at the thiophene ring (products **60** and **61**) did not substantially affect potency. In this case, in contrast with previously described behaviour of **Ia** series, even when R was an *ortho*-methyl group (compound **59**) moderate COX-2 inhibitory activity was detected. In conclusion, substituent R gives rise to pronounced differences in activity for compounds **Ia** but not for derivatives **Ib**, suggesting that template **Ib** is probably more robust than **Ia**. It is also remarkable that even though derivatives **Ia** were potent COX-2 inhibitors with $IC_{50} < 100$ nM, outstanding results were obtained for compounds **Ib** such as **8** and **61** that were extremely potent ($IC_{50} = 2.1$ and 5.4 nM, respectively) and specific (SI = 10,702 and >18,622, respectively) COX-2 inhibitors.

Afterwards, the effect of nature and volume of radical R^4 in inhibitory activity of proposed series **Ia** and **Ib** was studied (Table 4). Up to this point our investigation had been focused on 6-trifluoromethylpyrimidines, but we encountered that potency was not substantially affected by the presence of a large variety of radicals at position R^4. Thus, 6-alkylpyrimidines **62**–**65** exhibited HWB COX-2 IC_{50} values similar to the corresponding 6-trifluoromethyl analogues **6** and **8**, although sterically demanding 6-*tert*-butylsubstituent (see compounds **64** and **65**) caused a mild decrease in potency. Regarding selectivity, SI for 6-alkylpyrimidines were lower than those for the corresponding 6-trifluoromethylpyrimidines (compare compounds **62** vs **6** and **65** vs **8**). Interestingly, 6-chloro and 6-methoxypyrimidines **66**–**69** showed a remarkable improvement in potency and selectivity, indeed products **66**, **67** and **69** had unprecedentedly high selectivity indexes, although high ratios of selectivity do not guarantee the efficacy or safety of these compounds in vivo. Other 6-alkoxy derivatives **82**–**84** were also extremely potent and selective COX-2 inhibitors. Nevertheless, when oxygen in position 6 of the pyrimidine was unsubstituted ($R^4 = OH$) the resulting products **74** and **75** showed a noticeable decrease in activity. Other heteroatoms were tested in this position and thus potency of 6-thiopyrimidines **70** and **71** and 6-aminosubstituted pyrimidines **76**, **77** and **80** was similar to that of initially reported trifluoromethyl analogues **6** and **8**, although they were usually less selective. Oxidation of 6-ethylthio radical as in pyrimidines **72**, **73** and **81** caused a progressive loss of activity. In general, when different substituents were introduced at position R^4, activity of compounds **Ib** was not as severely affected as activity of products **Ia** (Table 4). To confirm this finding 6-unsubstituted ($R^4 = H$) pyrimidines **78** and **79** were tested and, to our surprise, dramatically differing biological data were obtained for them. Thus, compound **78** was inactive, whereas the corresponding analogue **79** was extremely potent and selective. In contrast to the large differences in activity found for derivatives **Ia** modified at R (see Table 3), variations at R^4 for the same series only moderately affected potency (Table 4, compounds **Ia** IC_{50} between 273.8 and 5.1 nM), except for said 6-unsubstituted pyrimidine **78**. Consequently, we concluded that nature and substitution of R strongly affect activity of pyrimidines **I**, while variations at position R^4 are useful to modulate potency and selectivity of these compounds.

Finally, to evaluate the effect of an additional substituent (R^5) in position 5 of pyrimidines **I**, 5-methyl and 5-ethyl substituted analogues of a selection of the more promising compounds obtained to this point were synthesized (products **85**–**93**, Table 5). 5-Methyl substituted pyrimidines **85** and **86** kept HWB COX-2 IC_{50} values similar to the corresponding unsubstituted analogues **6** and **8**, but they were generally less selective. The presence of a more sterically demanding substituent at position 5 of the central pyrimidine ring, as in 5-ethyl substituted compounds **87** and **91**, was detrimental to potency and selectivity.

3. Conclusions

New series of pyrimidines (**I**) are reported as COX-2 inhibitors. In vitro COX-2 inhibition results showed that inhibitory potency and selectivity of these compounds is dependent upon the nature of substituents at positions 2, 4 and 6 of the pyrimidine ring. In this regard, pyrimidines **I** exhibited optimum HWB COX-2 IC_{50} and SI values when R^1 was Me, the group $X[CH(R^3)]_nR^2$ was $NHCH_2R^2$ where R^2 was 4-fluorophenyl, 4-methylphenyl, phenyl, 2-thiophenyl or 3-thiophenyl, R^4 was CF_3, Cl, alkoxy or ^{i}Pr and R^5 preferably was H. The adequate combination of substituents in these positions allowed access to COX-2 inhibitors with diverse grades of potency and selectivity. Thus, compound **86** was a potent (IC_{50} (HWB) = 38.2 nM) but not very selective (SI > 78) COX-2 inhibitor, whereas product **25** which is only 2.5-fold more potent than rofecoxib (IC_{50} (HWB) = 83.6 nM) shows an outstanding selectivity index of >1195 (11-fold more selective than rofecoxib).

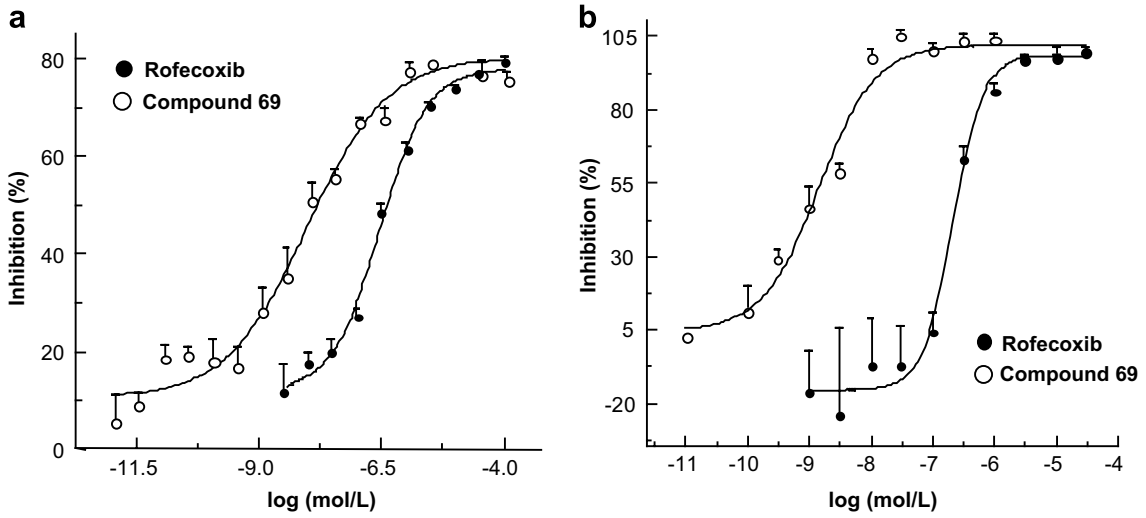


Figure 3. (a) Concentration–response curve for rofecoxib (IC_{50} = 292.0 nM) and compound **69** (IC_{50} = 12.7 nM) in the COX-2 PE assay. (b) Concentration-response curve for rofecoxib (IC_{50} = 211.0 nM) and compound **69** (IC_{50} = 1.2 nM) in the COX-2 HWB assay.

Compounds **8**, **43**, **61**, **63**, **66–69**, **71**, **77**, **79**, **80** and **82–84** are extremely potent (IC_{50} (HWB) between 10.9 and 0.3 nM) and specific (10- to 780-fold more selective than rofecoxib) COX-2 inhibitors. As a remarkable example of COX-2 inhibitory potency, activity of selected compound **69** compared to rofecoxib in both PE (Fig. 3a) and HWB (Fig. 3b) assays (HWB COX-2 IC_{50} = 1.2 nM) is illustrated. Compound **69** was also the most selective pyrimidine derivative of the series with a calculated HWB selectivity index of 81,300 (780-fold higher than rofecoxib).

4. Experimental

4.1. Chemistry protocols

Except otherwise specified, solvents and reagents were commercially obtained from Aldrich Co., USA and Maybridge Co., UK, and were used without further purification. All reported yields are of isolated products and are not optimized. Melting points were measured in open capillary tubes on a Büchi B-540 apparatus and are uncorrected. Elemental analyses are within ±0.4% of the theoretical values. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Brucker AC-200 spectrometer (operating at 200 MHz for ^{1}H and at 50 MHz for ^{13}C). Chemical shifts are reported as δ values (ppm) downfield relative to TMS (0.00 ppm) as an internal standard or to residual solvent peaks (DMSO-d_6). Spectral data are consistent with assigned structures. Column chromatography was carried out in flash mode on silica gel (Merck Kieselgel 60, 230–400 mesh) or in Dry Column Vacuum Chromatography (DCVC) mode on silica gel (Merck Silica gel 60, 0.015–0.040 mm).

4.2. General procedure for the synthesis of 4-aminopyrimidines 5–37, 44–55, 58–71 and 82–93 (GP1)

A mixture of the adequate precursor **4a–l** or **3h** (1 mmol) with Et_3N (2–4 mmol) as base unless otherwise stated and the corresponding amine (2–4 mmol) in CH_2Cl_2 or CH_3CN (7 mL) was stirred at a temperature of rt to 90 °C for 3–72 h. The solvent was distilled off under vacuum and the resulting residue purified by chromatography.

4.2.1. 4-(4-Benzylamino-6-trifluoromethylpyrimidin-2-yl)benzenesulfonamide (5). Compound **5** was prepared from **3h** and benzylamine following GP1. After flash chromatography the title compound was obtained (60% yield) as a dark syrup. ^{1}H NMR (CD_3OD) δ 4.60 (s, 2H, NHCH_2Ph), 6.73 (s, 1H, H-5), 7.08–7.29 (m, 5H, Ar-*H*), 7.90 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 8.41 (d, *J* = 8.0 Hz, 2H, Ar-*H*). ^{13}C NMR ($CDCl_3$ and CD_3OD) δ 45.5 (NH*C*H_2Ph), 102.1 (C-5), 125.2 (q, *J* = 219 Hz, *C*F_3), 127.8 (CH), 128.1 (CH), 128.7 (CH), 129.1 129.5 (CH), 140.2 (C), 141.5 (C), 146.4 (C), 154.8 (q, *J* = 45 Hz, C-6), 164.4 (C). Anal ($C_{18}H_{15}F_3N_4O_2S$) C, H, N, S.

4.2.2. Benzyl-[2-(4-methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]amine (6). Compound **6** was prepared from **4a** and benzylamine following GP1. After flash chromatography the title compound was obtained (75% yield) as a white solid; mp 196.0–198.2 °C. Anal ($C_{19}H_{16}F_3N_3O_2S$) C, H, N, S.

4.2.3. 4-[4-[(Thiophen-2-ylmethyl)amino]-6-trifluoromethylpyrimidin-2-yl]benzenesulfonamide (7). Compound **7** was prepared from **3h** and 2-thiophenemethylamine following GP1. After flash chromatography the title compound was obtained (94% yield) as a white solid; mp 184.0–186.0 °C. Anal ($C_{16}H_{13}F_3N_4O_2S_2$) C, H, N, S.

4.2.4. [2-(4-Methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]thiophen-2-ylmethylamine (8). Compound **8** was prepared from **4a** and 2-thiophenemethylamine following GP1. After flash chromatography the title compound was obtained (98% yield) as a white solid; mp 190.3–192.5 °C. Anal ($C_{17}H_{14}F_3N_3O_2S_2$) C, H, N, S.

4.2.5. 4-[4-[(Thiophen-3-ylmethyl)amino]-6-trifluoromethylpyrimidin-2-yl]benzenesulfonamide (9). Compound **9** was prepared from **3h** and 3-thiophenemethylamine following GP1. After flash chromatography the title compound was obtained (33% yield) as a white solid; mp 181.0–183.5 °C. Anal ($C_{16}H_{13}F_3N4O_2S_2$) C, H, N, S.

4.2.6. [2-(4-Methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]thiophen-3-ylmethylamine (10). Compound **10** was prepared from **4a** and 3-thiophenemethylamine following GP1. After flash chromatography the title compound was isolated (95% yield) as a solid; mp 203.0–205.5 °C. Anal ($C_{17}H_{14}F_3N_3O_2S_2$) C, H, N, S.

4.2.7. 4-[4-[(Pyridin-2-ylmethyl)amino]-6-trifluoromethylpyrimidin-2-yl]benzenesulfonamide (11). Compound **11** was prepared from **3h** and 2-(methylamino)pyridine following GP1. After flash chromatography the title compound was obtained (28% yield) as a yellow solid; mp 246.0–248.0 °C. Anal ($C_{17}H_{14}F_3N_5O_2S$) C, H, N, S.

4.2.8. [2-(4-Methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]pyridin-2-ylmethylamine (12). Compound **12** was prepared from **4a** and 2-(methylamino)pyridine following GP1. After flash chromatography the title compound was isolated (98% yield) as a white solid; mp 208.7–211.5 °C. Anal ($C_{18}H_{15}F_3N_4O_2S$) C, H, N, S.

4.2.9. 4-4-[(Pyridin-3-ylmethyl)amino]-6-trifluoromethylpyrimidin-2-yl]benzenesulfonamide (13). Compound **13** was prepared from **3h** and 3-(methylamino)pyridine following GP1. After flash chromatography the title compound was isolated (23% yield) as a yellow solid; mp 229.0–231.0 °C. Anal ($C_{17}H_{14}F_3N_5O_2S$) C, H, N, S.

4.2.10. [2-(4-Methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]pyridin-3-ylmethylamine (14). Compound **14** was obtained from **4a** and 3-(methylamino)pyridine following GP1. After flash chromatography the title compound was isolated (97% yield) as a grey solid; mp 225.0–227.5 °C. Anal ($C_{18}H_{15}F_3N_4O_2S$) C, H, N, S.

4.2.11. 4-[4-[(Pyridin-4-ylmethyl)amino]-6-trifluoromethylpyrimidin-2-yl]benzenesulfonamide (15). Compound **15** was obtained from **3h** and 4-(methylamino)pyridine following GP1. After flash chromatography the title compound was isolated (19% yield) as a dark oil. Anal ($C_{17}H_{14}F_3N_5O_2S$) C, H, N, S.

4.2.12. [2-(4-Methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]pyridin-4-ylmethylamine (16). Compound **16** was synthesized from **4a** and 4-(methylamino)pyridine following GP1. After flash chromatography the title compound was isolated (79% yield) as a pale yellow solid. Anal ($C_{18}H_{15}F_3N_4O_2S$) C, H, N, S.

4.2.13. 4-[4-[(Furan-2-ylmethyl)amino]-6-trifluoromethylpyrimidin-2-yl]benzenesulfonamide (17). Compound **17** was obtained from **3h** and furfurylamine following GP1. After flash chromatography, the title compound was isolated (94% yield) as a white solid; mp 212.0–214.0 °C. Anal ($C_{16}H_{13}F_3N_4O_3S$) C, H, N, S.

4.2.14. Furan-2-ylmethyl-[2-(4-methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]amine (18). Compound **18** was prepared from **4a** and furfurylamine following GP1. After flash chromatography the title compound was isolated (98% yield) as an almost white solid; mp 192.9–195.0 °C. Anal ($C_{17}H_{14}F_3N_3O_3S$) C, H, N, S.

4.2.15. 4-[4-[(Benzo[*b*]thiophen-2-ylmethyl)amino]-6-trifluoromethylpyrimidin-2-yl]benzenesulfonamide (19). Compound **19** was obtained from **3h** and 2-benzo[*b*]thiophenemethylamine following GP1. After flash chromatography the title compound was isolated (37% yield) as a white solid; mp 189.0–191.0 °C. Anal ($C_{20}H_{15}F_3N_4O_2S_2$) C, H, N, S.

4.2.16. Benzo[*b*]thiophen-2-ylmethyl-[2-(4-methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]amine (20). Compound **20** was synthesized from **4a** and 2-benzo[*b*]thiophenemethylamine following GP1. After flash chromatography the title compound was isolated (96% yield) as a solid; mp 215.6–218.0 °C. Anal ($C_{21}H_{16}F_3N_3O_2S_2$) C, H, N, S.

4.2.17. 4-[4-[(Benzo[*b*]thiophen-3-ylmethyl)amino]-6-trifluoromethylpyrimidin-2-yl]benzenesulfonamide (21). Compound **21** was obtained from **3h** and 3-benzo[*b*]thiophenemethylamine following GP1. After flash chromatography the title compound was isolated (29% yield) as a yellow solid; mp 224.0–226.0 °C. Anal ($C_{20}H_{15}F_3N_4O_2S_2$) C, H, N, S.

4.2.18. Benzo[*b*]thiophen-3-ylmethyl-[2-(4-methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]amine (22). Compound **22** was prepared from **4a** and 3-benzo[*b*]thiophenemethylamine following GP1. The yellow solid obtained after flash chromatography was washed with Et_2O and the title compound isolated (46% yield) as a white solid; mp 240.0–242.1 °C. Anal ($C_{21}H_{16}F_3N_3O_2S_2$) C, H, N, S.

4.2.19. 4-[4-(Cyclohexylmethylamino)-6-trifluoromethylpyrimidin-2-yl]benzenesulfonamide (23). Compound **23** was prepared from **3h** and cyclohexanemethylamine following GP1. After flash chromatography the title compound was isolated (37% yield) as a white solid; mp 198.0–200.0 °C. Anal ($C_{18}H_{21}F_3N_4O_2S$) C, H, N, S.

4.2.20. Cyclohexylmethyl-[2-(4-methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]amine (24). Compound **24** was obtained from **4a** and cyclohexanemethylamine following GP1. After flash chromatography the title compound was isolated (96% yield) as a white solid; mp 160.0–161.5 °C. Anal ($C_{19}H_{22}F_3N_3O_2S$) C, H, N, S.

4.2.21. [2-(4-Methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]thiazol-2-ylmethylamine (25). Compound **25** was prepared from **4a** and thiazol-2-ylmethylamine following GP1. After flash chromatography the title compound was isolated (89% yield) as a yellow solid; mp 194.0–196.4 °C. Anal ($C_{16}H_{13}F_3N_4O_2S_2$) C, H, N, S.

4.2.22. [2-(4-Methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]-(1-methyl-1*H*-pyrrol-2-ylmethyl)amine (26). Compound **26** was obtained from **4a** and (1-methyl-1*H*-pyrrol-2-yl)methylamine following GP1. After flash chromatography the title compound was isolated (70% yield) as a yellow solid; mp 209.5–212.0 °C. Anal ($C_{18}H_{17}F_3N_4O_2S$) C, H, N, S.

4.2.23. [2-(4-Methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]naphthalen-2-ylmethylamine (27). Compound **27** was obtained from **4a** and naphthalen-2-ylmethylamine following GP1. After flash chromatography the title compound was isolated (93% yield) as an off-white solid; mp 194.0–195.8 °C. Anal ($C_{23}H_{18}F_3N_3O_2S$) C, H, N, S.

4.2.24. (1*H*-Benzoimidazol-2-ylmethyl)-[2-(4-methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]amine (28). Compound **28** was obtained from **4a** and 2-(aminomethyl)benzimidazole following GP1. After flash chromatography the title compound was isolated (95% yield) as a pale rose solid; mp > 253.8 °C. Anal ($C_{20}H_{16}F_3N_5O_2S$) C, H; N, S.

4.2.25. [2-(4-Methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]pentylamine (29). Compound **29** was prepared from **4a** and pentylamine following GP1. After flash chromatography the title compound was isolated (97% yield) as an almost white solid; mp 119.6–122.1 °C. Anal ($C_{17}H_{20}F_3N_3O_2S$) C, H, N, S.

4.2.26. Isobutyl-[2-(4-methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]amine (30). Compound **30** was prepared from **4a** and isobutylamine following GP1. After flash chromatography the title compound was isolated (97% yield) as a white solid; mp 192.0–191.2 °C. Anal ($C_{16}H_{18}F_3N_3O_2S$) C, H, N, S.

4.2.27. Cyclopentylmethyl-[2-(4-methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]amine (31). Compound **31** was obtained from **4a** and cyclopentylmethylamine following GP1. After flash chromatography the title compound was isolated (95% yield) as a white solid; mp 171.6–173.2 °C. Anal ($C_{18}H_{20}F_3N_3O_2S$) C, H, N, S.

4.2.28. Cyclopentyl-[2-(4-methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]amine (32). Compound **32** was prepared from **4a** and cyclopentylamine following GP1. After flash chromatography the title compound was isolated (98% yield) as an off-white solid; mp 198.0–200.4 °C. Anal ($C_{17}H_{18}F_3N_3O_2S$) C, H; N, S.

4.2.29. Cyclohexyl-[2-(4-methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]amine (33). Compound **33** was prepared from **4a** and cyclohexylamine following GP1. After flash chromatography the title compound was isolated (92% yield) as a white solid; mp 154.4–156.3 °C. Anal ($C_{18}H_{20}F_3N_3O_2S$) C, H, N, S.

4.2.30. Cyclohex-3-enylmethyl-[2-(4-methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]amine (34). Compound **34** was obtained from **4a** and cyclohex-3-enylmethylamine following GP1. After flash chromatography the title compound was isolated (66% yield) as a white solid: mp 169.0–171.8 °C. Anal ($C_{19}H_{20}F_3N_3O_2S$) C, H, N, S.

4.2.31. Benzyl-[2-(4-methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]methylamine (35). Compound **35** was prepared from **4a** and *N*-benzylmethylamine following GP1. After flash chromatography the title compound was isolated (97% yield) as a white solid; mp 133.7–135.8 °C. Anal ($C_{20}H_{18}F_3N_3O_2S$) C, H, N, S.

4.2.32. Benzylethyl-[2-(4-methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]amine (36). Compound **36** was prepared from **4a** and *N*-benzylethylamine following GP1. After flash chromatography the title compound was isolated (93% yield) as a white solid; mp 139.9–141.9 °C. Anal ($C_{21}H_{20}F_3N_3O_2S$) C, H, N, S.

4.2.33. [2-(4-Methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]-(1-phenylethyl)amine (37). Compound **37** was prepared from **4a** and 1-phenylethylamine following GP1 and the title compound was isolated (95% yield) as a pale yellow solid; mp 186.0–187.8 °C. Anal ($C_{20}H_{18}F_3N_3O_2S$) C, H, N, S.

4.2.34. [2-(4-Methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]phenylamine (38). Aniline (130 μL, 1.34 mmol) was added to a suspension of NaH (60% in mineral oil, 0.16 g, 4.00 mmol) in THF (3 mL) at 0 °C and the mixture stirred at rt for 15 min. A solution of **4a** (0.30 g, 0.89 mmol) in THF (4 mL) was added dropwise to the previously described suspension at 0 °C and the resulting mixture stirred at rt for 22 h. The reaction was quenched with water (15 mL) and tha mixture extracted with EtOAc (3× 100 mL). The combined organic extracts were dried (Na_2SO_4), the solvents evaporated and the resulting residue purified by flash chromatography (3× 20 cm, EtOAc/hept 43:57) to yield the title compound **38** (0.22 g, 63% yield) as an off-white solid; mp 297.2–298.7 °C. ^{1}H NMR ($CDCl_3$) δ 3.09 (s, 3H, SO_2CH_3), 7.35–7.40 (m, 2H, Ar-*H* and H-5), 7.64–7.75 (m, 4H, Ar-*H*), 8.01 (d, J = 8.5 Hz, 2H, Ar-*H*), 8.46 (d, J = 8.5 Hz, 2H, Ar-*H*). ^{13}C NMR ($CDCl_3$) δ 44.3 (SO_2CH_3), 106.9 (C-5), 120.4 (q, J = 275 Hz, CF_3), 127.7 (CH), 128.9 (CH), 129.3 (CH), 129.7 (CH), 131.0 (CH), 139.5 (C), 140.7 (C), 143.0 (C), 156.8 (q, J = 36 Hz, C-6), 162.9 (C). Anal ($C_{18}H_{14}F_3N_3O_2S$) C, H, N, S.

4.2.35. (4-Isopropylphenyl)-[2-(4-methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]amine (39). Compound **39** was prepared from **4a** and 4-isopropylaniline according to the procedure previously described for the synthesis of compound **38**. The title compound was isolated (64% yield) as a yellowish solid; mp 255.0–257.5 °C. Anal ($C_{21}H_{20}F_3N_3O_2S$) C, H, N, S.

4.2.36. 4-Benzylsulfanyl-2-(4-methanesulfonylphenyl)-6-trifluoromethylpyrimidine (40). K_2CO_3 (0.41 g, 2.96 mmol) was added to a solution of **4a** (0.50 g, 1.48 mmol) and phenylmethanethiol (210 μL, 1.77 mmol) in DMF (7.4 mL) and the resulting suspension stirred at rt for 1 h 45 min. The reaction mixture

was diluted with EtOAc (100 mL) and filtered through a bed of silica gel washed with EtOAc (100 mL). The solvent was evaporated under reduced pressure and the resulting residue submitted to flash chromatography (3× 20 cm, AcOEt/Hept 35:65) to yield the title compound **40** (0.66 g, 99% yield) as a white solid; mp 161.0–162.8 °C. ^{1}H NMR ($CDCl_3$) δ 3.11 (s, 3H, SO_2CH_3), 4.63 (s, 2H, SCH_2), 7.28–7.47 (m, 6H, H-5 and Ar-*H*), 8.07 (d, J = 8.5 Hz, 2H, Ar-*H*), 8.66 (d, J = 8.5 Hz, 2H, Ar-*H*). ^{13}C NMR ($CDCl_3$) δ 34.1 (SCH_2), 44.4 (SO_2CH_3), 113.4 (C-5), 120.4 (q, J = 275 Hz, CF_3), 127.6 (CH), 127.8 (CH), 128.7 (CH), 128.8 (CH), 129.4 (CH), 135.9 (C), 141.0 (C), 142.8 (C), 153.8 (q, J = 36 Hz, C-6), 162.7 (C), 173.1 (C). Anal ($C_{19}H_{15}F_3N_2O_2S_2$) C, H, N, S.

4.2.37. 2-(4-Methanesulfonylphenyl)-4-phenylmethanesulfinyl-6-trifluoromethylpyrimidine (41). A solution of **37** (0.21 g, 0.49 mmol) in CH_2Cl_2 (3 mL) was added to a suspension of [hydroxy(tosyloxy)iodo]benzene (0.21 g, 0.59 mmol) in CH_2Cl_2 (4 mL) and the mixture stirred at rt for 22 h and 2 h at 40 °C. The resulting solution was diluted with CH_2Cl_2 (100 mL) and extracted with H_2O (3× 100 mL). The combined organic extracts were dried (Na_2SO_4), the solvents evaporated under reduced presure and the resulting residue purified by flash chromatography (2× 20 cm, EtOAc/hept 50:50) to yield the title compound **41** (0.24 g, 98% yield) as a cream solid; mp 159.0–162.5 °C. ^{1}H NMR ($CDCl_3$) δ 3.11 (s, 3H, SO_2CH_3), 4.20 (d, J = 13.1 Hz, 1H, $SOCH_2$Ph), 4.48 (d, J = 13.1 Hz, 1H, $SOCH_2$Ph), 9.90–7.00 (m, 2H, Ar-*H*), 7.10–7.30 (m, 3H, Ar-*H*), 7.83 (s, 1H, H-5), 8.10 (d, J = 8.5 Hz, 2H, Ar-*H*), 8.68 (d, J = 8.5 Hz, 2H, Ar-*H*). ^{13}C NMR ($CDCl_3$) δ 44.3 (SO_2CH_3), 60.2 ($SOCH_2$Ph), 112.1 (C-5), 119.8 (q, J = 276 Hz, CF_3), 127.9 (CH), 128.5 (CH), 128.8 (CH), 129.7 (CH), 130.0 (CH), 139.5 (C), 143.7 (C), 157.8 (q, J = 37 Hz, C-6), 162.7 (C), 179.2 (C). Anal ($C_{19}H_{15}F_3N_2O_3S_2$) C, H, N, S.

4.2.38. 2-(4-Methanesulfonylphenyl)-4-phenylmethanesulfonyl-6-trifluoromethylpyrimidine (42). A solution of OXONE (0.80 g, 1.30 mmol) in H_2O (3 mL) was added to a solution of **37** (0.25 g, 0.59 mmol) in THF (7 mL) at 0 °C and the resulting mixture was stirred at rt for 22 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3× 70 mL). The combined organic layers were dried (Na_2SO_4) and the solvents evaporated under reduced pressure. After flash chromatography (3× 16 cm, EtOAc/hept 45:55 and 50:50) the title compound was isolated (0.15 g, 55% yield) as a cream solid; mp 174.0–176.5 °C. ^{1}H NMR ($CDCl_3$) δ 3.14 (s, 3H, SO_2CH_3), 4.80 (s, 2H, SO_2CH_2Ph), 7.20–7.30 (m, 5H, Ar-*H*), 8.02 (s, 1H, H-5), 8.14 (d, J = 8.4 Hz, 2H, Ar-*H*), 8.74 (d, J = 8.4 Hz, 2H, Ar-*H*). ^{13}C NMR ($CDCl_3$) δ 44.2 (SO_2CH_3), 58.1 (SO_2CH_2Ph), 116.0 (C-5), 119.6 (q, J = 276 Hz, CF_3), 125.7 (C), 128.0 (CH), 129.0 (CH), 129.3 (CH), 129.9 (CH), 131.0 (CH), 138.9 (C), 144.1 (C), 159.2 (q, J = 38 Hz, C-6), 164.3 (C), 167.9 (C). Anal ($C_{19}H_{15}F_3N_2O_4S_2$) C, H, N, S.

4.2.39. 2-(4-Methanesulfonylphenyl)-4-(thiophen-2-ylmethylsulfanyl)-6-trifluoromethylpyrimidine (43). Compound **43** was synthesized from **4a** and thiophen-2-ylmethanethiol according to the procedure previously described for the preparation of **40**. The title compound was isolated (33% yield) as a white solid; mp 148.8–152.0 °C. Anal ($C_{17}H_{13}F_3N_2O_2S_3$) C, H, N, S.

4.2.40. [2-(4-Methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]-(2-thiophen-2-ylethyl)amine (44). Compound **44** was prepared from **4a** and 2-thiophen-2-ylethylamine following GP1. The title compound was isolated (97% yield) as a solid; mp 143.5–144.8 °C. Anal ($C_{18}H_{16}F_3N_3O_2S_2$) C, H, N, S.

4.2.41. [2-(4-Methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]-[2-(1-methyl-1*H*-pyrrol-2-yl)-ethyl]amine (45). Compound **45** was prepared from **4a** and 2-(1-methyl-1*H*-pyrrol-2-yl)ethylamine following GP1. After flash chromatography the title compound was isolated (80% yield) as an almost white solid; mp 163.0–165.3 °C. Anal ($C_{19}H_{19}F_3N_4O_2S$) C, H, N, S.

4.2.42. [2-(4-Methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]-(4-methylbenzyl)amine (46). Compound **46** was synthesized from **4a** and 4-methylbenzylamine following GP1. After flash chromatography the title compound was isolated (99% yield) as a white solid; mp 165.8–167.0 °C. Anal ($C_{20}H_{18}F_3N_3O_2S$) C, H, N, S.

4.2.43. (4-Fluorobenzyl)-[2-(4-methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]amine (47). Compound **47** was prepared from **4a** and 4-fluorobenzylamine following GP1. After flash chromatography the title compound was isolated (98% yield) as an almost white solid; mp 171–173 °C. Anal ($C_{19}H_{15}F_4N_3O_2S$) C, H, N, S.

4.2.44. [2-(4-Methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]-(2-methylbenzyl)amine (48). Compound **48** was prepared from **4a** and 2-methylbenzylamine following GP1. After flash chromatography the title compound was isolated (77% yield) as a white solid; mp 221.0–223.5 °C. Anal ($C_{20}H_{18}F_3N_3O_2S$) C, H, N, S.

4.2.45. [2-(4-Methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]-(3-methylbenzyl)amine (49). Compound **49** was prepared from **4a** and 3-methylbenzylamine following GP1. After flash chromatography the title compound was isolated (58% yield) as a white solid; mp 190.0–192.3 °C. Anal ($C_{20}H_{18}F_3N_3O_2S$) C, H, N, S.

4.2.46. (4-Isopropylbenzyl)-[2-(4-methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]amine (50). Compound **50** was prepared from **4a** and 4-isopropylbenzylamine following GP1. After flash chromatography the title compound was isolated (98% yield) as a solid; mp 157.1–159.9 °C. Anal ($C_{22}H_{22}F_3N_3O_2S$) C, H, N, S.

4.2.47. (3,5-Difluorobenzyl)-[2-(4-methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]amine (51). Compound **51** was prepared from **4a** and 3,5-difluorobenzylamine following GP1. After flash chromatography the title compound was isolated (99% yield) as an almost white solid; mp 200.0–203.1 °C. Anal ($C_{19}H_{14}F_5N_3O_2S$) C, H, N, S.

4.2.48. [2-(4-Methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]-(4-trifluoromethylbenzyl)amine (52). Compound **52** was prepared from **4a** and 4-trifluoromethylbenzylamine following GP1. After flash chromatography the title compound was isolated (89% yield) as a white solid; mp 187.2–189.3 °C. Anal ($C_{20}H_{15}F_6N_3O_2S$) C, H, N, S.

4.2.49. [2-(4-Methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]-(4-trifluoromethoxybenzyl)amine (53). Compound **53** was prepared from **4a** and 4-trifluoromethoxybenzylamine following GP1. After flash chromatography the title compound was isolated (99% yield) as a pale yellow solid; mp 168.0–170.5 °C. Anal ($C_{20}H_{15}F_6N_3O_3S$) C, H, N, S.

4.2.50. [2-(4-Methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]-(4-methoxybenzyl)amine (54). Compound **54** was prepared from **4a** and 4-methoxybenzylamine following GP1. After flash chromatography the title compound was isolated (97% yield) as a white solid; mp 182.8–185.0 °C. Anal ($C_{20}H_{18}F_3N_3O_3S$) C, H, N, S.

4.2.51. [2-(4-Methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]-(4-methoxymethoxybenzyl)amine (55). Compound **55** was prepared from **4a** and 4-methoxymethoxybenzylamine following GP1. After flash chromatography the title compound was isolated (98% yield) as a solid; mp 144.2–146.5 °C. Anal ($C_{21}H_{20}F_3N_3O_4S$) C, H, N, S.

4.2.52. 4-[[2-(4-Methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-ylamino]methyl]phenol (56). A saturated solution of HCl in EtOH (2.25 L) was added to a solution of compound **55** (0.42 g, 0.90 mmol) in THF (1.35 mL) and the mixture stirred at rt for 4 h. The reaction was quenched with H_2O (1 mL) and 10% aqueous solution of NaOH added until pH = 6. The aqueous layer was extracted with EtOAc (3× 175 mL). The residue obtained after evaporation of the solvents at reduced pressure was submitted to flash chromatography (2× 16 cm, EtOAc/hept/^{i}PrNH$_2$ 70:30:3) to yield a yellow solid that was washed with Et_2O. The title compound was isolated (0.38 g, 98% yield) as an off-white solid; mp 225.0–227.1 °C. ^{1}H NMR (DMSO-d_6) δ 3.26 (s, 3H, SO_2CH_3), 4.61 (d, J = 5.2 Hz, 2H, NHCH_2Ar), 6.74 (d, J = 8.2 Hz, 2H, Ar-*H*), 6.90 (s, 1H, H-5), 7.21 (d, J = 8.2 Hz, 2H, Ar-*H*), 8.05 (d, J = 8.3 Hz, 2H, Ar-*H*), 8.53 (d, J = 8.3 Hz, 2H, Ar-*H*), 8.40–8.70 (m, 1H), 9.34 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 43.5 (SO_2CH_3), 101.6 (C-5), 115.2 (CH), 121.0 (q, J = 274 Hz, CF_3), 127.3 (CH), 128.6 (CH), 129.1 (CH), 141.4 (C), 142.6 (C), 151.9 (q, J = 34 Hz, C-6), 156.6 (C), 162.5 (C), 162.6 (C). Anal ($C_{19}H_{16}F_3N_3O_3S$) C, H, N, S.

4.2.53. Methanesulfonic acid 4-[[2-(4-methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-ylamino]methyl]-phenyl ester (57). MsCl (50 μL, 0.57 mmol) was added to a solution of compound **56** (0.16 g, 0.38 mmol) and DMAP (6 mg) in pyridine (760 μL) at 0 °C and the resulting suspension was stirred at rt for 21 h. The mixture was treated with water (8 mL) and extracted with EtOAc (3× 100 mL). The residue obtained after evaporation of the organic solvents was purified by flash chromatography (1.5× 16 cm, EtOAc/hept/^{i}PrNH$_2$ 70:30:3) and the title compound was isolated (0.06 g, 31% yield) as a white solid. ^{1}H NMR (DMSO-d_6) δ 3.25 (s, 3H, CH_3), 3.35 (s, 3H, CH_3), 4.78 (d, J = 5.5 Hz, 2H, NHCH_2Ar), 6.95 (s, 1H, H-5), 7.34 (d, J = 8.5 Hz, 2H, Ar-*H*), 7.52 (d, J = 8.5 Hz, 2H, Ar-*H*), 8.04 (d, J = 8.3 Hz, 2H, Ar-*H*), 8.50 (d, J = 8.3 Hz, 2H, Ar-*H*), 8.76 (t, J = 5.5 Hz, 1H, N*H*). ^{13}C NMR (DMSO-d_6) δ 37.4 (CH_3SO_3Ar), 43.1 (NHCH_2Ar), 43.4 (SO_2CH_3), 101.7 (C-5), 121.0 (q, J = 274 Hz, CF_3), 122.3 (CH), 127.3 (CH), 128.6 (CH), 129.3 (CH), 138.1 (C), 141.3 (C), 142.6 (C), 148.1 (C), 152.0 (q, J = 34 Hz, C-6), 162.5 (C), 162.8 (C). Anal ($C_{20}H_{18}F_3N_3O_5S_2$) C, H, N, S.

4.2.54. (4-Aminobenzyl)-[2-(4-methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]amine (58). Compound **58** was prepared from **4a** and 4-aminobenzylamine following GP1. After flash chromatography the title compound was isolated (97% yield) as a yellow solid; mp 200.0–202.5 °C. Anal ($C_{19}H_{17}F_3N_4O_2S$) C, H, N, S.

4.2.55. [2-(4-Methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]-(3-methylthiophen-2-ylmethyl)amine (59). Compound **59** was prepared from **4a** and (3-methylthiophen-2-yl)methylamine following GP1. After flash chromatography the title compound was isolated (56% yield) as a yellow solid; mp 225.0–226.8 °C. Anal ($C_{18}H_{16}F_3N_3O_2S_2$) C, H, N, S.

4.2.56. [2-(4-Methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]-(5-methylthiophen-2-ylmethyl)amine (60). Compound **60** was obtained from **4a** and (5-methylthiophen-2-yl)methylamine following GP1. After flash chromatography the title compound was isolated (81% yield) as white solid: mp 167.0–168.5 °C. Anal ($C_{18}H_{16}F_3N_3O_2S_2$) C, H, N, S.

4.2.57. (5-Chlorothiophen-2-ylmethyl)-[2-(4-methanesulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]amine (61). Compound **61** was prepared from **4a** and (5-chlorothiophen-2-yl)methylamine following GP1. After flash chromatography the title compound was isolated (84% yield) as a yellow solid; mp 165.5–167.4 °C. Anal ($C_{17}H_{13}ClF_3N_3O_2S_2$) C, H, N, S.

4.2.58. Benzyl-[6-isopropyl-2-(4-methanesulfonylphenyl)-pyrimidin-4-yl]amine (62). Compound **62** was prepared from **4b** and benzylamine following GP1. After flash chromatography the title compound was isolated (85% yield) as a yellow solid; mp 136.5–139.2 °C. Anal ($C_{21}H_{23}N_3O_2S$) C, H, N, S.

4.2.59. [6-Isopropyl-2-(4-methanesulfonylphenyl)pyrimidin-4-yl]thiophen-2-ylmethylamine (63). Compound **63** was prepared from **4b** and 2-thiophenemethylamine following GP1. After flash chromatography the title compound was isolated (97% yield) as a yellowish solid; mp 141.1–143.4 °C. Anal ($C_{19}H_{21}N_3O_2S_2$) C, H, N, S.

4.2.60. Benzyl-[6-*tert*-butyl-2-(4-methanesulfonylphenyl)-pyrimidin-4-yl]amine (64). Compound **64** was prepared

from **4c** and benzylamine following GP1. After flash chromatography the title compound was isolated (95% yield) as a white solid; mp 145.0–147.0 °C. Anal ($C_{22}H_{25}N_3O_2S$) C, H, N, S.

4.2.61. [6-*tert*-Butyl-2-(4-methanesulfonylphenyl)pyrimidin-4-yl]thiophen-2-ylmethylamine (65). Compound **65** was prepared from **4c** and 2-thiophenemethylamine following GP1. After flash chromatography the title compound was isolated (95% yield) as a white solid; mp 143.0–145.0 °C. Anal ($C_{20}H_{23}N_3O_2S_2$) C, H, N, S.

4.2.62. Benzyl-[2-(4-methanesulfonylphenyl)-6-methoxypyrimidin-4-yl]amine (66). Compound **66** was prepared from **4h** and benzylamine following GP1. After flash chromatography the title compound was isolated (59% yield) as an almost white solid; mp 124.0–126.5 °C. Anal ($C_{19}H_{19}N_3O_3S$) C, H, N, S.

4.2.63. [2-(4-Methanesulfonylphenyl)-6-methoxypyrimidin-4-yl]thiophen-2-ylmethylamine (67). Compound **67** was prepared from **4h** and 2-thiophenemethylamine following GP1. After flash chromatography the title compound was isolated (23% yield) as an off-white solid; mp 120.0–124.1 °C. Anal ($C_{17}H_{17}N_3O_3S_2$) C, H, N, S.

4.2.64. Benzyl-[6-chloro-2-(4-methanesulfonylphenyl)pyrimidin-4-yl]amine (68). Compound **68** was prepared from **4d** and benzylamine following GP1. After flash chromatography the title compound was isolated (97% yield) as a white solid; mp 144.0–145.7 °C. Anal ($C_{18}H_{16}ClN_3O_2S$) C, H, N, S.

4.2.65. [6-Chloro-2-(4-Methanesulfonylphenyl)pyrimidin-4-yl]thiophen-2-ylmethylamine (69). Compound **69** was prepared from **4d** and 2-thiophenemethylamine following GP1. After flash chromatography the title compound was isolated (87% yield) as a white solid; mp 167.0–169.1 °C. Anal ($C_{16}H_{14}ClN_3O_2S_2$) C, H, N, S.

4.2.66. Benzyl-[6-ethylsulfanyl-2-(4-methanesulfonylphenyl)pyrimidin-4-yl]amine (70). Compound **70** was prepared from **4l** and benzylamine following GP1. After flash chromatography the title compound was isolated (81% yield) as a white solid; mp 160.0–162.2 °C. Anal ($C_{20}H_{21}N_3O_2S_2$) C, H, N, S.

4.2.67. [6-Ethylsulfanyl-2-(4-methanesulfonylphenyl)pyrimidin-4-yl]thiophen-2-ylmethylamine (71). Compound **71** was prepared from **4l** and 2-thiophenemethylamine following GP1. After flash chromatography the title compound was isolated (99% yield) as a white solid; mp 152.0–153.9 °C. Anal ($C_{18}H_{19}N_3O_2S_3$) C, H, N, S.

4.2.68. Benzyl-[6-ethanesulfonyl-2-(4-methanesulfonylphenyl)pyrimidin-4-yl]amine (72). A solution of compound **70** (1.14 g, 2.85 mmol) in THF (28 mL) at 0 °C was treated with a solution of OXONE (4.37 g, 7.12 mmol) in H_2O (17 mL) and the resulting suspension was stirred at rt for 15 h. The reaction mixture was diluted with H_2O and extracted with EtOAc (2× 110 mL). The cream solid obtained after evaporation of the solvents was characterized as the title compound **72** (1.15 g, 87% yield); mp 170.0–173.0 °C. ^{1}H NMR ($CDCl_3$) δ 1.35 (t, J = 7.4 Hz, 3H, $SO_2CH_2CH_3$), 3.09 (s, 3H, SO_2CH_3), 3.46 (q, J = 7.4 Hz, 2H, $SO_2CH_2CH_3$), 4.4–5.0 (m, 2H, $NHCH_2Ph$), 6.02 (br s, 1H, N*H*), 7.09 (s, 1H, H-5), 7.30–7.40 (m, 5H, Ar-*H*), 8.01 (d, J = 8.6 Hz, 2H, Ar-*H*), 8.58 (d, J = 8.6 Hz, 2H, Ar-*H*). ^{13}C NMR (DMSO-d_6) δ 6.6 ($SO_2CH_2CH_3$), 43.4 (SO_2CH_3), 44.0 (CH_2), 45.0 (CH_2), 102.5 (C-5), 126.9 (CH), 127.2 (CH), 127.7 (CH), 128.5 (CH), 128.7 (CH), 128.9 (CH), 138.6 (C), 141.2 (C), 142.7 (C), 162.0 (C), 162.5 (C), 163.1 (C). Anal ($C_{20}H_{21}N_3O_4S_2$) C, H, N, S.

4.2.69. [6-Ethanesulfonyl-2-(4-methanesulfonylphenyl)-pyrimidin-4-yl]thiophen-2-ylmethylamine (73). Compound **73** was prepared from product **71** following the procedure previously described for the synthesis of compound **72**. After flash chromatography the title compound was isolated (78% yield) as a white solid: mp 151.0–152.5 °C. Anal ($C_{18}H_{19}N_3O_4S_3$) C, H, N, S.

4.2.70. 6-Benzylamino-2-(4-methanesulfonylphenyl)pyrimidin-4-ol (74). A solution of compound **72** (0.50 g, 1.16 mmol) in THF (10.4 mL) was treated with 50% aqueous solution of NaOH (190 mL). The mixture was stirred at 70 °C for 4 days. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (3× 350 mL). The yellow solid obtained after evaporation of the solvents at reduced pressure was washed with CH_2Cl_2 and MeOH, suspended in H_2O and 10% aqueous solution of NaOH was added until pH 10. The aqueous layer was extracted with EtOAc and the solvents were evaporated to yield the title compound **74** (0.14 g, 35% yield) as a solid; mp > 265 °C. ^{1}H NMR (DMSO-d_6) δ 3.25 (s, 3H, SO_2CH_3), 4.44 (d, J = 6.0 Hz, 2H, $NHCH_2Ph$), 5.22 (s, 1H, H-5), 7.19–7.33 (m, 5H, Ar-*H*), 7.58 (t, J = 6.0 Hz, 1H, N*H*), 8.00 (d, J = 8.4 Hz, 2H, Ar-*H*), 8.34 (d, J = 8.4 Hz, 2H, Ar-*H*). Anal ($C_{18}H_{17}N_3O_3S$) C, H, N, S.

4.2.71. 2-(4-Methanesulfonylphenyl)-6-[(thiophen-2-ylmethyl)amino]pyrimidin-4-ol (75). Compound **75** was prepared from product **73** following the procedure previously described for the synthesis of compound **74**. After flash chromatography the title compound was isolated (38% yield) as a yellow solid; mp 261.0–267.4 °C. Anal ($C_{16}H_{15}N_3O_3S_2$) C, H, N, S.

4.2.72. *N*-Benzyl-*N*′-isopropyl-2-(4-methanesulfonylphenyl)pyrimidine-4,6-diamine (76). A solution of compound **72** (0.18 g, 0.42 mmol) in isopropylamine (4 mL) was stirred under pressure at 100 °C for 6 days. The crude residue obtained after evaporation of the solvent was purified by flash chromatography (2× 16 cm, EtOAc/hept 45:55) to provide the title compound **76** (0.12 g, 71% yield) as an off-white solid; mp 69.7–73.4 °C. ^{1}H NMR ($CDCl_3$) δ 1.11 (d, J = 6.4 Hz, 6H, $CH(CH_3)_2$), 2.95 (s, 3H, SO_2CH_3), 3.72 (hept, J = 6.4 Hz, 1H, $CH(CH_3)_2$), 4.41 (d, J = 5.8 Hz, 2H, $NHCH_2$), 4.69 (d, J = 7.5 Hz, 1H, N*H*), 5.13 (s, 1H, H-5), 5.32 (d, J = 4.7 Hz, 1H, N*H*), 7.18–7.27 (m, 5H, Ar-*H*), 7.86 (d, J = 8.4 Hz, 2H, Ar-*H*), 8.41 (d, J = 8.4 Hz, 2H, Ar-*H*). ^{13}C NMR ($CDCl_3$) δ 22.6

($CH(CH_3)_2$), 42.8 ($CH(CH_3)_2$), 44.4 (SO_2CH_3), 45.8 ($NHCH_2$), 79.6 (C-5), 127.0 (CH), 127.2 (CH), 127.3 (CH), 128.6 (C), 128.7 (C), 138.4 (C), 140.9 (C), 143.9 (C), 161.5 (C), 162.6 (C), 163.4 (C). Anal ($C_{21}H_{24}N_4O_2S$) C, H, N, S.

4.2.73. *N*-Isopropyl-2-(4-methanesulfonylphenyl)-*N*′-thiophen-2-ylmethylpyrimidine-4,6-diamine (77). Compound **77** was prepared from product **69** and isopropylamine following the procedure described for the synthesis of compound **76**. The title compound was isolated (57% yield) as an oil. Anal ($C_{19}H_{22}N_4O_2S_2$) C, H, N, S.

4.2.74. Benzyl-[2-(4-methanesulfonylphenyl)pyrimidin-4-yl]amine (78). A solution of OXONE (4.44 g, 7.22 mmol) in H_2O (17 mL) was added dropwise to a solution of **94** (0.98 g, 2.89 mmol) in CH_2Cl_2 (29 mL) at 0 °C. The mixture was stirred for 2 h and the aqueous layer was extracted with CH_2Cl_2 (4× 300 mL). The crude residue obtained after evaporation of the solvent was purified by flash chromatography (3× 16 cm, EtOAc/hept 40:60 and 50:50) to provide the title compound (0.40 g, 36% yield) as an almost white solid; mp 186.3–187.3 °C. ^{1}H NMR (DMSO-d_6) δ 3.24 (s, 3H, SO_2CH_3), 4.73 (d, J = 5.9 Hz, 2H, $NHCH_2$), 7.17–7.43 (m, 6H, Ar-*H* and H-5), 7.99 (d, J = 8.4 Hz, 2H, Ar-*H*), 8.31 (t, J = 5.9 Hz, 1H, N*H*), 8.41 (d, J = 4.0 Hz, 1H, H-6), 8.45 (d, J = 8.4 Hz, 2H, Ar-*H*). ^{13}C NMR (DMSO-d_6) δ 43.4 (SO_2CH_3), 43.8 ($NHCH_2$), 113.1 (C-5), 126.8 (CH), 127.2 (CH), 127.4 (CH), 128.3 (CH), 139.5 (C), 141.7 (C), 142.1 (C), 152.9 (C-6), 157.3 (C), 159.3 (C). Anal ($C_{18}H_{17}N_3O_2S$) C, H, N, S.

4.2.75. [2-(4-Methanesulfonylphenyl)pyrimidin-4-yl]thiophen-2-ylmethylamine (79). Compound **79** was prepared from **95** following the procedure previously described for the synthesis of **78**. After flash chromatography the title compound was isolated (69% yield) as a cream solid; mp 145.6–148.0 °C. Anal ($C_{16}H_{15}N_3O_2S_2$) C, H, N, S.

4.2.76. *N,N*-Diethyl-2-(4-methanesulfonylphenyl)-*N*′-thiophen-2-ylmethylpyrimidine-4,6-diamine (80). Compound **83** was prepared from product **69** and diethylamine following the procedure previously described for the synthesis of compound **76**. After flash chromatography the title compound was isolated (83% yield) as a yellow solid; mp 149.0–151.5 °C. Anal ($C_{20}H_{24}N_4O_2S_2$) C, H, N, S.

4.2.77. [6-Ethanesulfinyl-2-(4-methanesulfonylphenyl)pyrimidin-4-yl]thiophen-2-ylmethylamine (81). Compound **81** was prepared from product **71** following the procedure previously described for the synthesis of compound **41**. After flash chromatography the title compound was isolated (40% yield) as a yellow solid; mp 152.0–153.9 °C. Anal ($C_{18}H_{19}N_3O_3S_3$) C, H, N, S.

4.2.78. [6-Ethoxy-2-(4-methanesulfonylphenyl)pyrimidin-4-yl]thiophen-2-ylmethylamine (82). Compound **82** was prepared from product **4i** and 2-thiophenemethylamine following GP1. After flash chromatography the title compound was isolated (59% yield) as a solid; mp 160–162.2 °C. Anal ($C_{18}H_{19}N_3O_3S_2$) C, H, N, S.

4.2.79. [2-(4-Methanesulfonylphenyl)-6-(2-methoxyethoxy)-pyrimidin-4-yl]thiophen-2-ylmethylamine (83). Compound **83** was prepared from **4j** and 2-thiophenemethylamine following GP1. After flash chromatography the title compound was isolated (67% yield) as a brown solid; mp 147.4–150.3 °C. Anal ($C_{19}H_{21}N_3O_4S_2$) C, H, N, S.

4.2.80. [6-Cyclopentyloxy-2-(4-methanesulfonylphenyl)-pyrimidin-4-yl]thiophen-2-ylmethylamine (84). Compound **84** was prepared from **4k** and 2-thiophenemethylamine following GP1. After flash chromatography the title compound was isolated (54% yield) as a cream solid; mp 184.0–184.6 °C. Anal ($C_{21}H_{23}N_3O_3S_2$) C, H, N, S.

4.2.81. [5-Methyl-2-(4-methylsulfonylphenyl)-6-trifluoromethylpyrimidin-4-yl]benzylamine (85). Compound **85** was prepared from **4e** and benzylamine following GP1 and using Cs_2CO_3 as a base. After flash chromatography the title compound was isolated (66% yield) as a white solid; mp 194.0–196.5 °C. Anal ($C_{20}H_{18}F_3N_3O_2S$) C, H, N, S.

4.2.82. [2-(4-Methanesulfonylphenyl)-5-methyl-6-trifluoromethylpyrimidin-4-yl]thiophen-2-ylmethylamine (86). Compound **86** was prepared from **4e** and 2-thiophenemethylamine following GP1 and using Cs_2CO_3 as a base. After flash chromatography the title compound was isolated (16% yield) as an oil. Anal ($C_{18}H_{16}F_3N_3O_2S_2$) C, H, N, S.

4.2.83. [2-(4-Methanesulfonylphenyl)-5-ethyl-6-trifluoromethylpyrimidin-4-yl]thiophen-2-ylmethylamine (87). Compound **87** was prepared from **4f** and 2-thiophenemethylamine following GP1 and using Cs_2CO_3 as a base. After flash chromatography the title compound was isolated (41% yield) as a yellow solid; mp 168.0–171.0 °C. Anal ($C_{19}H_{18}F_3N_3O_2S_2$) C, H, N, S.

4.2.84. [6-Chloro-2-(4-methanesulfonylphenyl)pyrimidin-4-yl]-(4-methylbenzyl)amine (88). Compound **88** was prepared from **4d** and 4-methylbenzylamine following GP1. After flash chromatography the title compound was isolated (86% yield) as a white solid; mp 158.5–159.9 °C. Anal ($C_{20}H_{18}F_3N_3O_2S$) C, H, N, S.

4.2.85. [6-Chloro-2-(4-methanesulfonylphenyl)-5-methylpyrimidin-4-yl]-(4-methylbenzyl)amine (89). Compound **89** was prepared from **4g** and 4-methylbenzylamine following GP1 and using Cs_2CO_3 as a base. After flash chromatography the title compound was isolated (47% yield) as a yellow solid; mp 182.0–186.0 °C. Anal ($C_{21}H_{20}F_3N_3O_2S$) C, H, N, S.

4.2.86. *N*-(4-Fluorobenzyl)-[2-(4-methanesulfonylphenyl)-5-methyl-6-trifluoromethylpyrimidin-4-yl]amine (90). Compound **90** was prepared from **4e** and 4-fluorobenzylamine following GP1 and using Cs_2CO_3 as a base. After flash chromatography the title compound was iso-

lated (32% yield) as a solid; mp 169.0–173.0 °C. Anal ($C_{20}H_{17}F_4N_3O_2S$) C, H, N, S.

4.2.87. (4-Fluorobenzyl)-[2-(4-methanesulfonylphenyl)-5-ethyl-6-trifluoromethylpyrimidin-4-yl]amine (91). Compound **91** was prepared from **4f** and 4-fluorobenzylamine following GP1 and using Cs_2CO_3 as a base. After flash chromatography the title compound was isolated (16% yield) as a yellow solid; mp 189.0–192.0 °C. Anal ($C_{21}H_{19}F_4N_3O_2S$) C, H, N, S.

4.2.88. [6-Chloro-2-(4-methanesulfonylphenyl)pyrimidin-4-yl]-(4-fluorobenzyl)amine (92). Compound **92** was prepared from **4d** and 4-fluorobenzylamine following GP1. After flash chromatography the title compound was isolated (24% yield) as a beige solid; mp 134.0–137.5 °C. Anal ($C_{18}H_{15}ClFN_3O_2S$) C, H, N, S.

4.2.89. [6-Chloro-2-(4-methanesulfonylphenyl)-5-methylpyrimidin-4-yl]-(4-fluorobenzyl)amine (93). Compound **93** was prepared from **4g** and 4-fluorobenzylamine following GP1 and using Cs_2CO_3 as a base. After flash chromatography the title compound was isolated (51% yield) as a yellow solid; mp 181.0–184.0 °C. Anal ($C_{19}H_{17}ClFN_3O_2S$) C, H, N, S.

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Supplementary data

Description of the in vitro assays for COX-1 and COX-2 inhibitory activity determination; full experimental procedures for the synthesis of intermediate compounds **2**–**4** and **95**–**94**; characterization data (^{1}H NMR, ^{13}C NMR) for compounds **2**–**4** and **5**–**95**; elemental analyses. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2007.11.079.

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23. Unpublished results.