Synthesis and Biological Evaluation of the 1,5-Diarylpyrazole Class of Cyclooxygenase-2 Inhibitors: Identification of 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (SC-58635, Celecoxib)

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A series of sulfonamide-containing 1,5-diarylpyrazole derivatives were prepared and evaluated for their ability to block cyclooxygenase-2 (COX-2) *in vitro* and *in vivo*. Extensive structure−activity relationship (SAR) work was carried out within this series, and a number of potent and selective inhibitors of COX-2 were identified. Since an early structural lead (**1f**, SC-236) exhibited an unacceptably long plasma half-life, a number of pyrazole analogs containing potential metabolic sites were evaluated further *in vivo* in an effort to identify compounds with acceptable pharmacokinetic profiles. This work led to the identification of **1i** (4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide, SC-58635, celecoxib), which is currently in phase III clinical trials for the treatment of rheumatoid arthritis and osteoarthritis.

Introduction

Prostaglandins (PGs) elicit a variety of important beneficial and untoward biological responses. Among the undesirable properties of prostaglandins is their ability to induce pain, fever, and symptoms associated with the inflammatory response. Nonsteroidal anti-inflammatory drugs (NSAIDs) block the formation of prostaglandins and have analgesic, antipyretic, and anti-inflammatory activity.[1] However, treatment with NSAIDs, particularly chronically, often leads to disruption of beneficial prostaglandin-regulated processes.[2,3] The principal side effect associated with chronic consumption of NSAIDs is significant gastrointestinal irritation[4] and the formation of life-threatening gastrointestinal ulcers, which considerably limits the therapeutic potential of this class of drug. Alternative treatment of inflammation with glucocorticoids may also lead to a variety of undesirable side effects, particularly during extended periods of therapy.[5]

In the past it was thought that cyclooxygenase (COX) was a single enzyme present constitutively in most cells. This led to the widely held notion that inhibition of cyclooxygenase would unavoidably lead to both beneficial and detrimental effects.[6,7] However, recently it was observed that cyclooxygenase activity dramatically increased in inflammatory states and that cellular COX activity can be induced by inflammatory cytokines and endotoxins. This suggested that a second form of COX existed, an inducible form (COX-2) that is expressed during inflammatory conditions, along with a constitutive form (COX-1) that produces physiologically important PGs and is present in tissues such as the gastrointestinal tract and kidney.[8−10] Current NSAIDs inhibit both forms of the enzyme, with many demonstrating a selectivity for COX-1. It is believed that it is the inhibition of COX-1 that causes the side effects seen with NSAIDs. The discovery of COX-2 led to the recognition that selective inhibitors of COX-2 would constitute a novel approach to the treatment of inflammation with diminished side effects.[11]

Recently a number of selective inhibitors of COX-2 were shown to possess anti-inflammatory activity with little or no gastric side effects.[12,13] To date, two distinct structural classes of molecules have been reported as selective inhibitors of COX-2. NS-398[14] and L-745,337[15] are members of the methanesulfonanilide class of inhibitors, and DuP 697,[16] SC-57666,[17] and **39** (SC-58125)[18] are a few of the many examples of the tricyclic inhibitor class.[19]

In this paper we report the synthesis and structure−activity relationship (SAR) studies of the 1,5-diarylpyrazole series of selective COX-2 inhibitors related to the previously reported **39**. This study led to the identification of **1i** (SC-58635, celecoxib) which is currently undergoing evaluation in phase III clinical trials.

Chemistry

The spatial orientation of the two aromatic rings of the tricyclic inhibitor class was known to be critical for cyclooxygenase inhibition. We found that the two appropriately substituted aromatic rings must reside on adjacent positions about the central ring for COX-2 inhibitory activity. For example, the 1,3-regioisomer of SC-58125 was found to be devoid of both COX-1 and COX-2 activity. The general method employed for the

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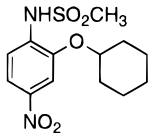
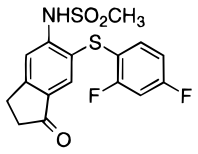
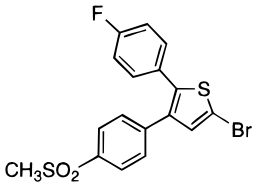


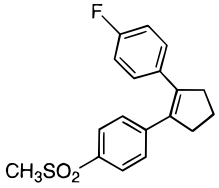
NS-398



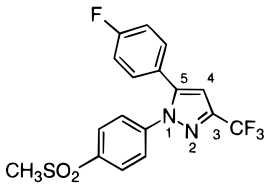
L-745,337



DuP 697



SC-57666



39 (SC-58125)

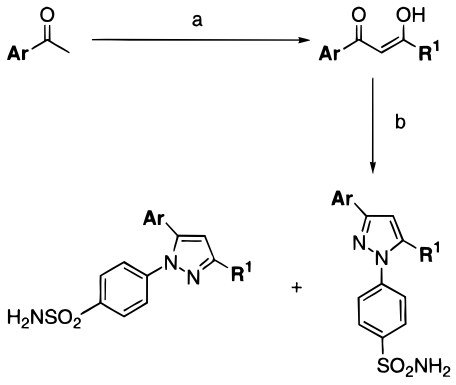
preparation of 1,5-diarylpyrazoles **1**−**3** is illustrated in Scheme 1. Claisen condensation of an acetophenone with either ethyl trifluoroacetate, ethyl difluoroacetate, or dimethyl oxalate provided the expected 1,3-dicarbonyl adduct in good yield. Reaction with (4-sulfamoylphenyl)hydrazine (or [4-(methylsulfonyl)phenyl]hydrazine for **39**) provided a mixture of 1,5-diarylpyrazole **1**, **2**, or **3** and 1,3-diarylpyrazole **4**, **5**, or **6**. The regioisomers were generally separable by flash chromatography. However, the 1,5-diarylpyrazole could be generated almost exclusively by carrying out the condensation in the presence of the hydrochloride salt of the phenylhydrazine in either refluxing ethanol or methyl *tert*-butyl ether (MTBE). This method proved successful for the preparation of analogs where $R^1 = CF_3$, CF_2H, and CO_2Me. Alternately, the 1,5-diarylpyrazoles could be prepared from epoxy ketones **7** as illustrated in Scheme 2. This method was utilized when little regiochemical bias was expected using the method described in Scheme 1 (*i.e.*, where R^1 = alkyl or aryl).

A number of 3-substituted pyrazole variants were accessible from the 3-carbomethoxy analogs **3** (Scheme 3). After saponification to acid **10**, primary and secondary amides **11** and **12** were readily obtained. Dehydration of **11** with oxalyl chloride furnished 3-cyano analogs **13**. Reduction of acid **10** with borane provided alcohol **14**, which could be alkylated (**15**), converted to fluoride **16** with diethylaminosulfur trifluoride (DAST), or mesylated and displaced by cyanide to give **17**.

A 3-methoxypyrazole analog (**19**) was synthesized from 3-keto-3-phenylpropionic acid as shown in Scheme 4. Condensation with (4-sulfamoylphenyl)hydrazine provided pyrazolone **18** which was O-methylated to provide **19**.

4-Halogenated 3-substituted pyrazoles **20** were prepared by treatment of an acetic acid solution of a selected pyrazole with either chlorine or bromine (Scheme 5). Chlorination could alternately be carried out using SO_2Cl_2. 4-Halopyrazoles **21** were prepared by halogenation of 3-carbomethoxypyrazoles (R = CO_2Me) followed by saponification and thermolysis. Additional 4-substituted pyrazoles were synthesized as shown in Scheme

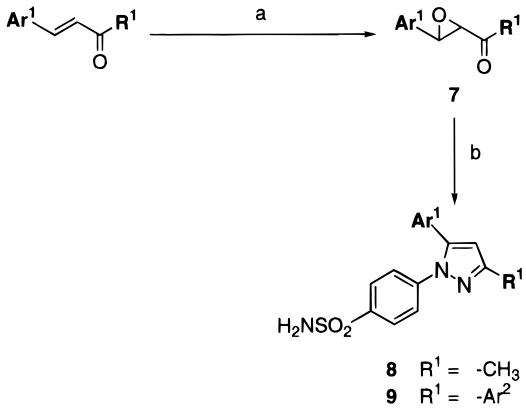
Scheme 1[a]



1 R^1 = -CF_3 **4** R^1 = -CF_3
2 R^1 = -CHF_2 **5** R^1 = -CHF_2
3 R^1 = -CO_2Me **6** R^1 = -CO_2Me

[a] (a) 25% NaOMe/MeOH, MTBE, $R^1CO_2R^2$; (b) (4-sulfamoylphenyl)hydrazine-HCl, EtOH, reflux.

Scheme 2[a]



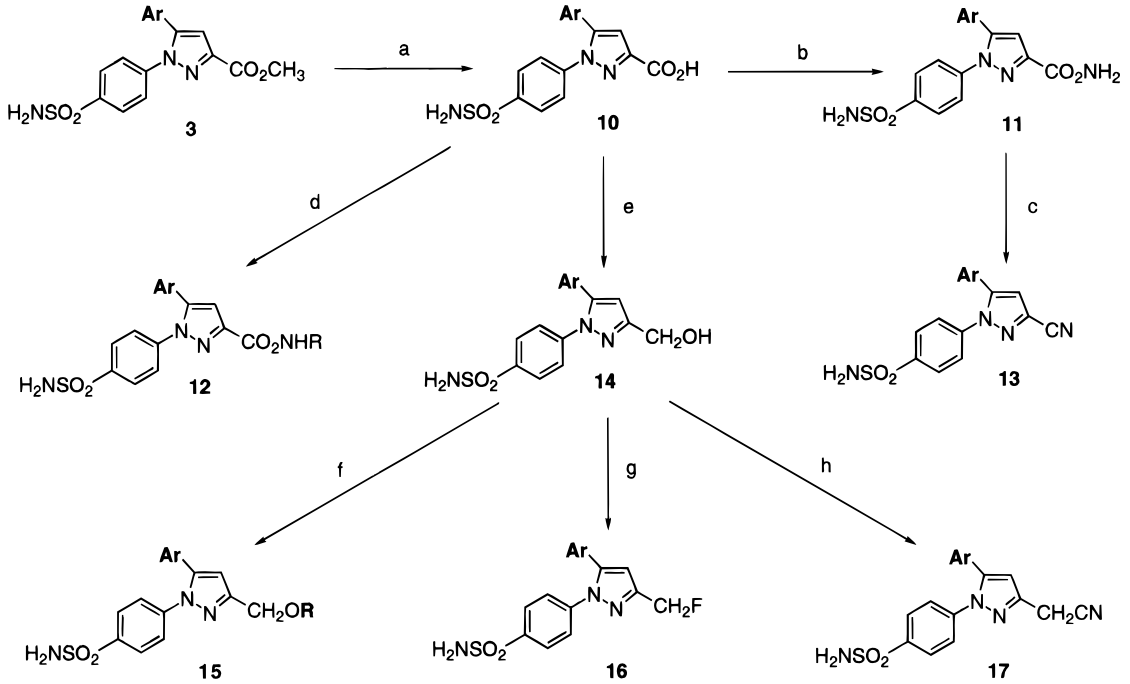
8 R^1 = -CH_3
9 R^1 = -Ar^2

[a] (a) 30% H_2O_2, NaOH, EtOH; (b) (4-sulfamoylphenyl)hydrazine-HCl, EtOH, AcOH.

6. Condensation of an appropriately substituted acetophenone with dimethylformamide (DMF) dimethyl acetal provided an enamine which was subsequently treated with (4-sulfamoylphenyl)hydrazine to provide pyrazoles **22**. The substituted acetophenones could also be condensed with ethyl trifluoroacetate followed by (4-sulfamoylphenyl)hydrazine to provide, for example, **24**. However, Claisen condensation under these conditions generally gave poor yields of the corresponding diketone when R was either alkyl or methoxy. Instead, the substituted acetophenone was deprotonated with sodium hexamethyldisilazide and acylated with *N*-(trifluoroacetyl)imidazole to provide the requisite 1,3-diketone. Condensation of the diketone with (4-sulfamoylphenyl)hydrazine in the usual manner gave tetrasubstituted pyrazoles **25**. Demethylation of **25** (R = OMe) gave pyrazolone **26**.

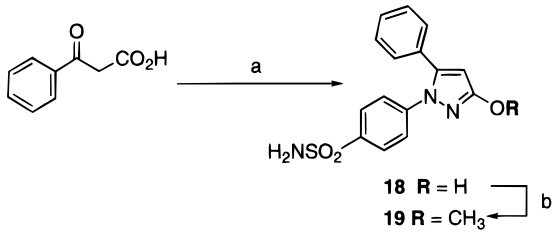
Additionally, two analogs were prepared in which the substituents of the two aromatic rings were reversed (*i.e.*, the 4-sulfamoylphenyl is at the 5-position of the pyrazole ring, instead of the 1-position) as shown in Scheme 7. Bis-*p*-methoxybenzyl-protected 4-sulfamoylacetophenone was condensed with ethyl trifluoroacetate followed by a 4-substituted phenylhydrazine to give pyrazole **27**. Deprotection with ceric ammonium nitrate (CAN) provided the reversed analogs **28**.

Scheme 3[a]



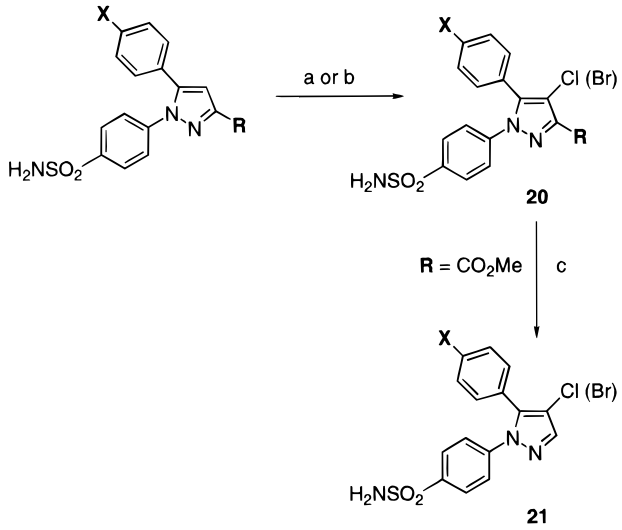
[a] (a) NaOH, MeOH; (b) NH_3(g), MeOH, cat. NaCN; (c) 1. DMF, $(COCl)_2$, 2. pyridine; (d) 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC), hydroxybenzotriazole hydrate (HOBT), DMF, RNH_2; (e) BH_3−THF; (f) RX; (g) DAST; (h) 1. MsCl, 2. NaCN.

Scheme 4[a]



[a] (a) (4-Sulfamoylphenyl)hydrazine-HCl, MeOH, reflux; (b) MeI.

Scheme 5[a]



[a] (a) Br_2 or Cl_2, HOAc; (b) SO_2Cl_2; (c) 1. NaOH, H_2O, THF, 2. Δ, $-CO_2$.

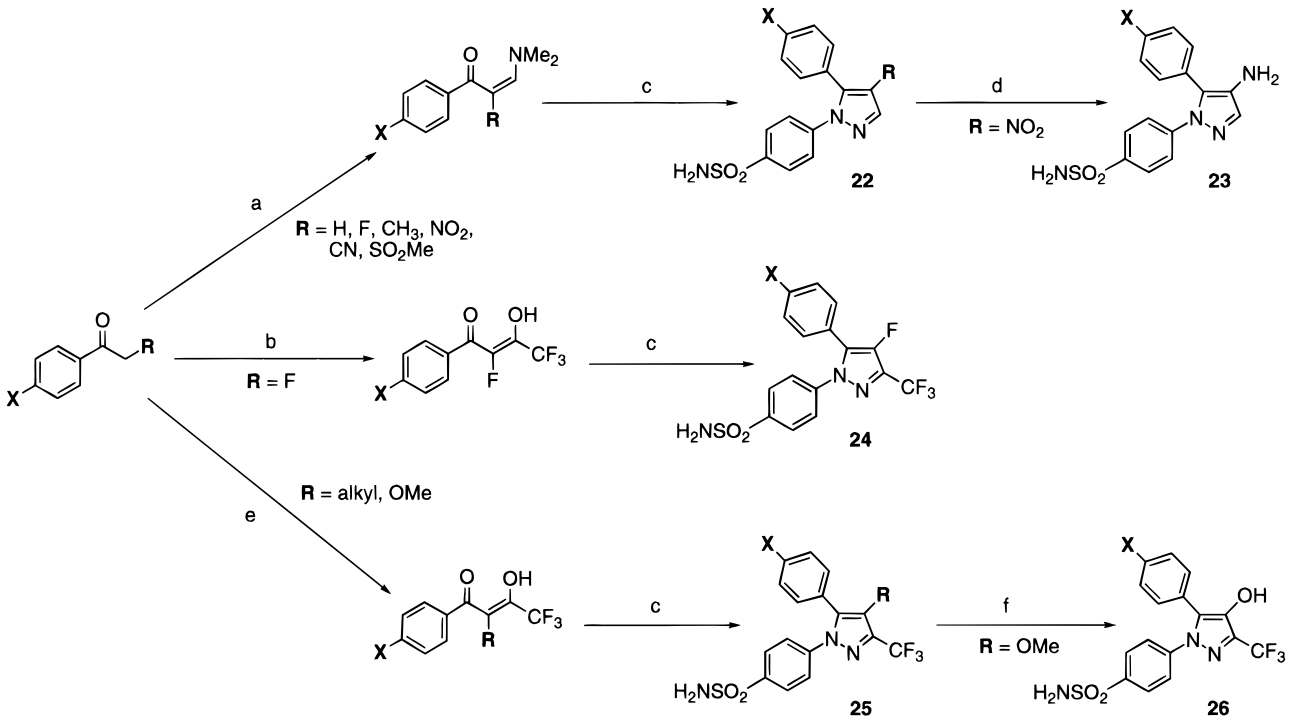
Biology

All compounds described herein were evaluated for their ability to block recombinant human COX-1 and COX-2.[20−23] Selected compounds were evaluated *in vivo* in the rat carrageenan-induced foot pad edema model,[18,24] the rat adjuvant-induced arthritis model,[26] and the rat carrageenan-induced hyperalgesia model.[18,26]

Results and Discussion

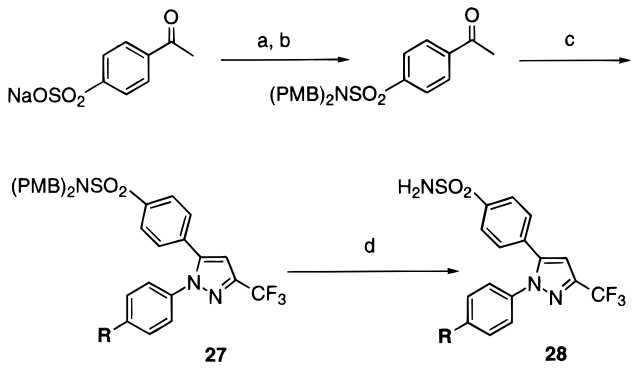
Using **39** as a template, numerous sites of modification about the pyrazole ring system were explored. The initial modification, conversion of the methyl sulfone to a sulfonamide, provided superior *in vitro* and *in vivo* results within this particular series and was held constant throughout most of the SAR studies. Since the 5-aryl substituent offered the most flexibility with regards to maintenance of COX-2 inhibitory activity, we thoroughly investigated modifications at this site in order to provide compounds with a range of physical properties (*i.e.*, water solubility, log *P*, pK_a, ionizability, etc.). In Tables 1−3, the 3-position on the pyrazole ring was held constant as either CF_3 or CHF_2, two series of analogs with essentially equivalent *in vitro* potency and selectivity. A number of monosubstituted 5-aryl derivatives are shown in Table 1. In general, introduction of substituents to the 2- or 4-position of this aromatic ring resulted in more potent COX-2 inhibitors than 3-substituted analogs (**1c**,**h**). Analogs which contained an electron-withdrawing group had no COX-1 activity and, at best, poor COX-2 activity (**1k**,**l**, **2c**−**f**). Electron-donating groups, on the other hand, tended to increase both COX-1 and COX-2 potency, resulting in compounds with what we considered unacceptable COX-1 inhibitory potency (**1o**,**q**, **2g**). The potent COX-1 activity of these analogs could be modulated, with little effect on COX-2 potency, simply by introduction of a substituent α to the para electron-donating group (Table 2). Halo (**2h**,**i**), methyl (**1x**), and methoxy (**1z**) substituents all worked well in this regard. In general, introduction of substituents to both α-positions decreased COX-1 potency even further (**2j**,**k**, **1ad**), again with little effect on COX-2 potency.

Scheme 6[a]



[a] (a) $Me_2NCH(OMe)_2$, Δ; (b) 25% NaOMe/MeOH, MTBE, CF_3CO_2Et; (c) (4-sulfamoylphenyl)hydrazine-HCl, EtOH, reflux; (d) NH_2NH_2, EtOH, 10% Pd/C; (e) $NaN(TMS)_2$, *N*-(trifluoroacetyl)imidazole; (f) NaSMe.

Scheme 7[a]



[a] (a) 1. $SOCl_2$, 2. NH_4OH; (b) NaH, DMSO, 4-methoxybenzyl bromide (PMBBr); (c) 1. NaOMe, CF_3CO_2Et, 2. (4-R-phenyl)hydrazine-HCl, pyridine, EtOH, 25 °C; (d) ceric ammonium nitrate (CAN), CH_3CN, H_2O.

There was, however, some sensitivity to steric hindrance at the 4-position of this aromatic ring, particularly with regards to COX-2 potency. For example, the 4-ethyl analog **1j** was about 20-fold less potent vs COX-2 compared to the 4-methyl analog **1i** (Table 1). Similarly, the 4-ethoxy analog **1p** was an 80 times less potent inhibitor of COX-2 than 4-methoxy analog **1o**.

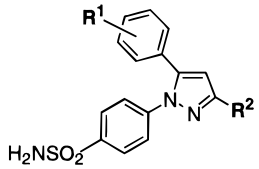
Other disubstituted analogs exhibited good potency and selectivity as long as one of the substituents was at the 4-position of the aromatic ring (*i.e.*, **1ae**,**af**,**ah**) (Table 2). As shown in Table 3, some heterocycles and carbocycles also exhibited excellent potency and selectivity, while others, most notably pyridyl (**1ai**−**ak**), were very poor COX-2 inhibitors. It is interesting to note that cyclohexenyl can successfully replace the 5-aryl group (**1ap**). Again, an aryl group with a substituent α to a para electron-donating group dramatically increased the COX-1/COX-2 selectivity (*i.e.*, **2n** vs **1at**).

The 3-position of the pyrazole ring tended to be very tolerant of a variety of functionality and seemed to have very few steric restrictions. In general, trifluoromethyl and difluoromethyl substituents provided superior potency and selectivity (Table 4). Cyano, some substituted amides, and selected aryl and heteroaryl derivatives were also good COX-2 inhibitors. Although a 3-methyl analog (**8a**) was not a good inhibitor of COX-2, various monosubstituted methyl derivatives were (**14a**, **15a**, **16a, 17a**).

The 4-position of the pyrazole ring was not nearly so tolerant of steric bulk. In fact, nothing larger than ethyl had good COX-2 inhibitory activity (Table 5). Substitution of the 4-position with halo or methyl provided not only very potent inhibitors of COX-2 but also fairly potent inhibitors of COX-1 (**20a**, **24**, **25a**). Ethyl seemed to be optimal, with regards to potency and selectivity (**25b**). Interestingly, removal of the 3-trifluoromethyl group in the 4-chloro, 4-bromo, or 4-cyano series significantly increased selectivity, with little effect on COX-2 potency (**21a**,**b, 22d**). In general, replacement of the 3-trifluoromethyl group in **20a** with other functional groups resulted in fairly potent but poorly selective inhibitors (**20b**−**g**).

A 4-(methylsulfonyl)phenyl or 4-sulfamoylphenyl substituent on the 1-position of the pyrazole ring was absolutely critical for good COX-2 inhibitory activity (Table 6). In general, the sulfonamides were superior based on overall *in vivo* efficacy data. N-Methylation or N,N-dimethylation of the sulfonamide (**29, 30**) resulted in compounds with no COX-2 inhibitory activity. Reversal of the sulfonamido group to a methanesulfonamido moiety (**31**) likewise resulted in no inhibitory activity. Two functional groups which could potentially dispose a pair of oxygen atoms in a similar spatial arrangement as a sulfonyl group were also explored. However, neither nitro (**32**) nor trifluoroacetyl (**33**) had any inhibitory activity.

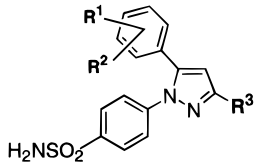
Table 1. *In Vitro* COX-1 and COX-2 Enzyme Data for Monosubstituted 5-Aryl Analogs



			IC_{50} (μM)[a]				
compd	R^1	R^2	COX-1	COX-2	mp (°C)[b]	formula	anal.
1a	H	CF_3	55.1	0.032	164−165	$C_{16}H_{12}F_3N_3O_2S$	C,H,N
1b	2-F	CF_3	29.5	0.058	165−166	$C_{16}H_{11}F_4N_3O_2S$	C,H,N
1c	3-F	CF_3	>100	7.73	143−144	$C_{16}H_{11}F_4N_3O_2S$	C,H,N
1d	4-F	CF_3	25.5	0.041	168−169	$C_{16}H_{11}F_4N_3O_2S$	C,H,N
1e	2-Cl	CF_3	31.3	0.056	159−160	$C_{16}H_{11}ClF_3N_3O_2S$	C,H,N
1f	4-Cl	CF_3	17.8	0.01	143−145	$C_{16}H_{11}ClF_3N_3O_2S$	C,H,N
2a	4-Cl	CHF_2	5.7	0.01	185−186	$C_{16}H_{12}ClF_2N_3O_2S$	C,H,N
1g	2-Me	CF_3	33.9	0.069	126−128	$C_{17}H_{14}F_3N_3O_2S$	C,H,N
1h	3-Me	CF_3	18.1	0.11	135−137	$C_{17}H_{14}F_3N_3O_2S$	C,H,N
1i	4-Me	CF_3	15.0	0.040	157−159	$C_{17}H_{14}F_3N_3O_2S$	C,H,N
2b	4-Me	CHF_2	12.5	0.013	158−159	$C_{17}H_{15}F_2N_3O_2S$	C,H,N
1j	4-Et	CF_3	29.0	0.86	−	$C_{18}H_{16}F_3N_3O_2S$	C,H,N
1k	4-CF_3	CF_3	>100	8.23	144−145	$C_{17}H_{11}F_6N_3O_2S$	C,H,N
2c	4-CN	CHF_2	>100	29.7	222−224	$C_{17}H_{12}F_2N_4O_2S$	C,H,N
2d	4-SO_2Me	CHF_2	>100	>100	209−210	$C_{17}H_{15}F_2N_3O_4S_2$	C,H,N
2e	4-$CONH_2$	CHF_2	>100 (2)	>100 (2)	235−236	$C_{17}H_{14}F_2N_4O_3S$	HRMS
2f	4-CO_2H	CHF_2	>100 (2)	46.8 (2)	263 dec	$C_{17}H_{13}F_2N_3O_4S$	C,H,N
1l	4-NO_2	CF_3	>100	2.63	169−172 dec	$C_{16}H_{11}F_3N_4O_4S$	C,H,N,S
1m	4-OH	CF_3	>100	>100	210−212	$C_{16}H_{12}F_3N_3O_3S$	HRMS
1n	2-OMe	CF_3	>100	0.29	167−168	$C_{17}H_{14}F_3N_3O_3S$	C,H,N
1o	4-OMe	CF_3	2.58	0.008	153−154	$C_{17}H_{14}F_3N_3O_3S$	C,H,N
2g	4-OMe	CHF_2	0.83	0.015	133−135	$C_{17}H_{15}F_2N_3O_3S$	C,H,N
1p	4-OEt	CF_3	28.2	0.64	141−142	$C_{18}H_{16}F_3N_3O_3S$	C,H,N
1q	4-SMe	CF_3	1.19	0.009	165−166	$C_{18}H_{16}F_3N_3O_3S$	C,H,N
1r	4-NH_2	CF_3	1.32	0.34	124−127 dec	$C_{16}H_{13}F_3N_4O_2S$	HRMS
1s	2-NMe_2	CF_3	>100	14.3	76−80	$C_{18}H_{17}F_3N_4O_2S{\cdot}0.25H_2O$	C,H,N
1t	4-NHMe	CF_3	13.8	0.016	91 sub	$C_{17}H_{15}F_3N_4O_2S$	C,H,N
1u	4-NMe_2	CF_3	3.29	0.0047	−	$C_{18}H_{17}F_3N_4O_2S{\cdot}H_2O$	C,H,N
1v	4-CH_2OH	CF_3	>1000	93.3	−	$C_{17}H_{14}F_3N_3O_3S$	C,H,N
1w	4-CO_2H	CF_3	>250	11.2	238−240	$C_{17}H_{12}F_3N_3O_4S$	HRMS

[a] Average of at least three determinations except where noted in parentheses. [b] − = not determined.

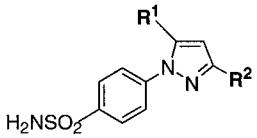
Table 2. *In Vitro* COX-1 and COX-2 Enzyme Data for Disubstituted 5-Aryl Analogs

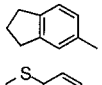
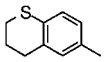
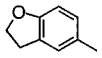
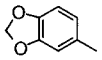
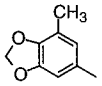


			IC_{50} (μM)[a]				
compd	R^1,R^2	R^3	COX-1	COX-2	mp (°C)[b]	formula	anal.
2h	3-fluoro-4-methoxy	CHF_2	36.0	0.05	159−161	$C_{17}H_{14}F_3N_3O_3S$	C,H,N
2i	3-chloro-4-methoxy	CHF_2	27.6	0.027	160	$C_{17}H_{14}ClF_2N_3O_3S$	C,H,N,Cl,S
1x	3-methyl-4-methoxy	CF_3	15.4	0.0093	141−142	$C_{18}H_{16}F_3N_3O_3S$	HRMS
1y	3-ethyl-4-methoxy	CF_3	38.0	0.43	−	$C_{19}H_{18}F_3N_3O_3S$	C,H,N
1z	3,4-dimethoxy	CF_3	>100	0.60	192−193	$C_{18}H_{16}F_3N_3O_4S$	C,H,N
1aa	3-methyl-4-(methylthio)	CF_3	6.33	0.0037	−	$C_{18}H_{16}F_3N_3O_2S_2$	C,H,N
1ab	3-fluoro-4-(dimethylamino)	CF_3	3.8	0.0057	132−134	$C_{18}H_{16}F_4N_4O_2S$	C,H,N
1ac	3-chloro-4-(methylamino)	CF_3	77.7	0.027	−	$C_{17}H_{14}ClF_3N_4O_2S{\cdot}0.25H_2O$	C,H,N
2j	3,5-dichloro-4-methoxy	CHF_2	77.0	0.021	170−173	$C_{17}H_{13}Cl_2F_2N_3O_3S$	C,H,N
2k	3,5-difluoro-4-methoxy	CHF_2	63.6	0.35	149−150	$C_{17}H_{13}F_4N_3O_3S$	C,H,N
1ad	3-chloro-4-methoxy-5-methyl	CF_3	>100	0.066	−	$C_{18}H_{15}ClF_3N_3O_3S$	C,H,N
1ae	3,4-dichloro	CF_3	17.4	0.015	145−147	$C_{16}H_{10}Cl_2F_3N_3O_2S$	C,H,N,Cl
1af	2,4-dichloro	CF_3	31.2	0.056	153−155	$C_{16}H_{10}Cl_2F_3N_3O_2S$	C,H,N
1ag	2,5-dichloro	CF_3	>100	>100	184−185	$C_{16}H_{10}Cl_2F_3N_3O_2S{\cdot}0.25H_2O$	C,H,N,Cl
1ah	2,4-dimethyl	CF_3	81.8	0.12	−	$C_{17}H_{16}F_3N_3O_2S$	C,H,N
2l	2,5-dimethyl	CHF_2	>100	>100	159−161	$C_{18}H_{17}F_2N_3O_2S$	C,H,N

[a] Average of at least three determinations. [b] − = not determined.

Table 3. *In Vitro* COX-1 and COX-2 Enzyme Data for Miscellaneous 5-Aryl Analogs



			IC50 (μM)[a]				
compd	R^1	R^2	COX-1	COX-2	mp (°C)[b]	formula	anal.
1ai	2-pyridyl	CF_3	93.3	45.6	–	$C_{15}H_{11}F_3N_4O_2S$	C,H,N
1aj	3-pyridyl	CF_3	>100 (2)	45.0	202–204	$C_{15}H_{11}F_3N_4O_2S$	C,H,N
1ak	4-pyridyl	CF_3	209	64.7	236–238	$C_{15}H_{11}F_3N_4O_2S$	C,H,N
1al	5-bromo-2-thienyl	CF_3	2.91	0.012	–	$C_{14}H_9BrF_3N_3O_2S_2$	C,H,N,Br
1am	5-chloro-2-thienyl	CF_3	4.69	0.026	161–165	$C_{14}H_9ClF_3N_3O_2S_2$	HRMS
2m	5-methyl-2-furyl	CHF_2	>100	3.29	177–179	$C_{15}H_{13}F_2N_3O_3S$	C,H,N
1an	3-benzothienyl	CF_3	70.7	0.35	164–165	$C_{18}H_{12}F_3N_3O_2S_2$	C,H,N
1ao	2-benzofuryl	CF_3	>100	0.89	227–228	$C_{14}H_{12}F_3N_3O_3S$	C,H,N
1ap	1-cyclohexenyl	CF_3	>100	0.084	135–138	$C_{16}H_{16}F_3N_3O_2S$	HRMS
1aq		CF_3	15.2	0.031	118–120	$C_{19}H_{16}F_3N_3O_2S$	C,H,N
1ar		CF_3	12.9	0.23	–	$C_{19}H_{16}F_3N_3O_2S_2$	C,H,N
1as		CF_3	1.21	0.021	152–153	$C_{18}H_{14}F_3N_3O_3S$	C,H,N
2n		CHF_2	1.92	0.024	214–218	$C_{17}H_{13}F_2N_3O_4S$	C,H,N
1at		CF_3	674	0.052 (2)	–	$C_{18}H_{14}F_3N_3O_4S$	C,H,N

[a] Average of at least three determinations except where noted in parentheses. [b] – = not determined.

Reversal of the functionality on the two phenyl rings of **1d**,**o** provided compounds **28a**,**b**, both of which were very potent inhibitors of both COX-1 and COX-2 (Table 7).

Finally, several 3-(trifluoromethyl)-1,5-diarylpyrazoles lacking the sulfonamide moiety were prepared for comparative purposes (Table 8). The striking feature of all of these compounds was their activity against COX-1. Of the symmetrical analogs, the 4-chloro and 4-methoxyphenyl derivatives **35** and **36** were very potent COX-1 inhibitors. Interestingly, one of the unsymmetrically substituted pyrazoles (**37**) was an inhibitor of both COX-1 and COX-2, whereas the other regioisomer (**38**, SC-560) was a very potent and highly selective inhibitor of COX-1.

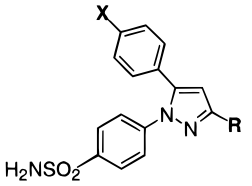
In summary, we have found that within the 1,5-diarylpyrazole class of COX-2 inhibitors, the *p*-sulfamoylphenyl group was essential for good COX-2 inhibitory potency and *in vivo* efficacy. Also, although there was substantial flexibility in functionality allowed at the 3-position of the pyrazole, trifluoromethyl and difluoromethyl were optimal in terms of potency and selectivity. In addition, substituents on the phenyl moiety at the 5-position of the pyrazole ring had profound effects on both *in vitro* potency and selectivity.

At an early stage of the efforts within this series, we found that a promising lead compound, **1f** (SC-236), although very potent and efficacious, had an extremely long plasma half-life. In order to identify a molecule with a more acceptable terminal phase elimination half-life, several analogs containing potential metabolic sites were evaluated in the male rat (Table 9, Figure 1). Replacement of the 4-chloro substituent of **1f** with either methyl (**1i**) or methoxy (**1o**) shortened the half-life considerably to approximately 3−6 h, as did replacement of the trifluoromethyl group of **1f** with a difluoromethyl group (**2a**, 4.5 h). Changing the trifluoromethyl group of **1i** to a difluoromethyl (**2b**), however, had little effect on the plasma half-life (3.5 vs 3.3 h, respectively). The 3-fluoro-4-methoxy derivative **2h** had a half-life of 3.5 h, nearly identical with that of both **1i** and **2b**.

Some of the more promising compounds were evaluated further *in vivo* in a rat carrageenan-induced foot pad edema model, a rat adjuvant-induced arthritis model, and a rat carrageenan-induced hyperalgesia model. The gastric toxicity of these compounds was also assessed 5 h after dosing in a fasted rat model. The data for these compounds, along with some standard NSAIDs as comparators, are shown in Table 10. Most of these pyrazole analogs were as efficacious as standard NSAIDs. However, most notably, the majority exhibited no GI damage at 200 mg/kg. Two compounds which did show GI side effects, **2g** and **20a**, were very potent inhibitors of *both* COX-1 and COX-2, so this result was not entirely unexpected. Likewise, standard NSAIDs showed a propensity for GI damage, with a UC_{50} as low as 2.9 mg/kg, for piroxicam, as an example.

Based on its overall biological profile, **1i** was chosen for further investigation. In a number of inflammation models, **1i** demonstrated potent, oral anti-inflammatory activity. It reduced acute inflammation in the carra-

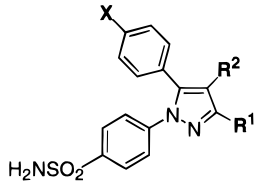
Table 4. *In Vitro* COX-1 and COX-2 Enzyme Data for 3-Substituted Analogs



			IC_{50} (μM)[a]				
compd	R	X	COX-1	COX-2	mp (°C)[b]	formula	anal.
1a	CF_3	H	55.1	0.032			
2o	CHF_2	H	33.7	0.13	171−172	$C_{16}H_{12}F_2N_3O_2S$	HRMS
16a	CH_2F	H	>100	0.20	162−163	$C_{16}H_{14}F\ N_3O_2S$	C,H,N
22a	H	F	>100	>100	183−184	$C_{15}H_{12}FN_3O_2S{\cdot}0.25H_2O$	C,H,N,S
8a	CH_3	H	>100	62.8	−	$C_{16}H_{15}N_3O_2S$	C,H,N
14a	CH_2OH	Cl	>100 (2)	0.83	192−194	$C_{16}H_{14}ClN_6O_2S$	C,H,N
17a	CH_2CN	Cl	>100 (2)	0.12	212−214	$C_{17}H_{13}N_4O_2S$	C,H,N
15a	CH_2OCH_2Ph	Cl	8.98	0.029	192−193	$C_{23}H_{20}ClN_3O_3S$	C,H,N,S,Cl
9a	4-methoxyphenyl	Cl	8.49 (2)	0.10	−	$C_{22}H_{18}ClN_3O_3S$	C,H,N
9b	5-chloro-2-thienyl	Cl	>100	0.052	−	$C_{19}H_{13}Cl_2N_3O_2S_2$	C,H,N
13a	CN	F	>100	0.34 (2)	184−185	$C_{16}H_{11}FN_4O_2S$	C,H,N,S
10a	CO_2H	F	>100	>100	245−246	$C_{16}H_{12}F_3N_3O_4S$	C,H,N,S
3a	CO_2Me	F	>100	100	235−237	$C_{17}H_{14}FN_3O_4S$	C,H,N,S
11a	$CONH_2$	F	>100	>100 (2)	214−216	$C_{16}H_{13}FN_4O_3S$	C,H,N,S
12a	CONH(3-chlorophenyl)	F	1.92	0.056	207−212	$C_{22}H_{16}ClFN_4O_3S$	C,H,N,S,Cl
19	OMe	H	>100	>100	−	$C_{16}H_{15}N_3O_3S{\cdot}0.25H_2O$	C,H,N

[a] Average of at least three determinations except where noted in parentheses. [b] − = not determined.

Table 5. *In Vitro* COX-1 and COX-2 Enzyme Data for 4-Substituted Analogs



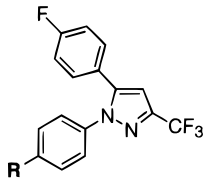
				IC_{50} (μM)[a]				
compd	R^1	R^2	X	COX-1	COX-2	mp (°C)[b]	formula	anal.
20a	CF_3	Cl	Cl	0.065	0.0053	180−182	$C_{16}H_{10}Cl_2F_3N_3O_2S$	C,H,N
24	CF_3	F	H	0.83	0.0017	−	$C_{16}H_{11}F_4N_3O_2S$	C,H,N
25a	CF_3	Me	Cl	0.93	0.022	154−155	$C_{17}H_{13}ClF_3N_3O_2S$	C,H,N
25b	CF_3	Et	Cl	29.8	0.028	−	$C_{18}H_{15}ClF_3N_3O_2S$	C,H,N
25c	CF_3	*n*-Pr	F	>100 (2)	>100 (2)	128−129	$C_{19}H_{17}F_4N_3O_2S$	C,H,N
25d	CF_3	OMe	H	>100	0.08	137−138	$C_{17}H_{14}F_3N_3O_3S$	C,H,N
26	CF_3	OH	H	>100	3.58	196−197	$C_{16}H_{12}F_3N_3O_3S{\cdot}0.25H_2O$	C,H,N
21a	H	Cl	H	31.0	0.049	176−178	$C_{15}H_{12}ClN_3O_2S$	C,H,N,S,Cl
21b	H	Br	Cl	8.71	0.031	209−210	$C_{15}H_{11}BrClN_3O_2S$	C,H,N
22b	H	F	H	56.5 (2)	4.66	194−194.5	$C_{15}H_{12}FN_3O_2S{\cdot}0.25H_2O$	C,H,N
22c	H	CH_3	H	>100	47.1	171−172	$C_{16}H_{15}N_3O_2S$	C,H,N
22d	H	CN	CH_3	>100 (2)	0.076	−	$C_{17}H_{14}N_4O_2S{\cdot}0.2H_2O$	C,H,N
22e	H	NO_2	H	12.2 (2)	0.29	−	$C_{15}H_{12}N_4O_4S$	C,H,N
22f	H	SO_2Me	Cl	52.0	19.8	182−185	$C_{16}H_{14}ClN_3O_4S_2$	C,H,N
23	H	NH_2	H	5.1	29.7	−	$C_{15}H_{14}N_4O_2S{\cdot}0.25H_2O$	C,H,N
20b	CH_3	Cl	H	0.58	0.028	−	$C_{16}H_{14}ClN_3O_2S$	C,H,N
20c	CH_2OH	Cl	Cl	0.17	0.34	203−204	$C_{16}H_{13}Cl_2N_3O_3S$	C,H,N
20d	CN	Cl	Cl	0.14	0.010	223−224	$C_{16}H_{10}Cl_2N_4O_2S$	C,H,N,S,Cl
20e	CO_2H	Cl	Cl	>100	70.0	246 dec	$C_{16}H_{11}Cl_2N_3O_4S$	C,H,N,S,Cl
20f	CO_2Me	Cl	Cl	0.41	0.16	227−229	$C_{17}H_{13}N_3O_4S$	HRMS
20g	$CONH_2$	Cl	Cl	8.8	1.09	−	$C_{16}H_{12}N_4O_3S$	HRMS

[a] Average of at least three determinations except where noted in parentheses. [b] − = not determined.

geenan edema assay with an ED_{50} of 7.1 mg/kg and reduced chronic inflammation in the adjuvant arthritis model with an ED_{50} of 0.37 mg/kg/day. In addition, it also exhibited analgesic activity in the Hargreaves hyperalgesia model with an ED_{50} of 34.5 mg/kg. These data indicated that **1i** had potency equivalent to that of standard NSAIDs, yet showed no acute GI toxicity in rats at doses up to 200 mg/kg. In addition, it displayed no chronic GI toxicity in rats at doses up to 600 mg/kg/day over 10 days. All standard NSAIDs showed severe toxicity at these doses. **1i** has good bioavailability, is well distributed, and has an excellent safety profile. Furthermore, it is cleared by metabolism to the corresponding hydroxymethyl (**1v**) and carboxylic acid (**1w**) analogs, both of which exhibit no COX-1 and poor COX-2 inhibitory activity.

In phase I clinical trials, **1i** exhibited a half-life of 12 h and a T_{max} of about 2 h in humans. In a postextrac-

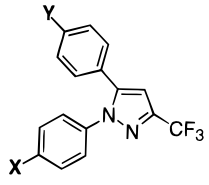
Table 6. *In Vitro* COX-1 and COX-2 Enzyme Data for 1-Aryl Derivatives



		IC_{50} (μM)[a]				
compd	R	COX-1	COX-2	mp (°C)[b]	formula	anal.
39	SO_2CH_3	>1000	0.10			
1d	SO_2NH_2	25.5	0.041			
29	SO_2NHCH_3	>100	>100	–	$C_{17}H_{13}F_4N_3O_2S$	HRMS
30	$SO_2N(CH_3)_2$	>100	>100	–	$C_{18}H_{15}F_4N_3O_2S$	HRMS
31	$NHSO_2CH_3$	>100 (2)	>100	160–161	$C_{17}H_{13}F_4N_3O_2S$	C,H,N
32	NO_2	1.75	>100	111–113	$C_{16}H_9F_4N_3O_2$	C,H,N
33	$COCF_3$	>100	>100	–	$C_{18}H_9F_7N_2O$	C,H,N

[a] Average of at least three determinations except where noted in parentheses. [b] – = not determined.

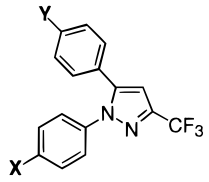
Table 7. *In Vitro* COX-1 and COX-2 Enzyme Data for "Reversed" Analogs



			IC_{50} (μM)[a]				
compd	X	Y	COX-1	COX-2	mp (°C)[b]	formula	anal.
1d	SO_2NH_2	F	25.5	0.041			
28a	F	SO_2NH_2	0.08	0.010	–	$C_{16}H_{11}F_4N_3O_2S$	HRMS
1o	SO_2NH_2	OMe	2.58	0.008			
28b	OMe	SO_2NH_2	<0.001	0.0067	173–174	$C_{17}H_{14}F_3N_3O_3S$	HRMS

[a] Average of at least three determinations. [b] – = not determined.

Table 8. *In Vitro* Data for Selected Non-Sulfonamide-Containing 3-(Trifluoromethyl)-1,5-diarylpyrazoles



			IC_{50} (μM)[a]				
compd	X	Y	COX-1	COX-2	mp (°C)	formula	anal.
34	H	H	0.97	>100	94.2–95.6	$C_{16}H_{11}F_3N_2$	C,H,N
35	Cl	Cl	0.055	4.79	81.7–83.6	$C_{16}H_9Cl_2F_3N_2$	C,H,N
36	OMe	OMe	0.005	0.75	95.5–97.4	$C_{18}H_{15}F_3N_2O_2$	C,H,N
37	Cl	OMe	0.018	0.75	64.3–67.7	$C_{17}H_{12}ClF_3N_2O$	C,H,N
38	OMe	Cl	0.007	74.9	64.1–67.7	$C_{17}H_{12}ClF_3N_2O$	C,H,N

[a] Average of at least three determinations.

Table 9. Pharmacokinetics of Selected Pyrazoles in Male Rat

compd	dose (mg/kg)	route	plasma half-life (h)
39	10	iv	221
1f	20	oral	117
1o	10	oral	5.6
2a	10	iv	4.5
1i	10	iv	3.5
2h	10	iv	3.5
2b	10	oral	3.3

tion dental pain study in man at a dose of 100 mg, it was at least as effective as aspirin, with an onset of about 45 min.[27] Currently, **1i** is being evaluated in phase III clinical trials, targeting the treatment of rheumatoid arthritis and osteoarthritis.

Experimental Section

Biological Methods. Expression and purification of recombinant human COX-1 and COX-2 enzymes,[23] *in vitro* COX-1 and COX-2 enzyme assays,[23] and the rat gastric toxicity studies[18] have been described previously.

Rat Carrageenan-Induced Foot Pad Edema Assay.[18,24] Male Sprague–Dawley rats (195–250 g, Charles River Laboratories) were fasted with free access to water at least 16 h prior to experiments. The rats were dosed orally with a 1 mL suspension of test compound in vehicle (0.5% methyl cellulose and 0.025% Tween-20) or with vehicle alone. One hour later a subplantar injection of 0.1 mL of a 1% solution of carrageenan in 0.9% sterile saline was administered to the right hind foot pad. Paw volume was measured with a displacement plethysmometer 3 h after carrageenan injection.

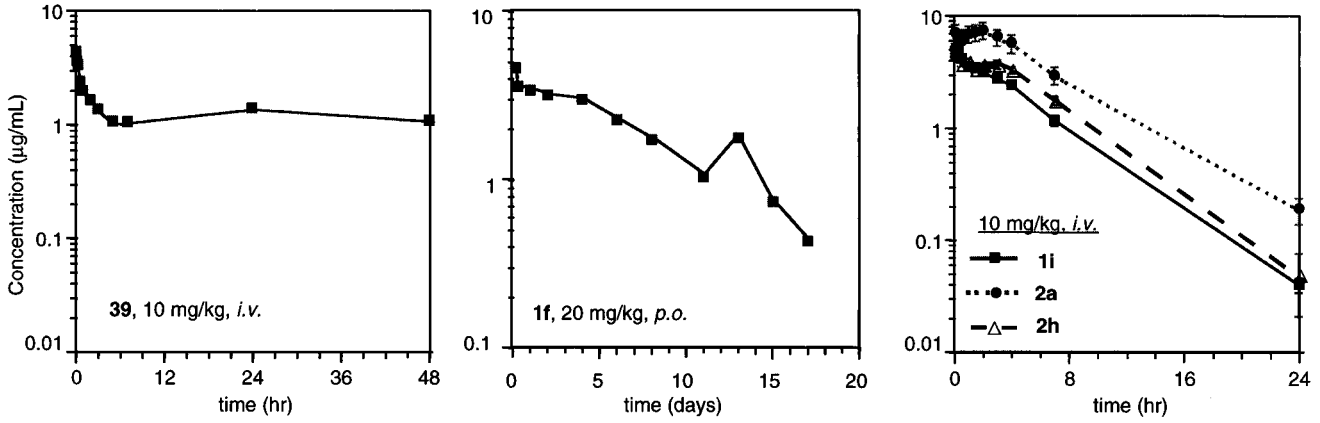


Figure 1. Pharmacokinetics of selected pyrazoles in male rat.

Table 10. *In Vivo* Data for Selected Analogs and Standards

	ED_{50} (mg/kg)			
compd	rat adjuvant arthritis[a]	rat carrageenan edema[b]	rat hyperalgesia[b]	rat gastric damage % ulceration @ 200 mg/kg[c]
1a	0.29	50% @ 30		0
1f	0.07	5.4	6.6	0
1i	0.37	7.1	34.5	0
2a	0.63	13.0	7.7	0
2b	0.35	2.4	37.3	0
2g	0.01	13.7	36.0	100
2h	0.05	18.6	33.0	0
13a	0.51	7.5	67.1	0
20a	0.006	8.8		80
21a	0.33	9.2	32.3	0
39	0.41	10.5	58.3	0
indomethacin	0.11	1.15	4.1	UC_{50} = 7 mg/kg
piroxicam	0.15	2.4	52% @ 10	UC_{50} = 2.9 mg/kg
naproxen	0.94	1.6	66% @ 10	UC_{50} = 255 mg/kg

[a] ED_{50} values were determined using a minimum of four dose points, 8−10 animals/group. [b] ED_{50} values were determined using a minimum of four dose points, 5 animals/group. [c] Percent ulceration based on 10 animals.

Rat Carrageenan-Induced Hyperalgesia Assay.[18,26] Male Sprague−Dawley rats were treated as described above. Three hours after carrageenan injection, the rats were placed in a Plexiglass container with a transparent floor with a high intensity lamp heat source positioned under it. After an initial 20 min period, thermal stimulation was begun on either the injected foot or the contralateral uninjected foot. A photoelectric cell turned off the lamp and timer when light was interrupted by paw withdrawal. The withdrawal latency period in seconds was determined for the control and drug-treated groups, and percent inhibition of the stimulus-induced decrease in withdrawal latency was determined.

Rat Adjuvant-Induced Arthritis Assay.[25] Arthritis was induced in male Lewis rats (125−150 g, Harlan Sprague−Dawley) by injection of 1 mg of *Mycobacterium butyricum* (Difco Laboratories) in 50 μL of mineral oil into the right hind foot pad. Fourteen days after injection of adjuvant, the contralateral left foot volume was measured with a displacement plethysmometer. Animals with paw volumes 0.37 mL greater than normal paws were then randomized and treated with test compound (as a suspension in 0.5% methyl cellulose and 0.025% Tween-20), beginning on day 15 postadjuvant injection. Animals were dosed twice daily by gavage at the indicated doses with a volume of 1.0 mL/day. Compound administration was continued until final assessment on day 25 postadjuvant injection, and the mean inhibition was determined on the basis of an average of 8−10 animals. The typical increase in contralateral paw volume measured on day 25 was 1.4−1.9 mL.

Chemistry. Melting points were determined using a Thomas Hoover or Mettler FP900 Thermosystem melting point apparatus and are uncorrected. High-field ^1H and ^{19}F NMR spectra were recorded on GE QE-300 and Varian VXR-300 spectrometers at 300 and 282 MHz, respectively. Chemical shifts are reported in parts per million relative to internal tetramethylsilane. High-resolution mass spectra were obtained on a Finnigan MAT-8430 or MAT-90 instrument with electron impact (EI) or fast atom bombardment (FAB) ionization. Microanalyses were performed by the Searle Physical Methodology Department and Galbraith Laboratories, Inc. Elemental data for all new compounds are within ±0.4% of the theoretical values. All yields reported are unoptimized.

4-[5-(4-Chlorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1f). Step 1: Preparation of 4,4,4-Trifluoro-1-(4-chlorophenyl)butane-1,3-dione. To a solution of ethyl trifluoroacetate (23.52 g, 166 mmol) in 75 mL of methyl *tert*-butyl ether (MTBE) was added 25% NaOMe in MeOH (40 mL, 177 mmol) over 2 min. A solution of 4′-chloroacetophenone (23.21 g, 150 mmol) in 20 mL of MTBE was added to this mixture dropwise over 5 min. After stirring for 15.75 h, 3 N HCl (70 mL) was added. The organic layer was collected, washed with brine (75 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 35.09 g of a yellow-orange solid. The solid was recrystallized from isooctane to give 31.96 g (85%) of the dione: mp 66−67°C.

Step 2: Preparation of 4-[5-(4-Chlorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide. (4-Sulfamoylphenyl)hydrazine hydrochloride (982 mg, 4.4 mmol) was added to a stirred solution of the dione from step 1 (1.00 g, 4.0 mmol) in 50 mL of EtOH. The mixture was heated to reflux and stirred for 20 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The residue was taken up in EtOAc, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a light brown solid. Recrystallization from EtOAc and isooctane furnished pyrazole **1f** (1.28 g, 80%): ^1H NMR ($CDCl_3/CD_3OD$) δ 5.2 (s, 2H), 6.8 (s, 1H), 7.16 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 8.5 Hz, 2H), 7.44 (d, J = 8.7, 2H), 7.91 (d, J = 8.7, 2H); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 106.42 (d, J = 0.03 Hz), 121.0 (q, J = 276 Hz), 125.5, 126.9, 127.3, 129.2, 130.1, 135.7, 141.5, 143.0,

143.9 (q, J = 37 Hz), 144.0; ^{19}F NMR ($CDCl_3/CD_3OD$) δ −62.9. HPLC analysis showed that the purified material contained ≤0.5% of the regioisomeric pyrazole **4f** (4-[3-(4-chlorophenyl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide).

4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1i). Step 1: Preparation of 1-(4-Methylphenyl)-4,4,4-trifluorobutane-1,3-dione. 4′-Methylacetophenone (5.26 g, 39.2 mmol) was dissolved in 25 mL of MeOH, and 25% NaOMe in MeOH (12 mL, 52.5 mmol) was added. The mixture was stirred for 5 min, and 5.5 mL (46.2 mmol) of ethyl trifluoroacetate was added. After refluxing for 24 h, the mixture was cooled to room temperature and concentrated; 10% HCl (100 mL) was added and the mixture extracted with 4 × 75 mL of EtOAc. The extracts were dried over $MgSO_4$, filtered, and concentrated to afford 8.47 g (94%) of a brown oil which was carried on without further purification.

Step 2: Preparation of 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide. The title compound was synthesized from the dione prepared in step 1 and (4-sulfamoylphenyl)hydrazine hydrochloride as described in step 2 above to give **1i** as a pale yellow solid (46%): ^{1}H NMR ($CDCl_3$) δ 2.20 (s, 3H), 4.95 (s, 2H), 6.76 (s, 1H), 7.10 (d, J = 8 Hz, 2H), 7.22 (d, J = 8 Hz, 2H), 7.47 (d, J = 8 Hz, 2H), 7.90 (d, J = 8 Hz, 2H).

The following examples utilize this standard 2-step sequence. In cases where the acetophenone was not commercially available, it was generally prepared using standard Friedel−Crafts acylation conditions.

4-[5-Phenyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1a). The title compound was synthesized from 4,4,4-trifluoro-1-phenyl-1,3-butanedione (Aldrich) using step 2 of the 2-step procedure described above in 33% yield: ^{1}H NMR (CD_3OD) δ 6.93 (s, 1H), 7.28 (m, 2H), 7.34−7.43 (m, 3H), 7.48 (d, J = 8 Hz, 2H), 7.93 (d, J = 8 Hz, 2H).

4-[5-(2-Fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1b). The title compound was synthesized from 2′-fluoroacetophenone using the 2-step procedure described above in 47% overall yield: ^{1}H NMR (CD_3OD) δ 6.98 (s, 1H), 7.11 (t, J = 8 Hz, 1H), 7.25 (ddd, J = 1, 8, 8 Hz, 1H), 7.40 (dd, J = 1, 8 Hz, 1H), 7.47 (m, 1H), 7.49 (d, J = 8 Hz, 2H), 7.92 (d, J = 8 Hz, 2H).

4-[5-(3-Fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1c). The title compound was synthesized from 3′-fluoroacetophenone using the 2-step procedure described above in 33% overall yield: ^{1}H NMR (CD_3OD) δ 7.01 (s, 1H), 7.09 (m, 2H), 7.17 (m, 1H), 7.38 (m, 1H), 7.52 (d, J = 8 Hz, 2H), 7.95 (d, J = 8 Hz, 2H).

4-[5-(4-Fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1d). The title compound was synthesized from 4′-fluoroacetophenone using the 2-step procedure described above in 66% overall yield: ^{1}H NMR (CD_3OD) δ 6.94 (s, 1H), 7.11 (t, J = 8 Hz, 2H), 7.32 (dd, J = 6, 8 Hz, 2H), 7.49 (d, J = 8 Hz, 2H), 7.96 (d, J = 8 Hz, 2H).

4-[5-(2-Chlorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1e). The title compound was synthesized from 2′-chloroacetophenone using the 2-step procedure described above in 45% overall yield: ^{1}H NMR ($CDCl_3$/CD_3OD) δ 6.80 (s, 1H), 7.3−7.5 (m, 6H), 7.88 (d, J = 8 Hz, 2H).

4-[5-(4-Chlorophenyl)-3-(difluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (2a). The title compound was synthesized from 4′-chloroacetophenone and ethyl difluoroacetate using the 2-step procedure described above in 57% overall yield: ^{1}H NMR (acetone-d_6) δ 6.72 (br s, 1H), 6.92 (s, 1H), 6.96 (t, J = 54.6 Hz, 1H), 7.38 (d, J = 8.7 Hz, 2H), 7.46 (d, J = 8.7 Hz, 2H), 7.54 (d, J = 8.6 Hz, 2H), 7.96 (d, J = 8.6 Hz, 2H); ^{19}F NMR (acetone-d_6) δ −113.97 (d, J = 54.6 Hz).

4-[5-(2-Methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1g). The title compound was synthesized from 2′-methylacetophenone using the 2-step procedure described above in 24% overall yield: ^{1}H NMR ($CDCl_3$) δ 2.0 (s, 3H), 4.8 (s, 2H), 6.5 (s, 1H), 7.2−7.45 (m, 7H), 7.83 (d, J = 8 Hz, 2H).

4-[5-(3-Methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1h). The title compound was synthesized from 3′-methylacetophenone using the 2-step procedure described above in 9% overall yield: ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H), 4.83 (s, 2H), 6.76 (s, 1H), 6.94 (m, 1H), 7.10 (s, 1H), 7.24 (m, 2H), 7.49 (d, J = 8 Hz, 2H), 7.90 (s, 2H).

4-[5-(4-Methylphenyl)-3-(difluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (2b). The title compound was synthesized from 4′-methylacetophenone and ethyl difluoroacetate using the 2-step procedure described above in 41% overall yield: ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3H), 4.92 (br s, 2H), 6.71 (s, 1H), 6.76 (t, J = 55.3 Hz, 1H), 7.10 (d, J = 8.3 Hz, 2H), 7.17 (d, J = 8.3 Hz, 2H), 7.44 (d, 2H, J = 8.9 Hz), 7.88 (d, J = 8.9 Hz, 2H); ^{19}F NMR ($CDCl_3$) δ −112.7 (d, J = 55.3 Hz).

4-[5-(4-Ethylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1j). The title compound was synthesized from 4′-ethylacetophenone using the 2-step procedure described above in 7% overall yield: ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J = 8 Hz, 3H), 2.67 (q, J = 8 Hz, 2H), 4.83 (s, 2H), 6.74 (s, 1H), 7.14 (d, J = 8 Hz, 2H), 7.21 (d, J = 8 Hz, 2H), 7.49 (d, J = 8 Hz, 2H), 7.90 (d, J = 8 Hz, 2H).

4-[3-(Trifluoromethyl)-5-[4-(trifluoromethyl)phenyl]-1*H*-pyrazol-1-yl]benzenesulfonamide (1k). The title compound was synthesized from 4-(trifluoromethyl)acetophenone using the 2-step procedure described above in 37% overall yield: ^{1}H NMR ($CDCl_3/CD_3OD$) δ 6.87 (s, 1H), 7.38 (d, J = 8 Hz, 2H), 7.47 (d, J = 8 Hz, 2H), 7.65 (d, J = 8 Hz, 2H), 7.49 (d, J = 8 Hz, 2H).

4-[5-(4-Cyanophenyl)-3-(difluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (2c). The title compound was synthesized from 4-acetylbenzonitrile and ethyl difluoroacetate using the 2-step procedure described above in 81% overall yield: ^{1}H NMR ($CDCl_3$) δ 4.85 (s, 2H), 6.78 (t, J = 54.5 Hz, 1H), 6.84 (s, 1H), 7.36 (d, J = 8.5 Hz, 2H), 7.44 (d, J = 8.9 Hz, 2H), 7.67 (d, J = 8.5 Hz, 2H), 7.95 (d, J = 8.7 Hz, 2H); ^{19}F NMR ($CDCl_3$) δ −112.92 (d, J = 54.5 Hz).

4-[3-(Difluoromethyl)-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrazol-1-yl]benzenesulfonamide (2d). The title compound was synthesized from 4-(methylthio)acetophenone and ethyl difluoroacetate using the 2-step procedure described above followed by oxidation with 3-chloroperoxybenzoic acid in 44% overall yield: ^{1}H NMR (acetone-d_6) δ 3.16 (s, 3H), 5.59 (s, 2H), 6.98 (t, J = 54.0 Hz, 1H), 7.16 (s, 1H), 7.56 (d, J = 7.5 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.96 (m, 4H); ^{19}F NMR (acetone-d_6) δ −113.6 (d, J = 54.5 Hz).

4-[1-[4-(Aminosulfonyl)phenyl]-3-(difluoromethyl)-1*H*-pyrazol-5-yl]benzamide (2e). Methyl 4-[1-[4-(aminosulfonyl)phenyl]-3-(difluoromethyl)-1*H*-pyrazol-5-yl]benzoate was prepared from 4-carbomethoxyacetophenone and ethyl difluoroacetate using the 2-step procedure described above. Amidation using the procedure described for the preparation of **20g** furnished **2e** in 85% yield: ^{1}H NMR (acetone-d_6) δ 3.53 (s, 2H), 6.94 (t, J = 55.2 Hz, 1H), 6.95 (s, 1H), 7.43 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 7.8 Hz, 2H), 7.93 (m, 4H); ^{19}F NMR (acetone-d_6) δ −113.6 (d, J = 54.5 Hz); HRMS m/z 393.0833 (calcd for $C_{17}H_{14}F_2N_4O_3S$ (M + 1), 393.0833).

4-[1-[4-(Aminosulfonyl)phenyl]-3-(difluoromethyl)-1*H*-pyrazol-5-yl]benzoic Acid (2f). Saponification of methyl 4-[1-[4-(aminosulfonyl)phenyl]-3-(difluoromethyl)-1*H*-pyrazol-5-yl]benzoate with NaOH as described for the preparation of **20e** furnished **2f** in 90% yield: ^{1}H NMR (CD_3OD) δ 5.48 (s, 2H), 6.87 (t, J = 54.6 Hz, 1H), 6.93 (s, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 6.9 Hz, 2H), 7.93 (d, J = 6.9 Hz, 2H), 7.99 (d, J = 8.4 Hz, 2H); ^{19}F NMR (CD_3OD) δ −113.6 (d, J = 55 Hz).

4-[5-(4-Nitrophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1l). The title compound was synthesized from 4′-nitroacetophenone using the 2-step procedure described above in 14% overall yield: ^{1}H NMR ($CDCl_3$) δ 4.90 (br s, 2H), 6.91 (s, 1H), 7.43 (d, J = 9.3 Hz, 2H), 7.46 (d, J = 9.3 Hz, 2H), 8.25 (d, J = 8.9 Hz, 2H); ^{19}F NMR ($CDCl_3$) δ −63.0 (s).

4-[5-(4-Aminophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1r). The title compound was synthesized from **1l** by catalytic reduction in the presence of 5% palladium on carbon in 73% yield: ^{1}H NMR (CD_3OD) δ 6.84 (s, 1H), 6.90 (d, J = 8.7 Hz, 2H), 7.11 (d, J = 8.7 Hz, 2H), 7.50 (d, J = 8.5 Hz, 2H), 7.92 (d, J = 8.5 Hz, 2H); ^{19}F NMR

(CD_3OD) δ −64.3 (s); HRMS *m/z* 382.0671 (calcd for $C_{16}H_{13}F_3N_4O_2S$, 382.0711).

4-[5-(2-Methoxyphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1n). The title compound was synthesized from 2′-methoxyacetophenone using the 2-step procedure described above in 36% overall yield: ^{1}H NMR (CD_3OD) δ 3.37 (s, 3H), 6.80 (s, 1H), 6.91 (d, J = 8 Hz, 1H), 7.03 (dt, J = 1, 8 Hz, 1H), 7.35−7.45 (m, 2H), 7.42 (d, J = 8 Hz, 2H), 7.88 (d, J = 8 Hz, 2H).

4-[5-(4-Methoxyphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1o). The title compound was synthesized from 4′-methoxyacetophenone using the 2-step procedure described above in 42% overall yield: ^{1}H NMR (CD_3OD) δ 3.79 (s, 3H), 6.87 (s, 1H), 6.91 (d, J = 8 Hz, 2H), 7.20 (d, J = 8 Hz, 2H), 7.49 (d, J = 8 Hz, 2H), 7.93 (d, J = 8 Hz, 2H).

4-[5-(4-Methoxyphenyl)-3-(difluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (2g). The title compound was synthesized from 4′-methoxyacetophenone and ethyl difluoroacetate using the 2-step procedure described above in 22% overall yield: ^{1}H NMR ($CDCl_3$) δ 3.83 (s, 3H), 4.96 (br s, 2H), 6.68 (s, 1H), 6.77 (t, J = 56.5 Hz, 1H), 6.88 (d, J = 8.86 Hz, 2H), 7.14 (d, J = 8.86 Hz, 2H), 7.45 (d, J = 8.86 Hz, 2H), 7.90 (d, J = 8.86 Hz, 2H); ^{19}F NMR ($CDCl_3$) δ −112.7 (d, J = 56.5 Hz).

4-[5-(4-Ethoxyphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1p). The title compound was synthesized from 4′-ethoxyacetophenone using the 2-step procedure described above in 5% overall yield: ^{1}H NMR ($CDCl_3$) δ 1.43 (t, J = 8 Hz, 3H), 4.09 (q, J = 8 Hz, 2H), 4.83 (s, 2H), 6.72 (s, 1H), 6.87 (d, J = 8 Hz, 2H), 7.14 (d, J = 8 Hz, 2H), 7.50 (d, J = 8 Hz, 2H), 7.90 (d, J = 8 Hz, 2H).

4-[5-[4-(Methylthio)phenyl]-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1q). The title compound was synthesized from 4′-(methylthio)acetophenone using the 2-step procedure described above in 75% overall yield: ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 3H), 3.66 (s, 2H), 6.67 (s, 1H), 7.02 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.7 Hz, 2H), 7.82 (d, J = 8.7 Hz, 2H); ^{19}F NMR ($CDCl_3$) δ −63.2 (s).

4-[5-[2-(*N*,*N*-Dimethylamino)phenyl]-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1s). Step 1: Preparation of 4-[5-(2-Nitrophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide. The title compound was synthesized from 2′-nitroacetophenone using the 2-step procedure described above in 48% overall yield: ^{1}H NMR ($CDCl_3$/CD_3OD) δ 6.77 (s, 1H), 7.45 (m, 3H), 7.73 (m, 2H), 7.87 (d, J = 8 Hz, 2H), 8.06 (d, J = 8 Hz, 1H). Anal. ($C_{16}H_{11}F_3N_4O_4S$) C, H, N.

Step 2: Preparation of 4-[5-(2-Aminophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide. The product of step 1 (2.35 g, 5.7 mmol), hydrazine hydrate (1.62 g, 50.5 mmol), and 10% Pd/C (0.25 g) were stirred in 100 mL of EtOH at room temperature for 12 h and at reflux for 2.5 h. The mixture was cooled, filtered through Celite, and concentrated to give 100% yield of the title compound as a white solid: ^{1}H NMR ($CDCl_3$) δ 4.83 (br s, 2H), 6.74 (m, 3H), 6.92 (d, J = 8 Hz, 1H), 7.23 (d, J = 8 Hz, 1H), 7.51 (d, J = 8 Hz, 2H), 7.85 (d, J = 8 Hz, 2H). Anal. ($C_{16}H_{13}F_3N_4O_2S\cdot 0.25\ H_2O$) C, H, N.

Step 3: Preparation of 4-[5-[2-(*N*,*N*-Dimethylamino)-phenyl]-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide. To a mixture of the product from step 2 (1.27 g, 3.3 mmol) and paraformaldehyde (3.19 g) in 75 mL of AcOH was added $NaBH_4$ (1.2 g, 19.1 mmol) in small portions, and the mixture was stirred at room temperature for 24 h. The mixture was poured into 50 mL of 25% NaOH and ice and extracted with EtOAc (4 × 50 mL). The combined extracts were dried over Na_2SO_4, filtered, and concentrated. Purification on a preparative TLC plate eluting with 2/97/1 MeOH/CH_2Cl_2/NH_4OH provided 0.75 g (53%) of **1s** as a yellow crystalline solid: ^{1}H NMR ($CDCl_3$) δ 2.14 (s, 6H), 4.70 (br s, 2H), 6.78 (s, 1H), 6.85 (d, J = 8 Hz, 1H), 7.07 (t, J = 8 Hz, 1H), 7.36 (m, 4H), 7.80 (d, J = 8 Hz, 2H).

4-[5-[4-(*N*,*N*-Dimethylamino)phenyl]-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1u). The title compound was synthesized from 4′-(*N*,*N*-dimethylamino)-acetophenone using the 2-step procedure described above in 32% overall yield: ^{1}H NMR ($CDCl_3$) δ 3.00 (s, 6H), 6.64 (m, 3H), 6.70 (s, 1H), 7.06 (d, J = 8 Hz, 2H), 7.52 (d, J = 8 Hz, 2H), 7.90 (d, J = 8 Hz, 2H).

4-[5-[4-(*N*-Methylamino)phenyl]-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1t). To a solution of **1u** (431 mg, 1.0 mmol) in 10 mL of MeOH was added 36 mg (0.17 mmol) of ruthenium(III) chloride hydrate followed by 30 wt % H_2O_2 (1.5 mL, 14.7 mmol) over 2 h. The reaction was quenched with 1 M KOH in MeOH (25 mL) and the mixture concentrated to give 1.24 g of a brown solid. The solid was purified on a preparative TLC plate eluting with 2/97/1 MeOH/CH_2Cl_2/NH_4Cl to give 52 mg (0.14 mmol, 12%) of **1t** as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 2.87 (s, 3H), 4.94 (br s, 2H), 5.32 (s, 1H), 6.54 (d, J = 8 Hz, 2H), 6.67 (s, 1H), 7.03 (d, J = 8 Hz, 2H), 7.50 (d, J = 8 Hz, 2H), 7.90 (d, J = 8 Hz, 2H).

4-[3-(Difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (2h). The title compound was synthesized from 3-fluoro-4-methoxyacetophenone and ethyl difluoroacetate using the 2-step procedure described above in 84% overall yield: ^{1}H NMR (DMSO-d_6) δ 3.85 (s, 3H), 7.3−6.9 (m, 5H), 7.48 (br s, 2H), 7.51 (d, J = 6.5 Hz, 2H), 7.85 (d, J = 6.5 Hz, 2H).

4-[5-(3-Chloro-4-methoxyphenyl)-3-(difluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (2i). The title compound was synthesized from 3-chloro-4-methoxyacetophenone and ethyl difluoroacetate using the 2-step procedure described above in 66% overall yield: ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 3H), 4.94 (br s, 2H), 6.71 (s, 1H), 6.76 (t, J = 54.8 Hz, 1H), 6.88 (d, J = 8.5 Hz, 1H), 7.00 (dd, J = 8.5, 2.2 Hz, 1H), 7.34 (d, J = 2.2 Hz, 1H), 7.45 (d, J = 8.7 Hz, 2H), 7.91 (d, J = 8.7 Hz, 2H); ^{19}F NMR ($CDCl_3$) δ −112.7 (d, J = 54.8 Hz).

4-[5-(3-Methyl-4-methoxyphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1x). The title compound was synthesized from 3-methyl-4-methoxyacetophenone using the 2-step procedure described above in 42% overall yield: ^{1}H NMR ($CDCl_3$) δ 2.14 (s, 3H), 3.80 (s, 3H), 5.69 (s, 2H), 6.69 (s, 1H), 6.74 (d, J = 8 Hz, 1H), 6.92 (dd, J = 1, 8 Hz, 1H), 7.06 (d, J = 1 Hz, 1H), 7.41 (d, J = 8 Hz, 2H), 7.84 (d, J = 8 Hz, 2H); HRMS *m/z* 411.0866 (calcd for $C_{18}H_{16}F_3N_3O_3S$, 411.0864).

4-[5-(3-Ethyl-4-methoxyphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1y). The title compound was synthesized from 3-ethyl-4-methoxyacetophenone using the 2-step procedure described above in 61% overall yield: ^{1}H NMR ($CDCl_3$) δ 1.08 (t, J = 7 Hz, 3H), 2.58 (q, J = 7 Hz, 2H), 3.85 (s, 3H), 4.93 (br s, 2H), 6.72 (s, 1H), 6.80 (d, J = 8 Hz, 1H), 7.00 (br d, J = 10 Hz, 1H), 7.02 (br s, 1H), 7.49 (d, J = 8 Hz, 2H), 7.91 (d, J = 8 Hz, 2H).

4-[5-(3,4-Dimethoxyphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1z). The title compound was synthesized from 3,4-dimethoxyacetophenone using the 2-step procedure described above in 27% overall yield: ^{1}H NMR (acetone-d_6) δ 3.64 (s, 3H), 3.81 (s, 3H), 6.75 (s, 2H), 6.87−6.91 (m, 2H), 6.96 (d, J = 8 Hz, 1H), 6.99 (s, 1H), 7.58 (d, J = 8 Hz, 2H), 7.98 (d, J = 8 Hz, 2H).

4-[5-[3-Methyl-4-(methylthio)phenyl]-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1aa). The title compound was synthesized from 3-methyl-4-(methylthio)-acetophenone using the 2-step procedure described above in 61% overall yield: ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3H), 2.49 (s, 3H), 4.89 (br s, 2H), 6.74 (s, 1H), 6.95 (br d, J = 8 Hz, 1H), 7.07 (d, 1H), 7.09 (br s, 1H), 7.50 (d, J = 8 Hz, 2H), 7.92 (d, J = 8 Hz, 2H).

4-[5-[3-Fluoro-4-(*N*,*N*-dimethylamino)phenyl]-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1ab). The title compound was synthesized from 3-fluoro-4-(*N*,*N*-dimethylamino)acetophenone using the 2-step procedure described above in 33% overall yield: ^{1}H NMR ($CDCl_3$) δ 2.94 (s, 6H), 4.94 (br s, 2H), 6.80 (m, 4H), 7.50 (d, J = 8 Hz, 2H), 7.94 (d, J = 8 Hz, 2H).

4-[5-[3-Chloro-4-(*N*-methylamino)phenyl]-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1ac). Step 1: Preparation of 4-[5-[3-Chloro-4-(*N*,*N*-dimethylamino)phenyl]-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide. The title compound was synthesized from

3-chloro-4-(*N*,*N*-dimethylamino)acetophenone using the 2-step procedure described above in 23% overall yield: ^{1}H NMR ($CDCl_3$) δ 2.87 (s, 6H), 4.90 (br s, 2H), 6.72 (s, 1H), 6.96 (d, J = 8 Hz, 2H), 7.32 (s, 1H), 7.50 (d, J = 8 Hz, 2H), 7.94 (d, J = 8 Hz, 2H); HRMS m/z 444.0656 (calcd for $C_{18}H_{16}ClF_3N_4O_2S$, 444.0634).

Step 2: Preparation of 4-[5-[3-Chloro-4-(*N*-methylamino)phenyl]-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide. Demethylation of the product from step 1 using the procedure described for **1t** provided **1ac** in 10% yield: ^{1}H NMR ($CDCl_3$) δ 2.94 (d, 3H), 4.60 (m, 1H), 4.94 (br s, 2H), 6.56 (d, J = 8 Hz, 1H), 6.69 (s, 1H), 6.90 (s, 1H), 7.21 (s, 1H), 7.50 (d, J = 8 Hz, 2H), 7.90 (d, J = 8 Hz, 2H).

4-[5-(3,5-Dichloro-4-methoxyphenyl)-3-(difluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (2j). The title compound was synthesized from 3,5-dichloro-4-methoxyacetophenone and ethyl difluoroacetate using the 2-step procedure described above in 66% overall yield: ^{1}H NMR ($CDCl_3$) δ 3.95 (s, 3H), 4.83 (s, 2H), 6.75 (s, 1H), 6.75 (t, J = 54.5 Hz, 1H), 7.18 (s, 2H), 7.48 (d, J = 8.7 Hz, 2H), 7.97 (d, J = 8.7 Hz, 2H); ^{19}F NMR ($CDCl_3$) δ −112.91 (d, J = 54.5 Hz).

4-[5-(3,5-Difluoro-4-methoxyphenyl)-3-(difluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (2k). The title compound was synthesized from 3,5-difluoro-4-methoxyacetophenone and ethyl difluoroacetate using the 2-step procedure described above in 65% overall yield: ^{1}H NMR ($CDCl_3$) δ 4.06 (s, 3H), 4.87 (s, 2H), 6.93−6.57 (m, 4H), 7.47 (d, J = 8.9 Hz, 2H), 7.96 (d, J = 8.7 Hz, 2H); ^{19}F NMR ($CDCl_3$) δ −112.90 (d, J = 54.7 Hz), −126.69 (d, J = 7.9 Hz).

4-[5-(3-Chloro-4-methoxy-5-methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1ad). The title compound was synthesized from 3-chloro-4-methoxy-5-methylacetophenone using the 2-step procedure described above in 38% overall yield: ^{1}H NMR ($CDCl_3$) δ 2.27 (s, 3H), 3.87 (s, 3H), 4.87 (s, 2H), 6.76 (s, 1H), 6.94 (s, 1H), 7.14 (s, 1H), 7.52 (d, J = 8 Hz, 2H), 7.96 (d, J = 8 Hz, 2H).

4-[5-(3,4-Dichlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (1ae). The title compound was synthesized from 3,4-dichloroacetophenone using the 2-step procedure described above in 46% overall yield: ^{1}H NMR ($CDCl_3$) δ 4.89 (s, 2H), 6.83 (s, 1H), 6.98 (d, J = 8 Hz, 1H), 7.47 (m, 4H), 7.98 (d, J = 8 Hz, 2H).

4-[5-(2,4-Dichlorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1af). The title compound was synthesized from 2,4-dichloroacetophenone using the 2-step procedure described above in 62% overall yield: ^{1}H NMR ($CDCl_3$) δ 6.80 (s, 1H), 7.36 (m, 5H), 7.87 (d, J = 8 Hz, 2H).

4-[5-(2,5-Dichlorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1ag). The title compound was synthesized from 2,5-dichloroacetophenone using the 2-step procedure described above in 46% overall yield: ^{1}H NMR ($CDCl_3$) δ 6.81 (s, 2H), 7.40 (m, 4H), 7.90 (d, J = 8 Hz, 2H).

4-[5-(2,4-Dimethylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1ah). The title compound was synthesized from 2,4-dimethylacetophenone using the 2-step procedure described above in 11% overall yield: ^{1}H NMR ($CDCl_3$) δ 1.96 (s, 3H), 2.36 (s, 3H), 6.67 (s, 1H), 7.07 (m, 3H), 7.40 (d, J = 8 Hz, 2H), 7.83 (d, J = 8 Hz, 2H).

4-[5-(2,5-Dimethylphenyl)-3-(difluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (2l). The title compound was synthesized from 2,5-dimethylacetophenone and ethyl difluoroacetate using the 2-step procedure described above in 69% overall yield: ^{1}H NMR (DMSO-d_6) δ 1.85 (s, 3H), 2.23 (s, 3H), 6.84 (s, 1H), 7.19−6.98 (m, 4H), 7.44−7.33 (m, 4H), 7.77 (d, J = 8.7 Hz, 2H).

4-[5-(2-Pyridyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]-benzenesulfonamide (1ai). The title compound was synthesized from 2-acetylpyridine using the 2-step procedure described above in 11% overall yield: ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 2H), 7.05 (s, 1H), 7.43 (m, 5H), 7.80 (t, 1H), 7.94 (d, J = 8 Hz, 2H).

4-[5-(3-Pyridyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]-benzenesulfonamide (1aj). The title compound was synthesized from 4,4,4-trifluoro-1-(3-pyridyl)-1,3-butanedione (Aldrich) using step 2 of the 2-step procedure described above in 5% overall yield: ^{1}H NMR ($CDCl_3$/CD_3OD) δ 6.93 (s, 1H), 7.40 (m, 3H), 7.61 (d, J = 8 Hz, 1H), 7.97 (d, J = 8 Hz, 2H), 8.53 (s, 1H), 8.61 (d, J = 8 Hz, 1H).

4-[5-(4-Pyridyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]-benzenesulfonamide (1ak). The title compound was synthesized from 4-acetylpyridine using the 2-step procedure described above in 8% overall yield: ^{1}H NMR (acetone-d_6) δ 6.79 (s, 2H), 7.25 (s, 1H), 7.35 (d, J = 4.6 Hz, 2H), 7.62 (d, J = 8.5 Hz, 2H), 8.00 (d, J = 8.5 Hz, 2H), 8.1 (m, 4H), 8.64 (d, 2H, J = 4.4 Hz).

4-[5-(5-Bromo-2-thienyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1al). The title compound was synthesized from 2-acetyl-5-bromothiophene using the 2-step procedure described above in 32% overall yield: ^{1}H NMR ($CDCl_3$/CD_3OD) δ 6.72 (d, J = 4 Hz, 1H), 7.83 (s, 1H), 7.03 (d, J = 4 Hz, 1H), 7.58 (d, J = 8 Hz, 2H), 8.03 (d, J = 8 Hz, 2H).

4-[5-(5-Chloro-2-thienyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1am). The title compound was synthesized from 2-acetyl-5-chlorothiophene using the 2-step procedure described above in 46% overall yield: ^{1}H NMR (acetone-d_6) δ 6.80 (br s, 2H), 7.06 (s, 2H), 7.14 (s, 1H), 7.75 (d, J = 8.7 Hz, 2H), 8.05 (d, J = 8.7 Hz, 2H); HRMS m/z 406.9784 (calcd for $C_{14}H_9ClF_3N_3O_2S_2$, 406.9777).

4-[3-(Difluoromethyl)-5-(5-methyl-2-furyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (2m). The title compound was synthesized from 2-acetyl-5-methylfuran and ethyl difluoroacetate using the 2-step procedure described above in 62% overall yield: ^{1}H NMR (DMSO-d_6/400 MHz) δ 3.34 (s, 3H), 6.16 (d, J = 3.2 Hz, 2H), 6.22 (d, J = 3.2 Hz, 2H), 7.24−6.96 (m, 2H), 7.52 (s, 2H), 7.64 (d, J = 8.8 Hz, 2H), 7.94 (d, J = 8.8 Hz, 2H).

4-[5-(3-Benzothienyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1an). The title compound was synthesized from 3-acetylbenzothiophene using the 2-step procedure described above in 36% overall yield: ^{1}H NMR ($CDCl_3$/CD_3OD) δ 6.98 (s, 1H), 7.47 (m, 5H), 7.87 (d, J = 8 Hz, 2H), 7.94 (d, J = 8 Hz, 2H).

4-[5-(Benzofuran-2-yl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1ao). The title compound was synthesized from 2-acetylbenzofuran using the 2-step procedure described above in 42% overall yield: ^{1}H NMR ($CDCl_3$/CD_3OD) δ 6.56 (s, 1H), 7.14 (s, 1H), 7.29 (d, J = 8 Hz, 1H), 7.36 (t, J = 8 Hz, 1H), 7.47 (d, J = 8 Hz, 1H), 7.54 (d, J = 8 Hz, 1H), 7.69 (d, J = 8 Hz, 2H), 8.07 (d, J = 8 Hz, 2H).

4-[5-(1-Cyclohexenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1ap). The title compound was synthesized from 1-acetyl-1-cyclohexene using the 2-step procedure described above in 10% overall yield: ^{1}H NMR (acetone-d_6) δ 1.65 (m, 4H), 2.13 (m, 4H), 5.92 (m, 1H), 6.75 (br s, 3H), 7.79 (d, J = 8.7 Hz, 2H), 8.04 (d, J = 8.7 Hz, 2H); HRMS m/z 371.0918 (calcd for $C_{16}H_{16}F_3N_3O_2S$, 371.0915).

4-[5-(5-Indanyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]-benzenesulfonamide (1aq). The title compound was synthesized from 5-acetylindan using the 2-step procedure described above in 22% overall yield: ^{1}H NMR ($CDCl_3$) δ 2.10 (m, 2H), 2.94 (m, 4H), 4.92 (s, 2H), 6.72 (s, 1H), 6.92 (d, J = 8 Hz, 1H), 7.14 (s, 1H), 7.20 (d, J = 8 Hz, 1H), 7.50 (d, J = 8 Hz, 2H), 7.90 (d, J = 8 Hz, 2H).

4-[5-(3,4-Dihydro-2*H*-1-benzothiopyran-6-yl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1ar). The title compound was synthesized from 6-acetyl-3,4-dihydro-2*H*-1-benzothiopyran using the 2-step procedure described above in 25% overall yield: ^{1}H NMR (acetone-d_6) δ 2.05 (m, 2H), 2.78 (t, J = 5 Hz, 2H), 3.05 (t, J = 5 Hz, 2H), 6.92 (d, 1H), 6.98 (s, 1H), 7.02 (d, J = 10 Hz, 1H), 7.12 (s, 1H), 7.58 (d, J = 10 Hz, 2H), 7.96 (d, J = 10 Hz, 2H).

4-[5-(2,3-Dihydrobenzofuran-5-yl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1as). The title compound was synthesized from 5-acetyl-2,3-dihydrobenzofuran using the 2-step procedure described above in 45% overall yield: ^{1}H NMR ($CDCl_3$) δ 3.15 (t, J = 6 Hz, 2H), 4.54 (t, J = 6 Hz, 2H), 5.71 (s, 2H), 6.68 (s, 1H), 6.69 (d, J = 8 Hz, 1H), 6.92 (dd, J = 1, 8 Hz, 1H), 7.07 (br s, 1H), 7.42 (d, J = 8 Hz, 2H), 7.85 (d, J = 8 Hz, 2H).

4-[3-(Difluoromethyl)-5-(1,3-benzodioxol-5-yl)-1*H*-pyrazol-1-yl]benzenesulfonamide (2n). The title compound was synthesized from 5-acetyl-1,3-benzodioxole and ethyl difluoroacetate using the 2-step procedure described above in 84% overall yield: ^{1}H NMR (DMSO-d_6) δ 6.06 (s, 2H), 7.3−6.7 (m, 5H), 7.49 (br s, 2H), 7.51 (d, J = 8.7 Hz, 2H), 7.86 (d, J = 8.7 Hz, 2H).

4-[5-(4-Methyl-1,3-benzodioxol-6-yl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1at). The title compound was synthesized from 6-acetyl-4-methyl-1,3-benzodioxole using the 2-step procedure described above in 42% overall yield: ^{1}H NMR ($CDCl_3$) δ 2.07 (s, 3H), 6.00 (s, 2H), 6.43 (s, 1H), 6.69 (d, J = 8 Hz, 1H), 7.50 (d, J = 8 Hz, 2H), 6.94 (d, J = 8 Hz, 2H).

4-[3-(Difluoromethyl)-5-phenyl-1*H*-pyrazol-1-yl]benzenesulfonamide (2o). The title compound was synthesized from acetophenone and ethyl difluoroacetate using the 2-step procedure described above in 58% yield: ^{1}H NMR ($CDCl_3$) δ 5.92 (br s, 2H), 6.71 (s, 1H), 6.74 (t, J = 54.5 Hz, 1H), 7.24−7.15 (m, 2H), 7.41−7.28 (m, 5H), 7.87 (d, J = 8.7 Hz, 2H); ^{19}F NMR ($CDCl_3$) δ −112.66 (d, J = 54.5 Hz); HRMS m/z 349.0737 (calcd for $C_{16}H_{12}F_2N_3O_2S$ (M + 1), 349.0696).

4-[4-Methoxy-5-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (25d). The title compound was prepared from 2-methoxyacetophenone using the 2-step procedure described above in 24% overall yield: ^{1}H NMR (acetone-d_6) δ 3.69 (s, 3H), 6.70 (s, 2H), 7.38−7.46 (m, 5H), 7.51 (d, J = 8 Hz, 2H), 7.92 (d, J = 8 Hz, 2H).

1,5-Diphenyl-3-(trifluoromethyl)pyrazole (34). The title compound was prepared from acetophenone and phenylhydrazine hydrochloride using the 2-step procedure described above in 36% yield: ^{1}H NMR (acetone-d_6) δ 7.00 (s, 1H), 7.31−7.47 (m, 10H); ^{19}F NMR (acetone-d_6) δ −63.10 (s).

1,5-Bis(4-chlorophenyl)-3-(trifluoromethyl)pyrazole (35). The title compound was prepared from 4′-chloroacetophenone and (4-chlorophenyl)hydrazine hydrochloride using the 2-step procedure described above in 49% yield: ^{1}H NMR (acetone-d_6) δ 7.06 (s, 1H), 7.36−7.54 (m, 8H); ^{19}F NMR (acetone-d_6) δ −63.22 (s).

1,5-Bis(4-methoxyphenyl)-3-(trifluoromethyl)pyrazole (36). The title compound was prepared from 4′-methoxyacetophenone and (4-methoxyphenyl)hydrazine hydrochloride using the 2-step procedure described above in 76% yield: ^{1}H NMR (acetone-d_6) δ 3.81 (d, J = 1.4 Hz, 3H), 3.85 (d, J = 1.4 Hz, 3H), 6.88 (s, 1H), 6.94 (dd, J = 8.9, 1.2 Hz, 2H), 7.01 (dd, J = 8.9, 1.2 Hz, 2H), 7.23 (dd, J = 8.9, 1.2 Hz, 2H), 7.27 (dd, J = 8.9, 1.4 Hz, 2H); ^{19}F NMR (acetone-d_6) δ −63.02 (s).

1-(4-Chlorophenyl)-5-(4-methoxyphenyl)-3-(trifluoromethyl)pyrazole (37). The title compound was prepared from 4′-methoxyacetophenone and (4-chlorophenyl)-hydrazine hydrochloride using the 2-step procedure described above in 48% yield: ^{1}H NMR ($CDCl_3$) δ 3.82 (s, 3H), 6.65 (s, 1H), 6.87 (d, J = 8.7 Hz, 2H), 7.13 (d, J = 8.7 Hz, 2H), 7.25 (d, J = 8.7 Hz, 2H), 7.33 (d, J = 8.7 Hz, 2H).

5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-(trifluoromethyl)pyrazole (38). The title compound was prepared from 4′-chloroacetophenone and (4-methoxyphenyl)-hydrazine hydrochloride using the 2-step procedure described above in 72% yield: ^{1}H NMR ($CDCl_3$) δ 3.82 (s, 3H), 6.72 (s, 1H), 6.87 (d, J = 8.6 Hz, 2H), 7.14 (d, J = 8.6 Hz, 2H), 7.21 (d, J = 9.0 Hz, 2H), 7.29 (d, J = 8.6 Hz, 2H); ^{19}F NMR ($CDCl_3$) δ −63.02.

4-(3-Methyl-5-phenyl-1*H*-pyrazol-1-yl)benzenesulfonamide (8a). The title compound was prepared from 1-benzoylacetone and (4-sulfamoylphenyl)hydrazine hydrochloride as in step 2 of the 2-step procedure described above in 26% yield: ^{1}H NMR (CD_3OD) δ 2.38 (s, 3H), 6.39 (s, 1H), 7.22 (m, 2H), 7.31−7.37 (m, 3H), 7.37 (d, J = 8 Hz, 2H), 7.88 (d, J = 8 Hz, 2H).

5-(4-Fluorophenyl)-1-(4-nitrophenyl)-3-(trifluoromethyl)-1*H*-pyrazole (32). The title compound was synthesized from 4,4,4-trifluoro-1-(4-fluorophenyl)-1,3-butanedione and 90% (4-nitrophenyl)hydrazine (10% water) using step 2 of the 2-step procedure described above to give a light yellow solid in 16% yield: ^{1}H NMR ($CDCl_3$) δ 6.78 (s, 1H), 7.12 (t, J = 8.5 Hz, 2H), 7.25 (m, 2H), 7.51 (d, J = 9.0 Hz, 2H), 8.24 (d, J = 9.0 Hz, 2H).

4-[1-(4-Fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-yl]benzenesulfonamide (28a). Step 1: Preparation of *N*,*N*-Bis(4-methoxybenzyl)-4-(aminosulfonyl)acetophenone. To a solution of 4-(aminosulfonyl)acetophenone (2.0 g, 9.0 mmol) in 25 mL of dimethyl sulfoxide (DMSO) was added NaOH (450 mg, 19.0 mmol). The reaction mixture was stirred for 45 min, and 4-methoxybenzyl bromide (3.5 g, 19.0 mmol) in DMSO (5 mL) was added. The mixture was stirred at room temperature for 24 h and partitioned between EtOAc and pH 7 buffer. The aqueous solution was extracted with EtOAc and the organic solution dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography on silica gel (2:1 hexane/EtOAc) to give 815 mg (21%) of the title compound.

Step 2: Preparation of *N*,*N*-Bis(4-methoxybenzyl)-4-[1-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]-benzenesulfonamide. The title compound was synthesized from the product of step 1 and (4-fluorophenyl)hydrazine hydrochloride using the 2-step procedure described above.

Step 3: Preparation of 4-[1-(4-Fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-yl]benzenesulfonamide. To a solution of the protected pyrazole from step 2 (50 mg, 0.08 mmol) in acetonitrile (1 mL) and water (0.3 mL) was added 360 mg (0.65 mmol) of ceric ammonium nitrate (CAN), and the mixture was stirred at room temperature for 16 h. The solution was poured into water (15 mL) and extracted with EtOAc (2 × 25 mL), and the combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography on silica gel (2:1 hexane/EtOAc) to give **28a** (13 mg, 42%): ^{1}H NMR (CD_3OD) δ 7.05 (s, 1H), 7.21 (t, 2H), 7.38 (dd, 2H), 7.46 (d, J = 8 Hz, 2H), 7.88 (d, J = 8 Hz, 2H); HRMS m/z 385.0508 (calcd for $C_{16}H_{11}F_4N_3O_2S$, 385.0508).

4-[1-(4-Methoxyphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-yl]benzenesulfonamide (28b). The title compound was prepared from (4-methoxyphenyl)hydrazine hydrochloride using the procedure described above for **28a** to afford **28b** in 55% yield: ^{1}H NMR (acetone-d_6) δ 3.86 (s, 3H), 6.68 (s, 2H), 7.01 (d, J = 8 Hz, 2H), 7.09 (s, 1H), 7.33 (d, J = 8 Hz, 2H), 7.52 (d, J = 8 Hz, 2H), 7.89 (d, J = 8 Hz, 2H); HRMS m/z 397.0702 (calcd for $C_{17}H_{14}F_3N_3O_3S$, 397.0708).

4-[5-[4-(Hydroxymethyl)phenyl]-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1v). A solution of **1i** (1.13 g, 3.0 mmol) and 0.64 g (3.6 mmol) of *N*-bromosuccinimide (NBS) in 40 mL of benzene was irradiated for 3 h with a sun lamp. The reaction mixture was partitioned between EtOAc and water and the organic phase washed with brine, dried over $MgSO_4$, and concentrated to yield an amber oil (1.16 g, 83%). The crude bromide was dissolved in 30 mL of acetone and 4 mL of water and refluxed for 120 h. After concentrating *in vacuo*, the residue was dissolved in EtOAc, dried over $MgSO_4$, and concentrated. The crude product was purified by radial band chromatography, eluting with 30% EtOAc/70% hexane, to give the alcohol as a yellow solid (0.23 g, 23%): ^{1}H NMR ($CDCl_3$) δ 4.47 (br s, 2H), 4.87 (s, 2H), 6.78 (s, 1H), 7.27 (d, J = 8 Hz, 2H), 7.40 (d, J = 8 Hz, 2H), 7.51 (d, J = 8 Hz, 2H), 7.90 (d, J = 8 Hz, 2H).

4-[1-[4-(Aminosulfonyl)phenyl]-3-(trifluoromethyl)-1*H*-pyrazol-5-yl]benzoic Acid (1w). To a solution of **1v** (111 mg, 0.25 mmol) in 3 mL of acetone was added 1.33 M Jones reagent dropwise until the orange color persisted (∼20 drops). The solution was concentrated *in vacuo* and dissolved in EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated to obtain the acid as a white solid (53 mg, 46%): ^{1}H NMR ($CDCl_3$/CD_3OD) δ 6.89 (s, 1H), 7.34 (d, J = 8 Hz, 2H), 7.47 (d, J = 8 Hz, 2H), 7.94 (d, J = 8 Hz, 2H), 8.07 (d, J = 8 Hz, 2H); HRMS m/z 411.0497 (calcd for $C_{17}H_{12}F_3N_3O_4S$, 411.0500).

4-[5-(4-Fluorophenyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (22a). 4′-Fluoroacetophenone (13.8 g, 100 mmol) was refluxed in dimethylformamide (DMF) dimethyl acetal (13 g, 109 mmol) for 23 h. The mixture was cooled and concentrated to give a yellow solid: ^{1}H NMR ($CDCl_3$) δ 2.94 (br s, 3H), 3.16 (br s, 3H), 5.68 (d, J = 12.3 Hz, 1H), 7.08 (t, J = 8.6 Hz, 2H), 7.81 (d, J = 12.3 Hz, 1H), 7.92 (2d, J = 8.6 Hz, 2H).

To a solution of the crude enamine (1.93 g, 10 mmol) in 30 mL of EtOH was added (4-sulfamoylphenyl)hydrazine hydrochloride (2.5 g, 11.2 mmol), and the mixture was refluxed for 17 h. The mixture was cooled, concentrated, and partitioned between EtOAc and water. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated. The tan solid was washed with CH_2Cl_2 and Et_2O and dried to give 2.36 g (74%) of **22a**: ^{1}H NMR (CD_3OD) δ 6.53 (d, J = 1.7 Hz, 1H), 7.06 (t, J = 8.6 Hz, 2H), 7.20 (m, 2H), 7.40 (d, J = 8.6 Hz, 2H), 7.76 (d, J = 1.7 Hz, 1H), 7.89 (d, J = 8.6 Hz, 2H).

4-[3-(Fluoromethyl)-5-phenyl-1*H*-pyrazol-1-yl]benzenesulfonamide (16a). Step 1: Preparation of 4-[3-(Hydroxymethyl)-5-phenyl-1*H*-pyrazol-1-yl]benzenesulfonamide. To a solution of 4.0 g (10.4 mmol) of methyl 1-[4-(aminosulfonyl)phenyl]-5-phenyl-1*H*-pyrazole-3-carboxylate (prepared using the procedure described for the synthesis of **3a**) in 50 mL of tetrahydrofuran (THF) was added lithium aluminum hydride (LAH; 0.592 g, 15.6 mmol) in portions, and the mixture was refluxed overnight. The mixture was cooled, quenched with 1 N $NaHSO_4$, and extracted with Et_2O (3×). The combined extracts were dried over $MgSO_4$ and concentrated to give 3.5 g of crude alcohol. Flash chromatography using 1:1 hexane/EtOAc provided the title compound.

Step 2: Preparation of 4-[3-(Fluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide. To a solution of the alcohol prepared in step 1 (212 mg, 0.64 mmol) in 4 mL of CH_2Cl_2 was added diethylaminosulfur trifluoride (DAST; 0.13 mL, 1.0 mmol). The reaction mixture was stirred at room temperature for 3 h and partitioned between water and CH_2Cl_2. The aqueous solution was extracted with dichloromethane and the organic solution washed with brine and concentrated. The residue was purified by flash chromatography on silica gel (1:1 hexane/EtOAc) to give **16a** (72 mg, 34%): ^{1}H NMR (acetone-d_6) δ 5.39 (s, 1H), 5.54 (s, 1H), 6.72 (s, 2H), 6.77 (d, J = 1 Hz, 1H), 7.30−7.36 (m, 2H), 7.39−7.45 (m, 3H), 7.50 (d, J = 8 Hz, 2H), 7.91 (d, J = 8 Hz, 2H).

4-[5-(4-Chlorophenyl)-3-(hydroxymethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (14a). To a solution of 3.8 g (10 mmol) of 4-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1*H*-pyrazole-3-carboxylic acid (prepared as described for the synthesis of **10a**) in 100 mL of THF at room temperature was added dropwise 30 mL of 1 M borane−THF complex. The mixture was heated at reflux for 16 h. The solution was cooled and MeOH added dropwise until gas evolution ceased. EtOAc (100 mL) was added, and the mixture was washed successively with 1 N HCl, brine, saturated $NaHCO_3$, and water, dried over $MgSO_4$, filtered, and concentrated. The resultant solid was recrystallized from EtOH/water to yield 2.6 g (71%) of **14a** as a white solid: ^{1}H NMR (DMSO-d_6) δ 4.50 (d, J = 8.0 Hz, 2H), 5.35 (t, J = 8.0 Hz, 1H), 6.63 (s, 1H), 7.26 (d, J =8.4 Hz, 2H), 7.40 (d, J = 8.7 Hz, 2H), 7.42 (br s, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.81 (d, J = 8.7 Hz, 2H).

4-[5-(4-Chlorophenyl)-3-(cyanomethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (17a). Step 1: Preparation of 4-[5-(4-Chlorophenyl)-3-(chloromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide. A mixture of **14a** (3.0 g, 8.2 mmol), THF (100 mL), lithium chloride (0.35 g, 8.2 mmol), *p*-toluenesulfonyl chloride (1.56 g, 8.2 mmol), and triethylamine (0.83 g, 8.2 mmol) was heated to reflux for 16 h. The reaction mixture was diluted with EtOAc and then washed with 1 N HCl, saturated $NaHCO_3$, and water, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography over silica gel with 1:1 EtOAc/hexane as eluant to yield 2.2 g (70%) of a white solid: mp 198−201 °C; ^{1}H NMR (DMSO-d_6) δ 4.80 (s, 2H), 6.80 (s, 1H), 7.28 (d, J = 8.7 Hz, 2H), 7.48−7.43 (m, 6H), 7.82 (d, J = 8.7 Hz, 2H).

Step 2: Preparation of 4-[5-(4-Chlorophenyl)-3-(cyanomethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide. The product from step 1 (0.35 g, 0.9 mmol), DMSO (15 mL), and sodium cyanide (0.2 g) were combined and stirred at 100 °C for 4 h. The reaction mixture was diluted with water (100 mL) and extracted with EtOAc. The organic layer was separated, washed with water, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography over silica gel using 1:1 EtOAc/hexane as eluant and then recrystallized from EtOAc/hexane to yield 0.25 g (74%) of **17a** as a white solid: ^{1}H NMR (DMSO-d_6/400 MHz) δ 4.15 (s, 2H), 6.72 (s, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.48−7.43 (m, 6H), 7.83 (d, J = 8.4 Hz, 2H).

4-[3-[(Benzyloxy)methyl]-5-(4-chlorophenyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (15a). A solution of **14a** (500 mg, 1.37 mmol) in THF was treated with sodium hydride (86 mg, 3.44 mmol) and stirred at room temperature for 30 min. Benzyl bromide (0.18 mL, 1.51 mmol) was added and the mixture heated to reflux for 6 h. After cooling, the mixture was diluted with 1 N HCl, extracted with EtOAc, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with 1:1.5 EtOAc/hexane and recrystallized from EtOAc/hexane to afford 310 mg (50%) of **15a** as a white solid: ^{1}H NMR ($CDCl_3$) δ 4.60 (s, 2H), 4.61 (s, 2H), 5.20 (br s, 2H), 6.54 (s, 1H), 7.11 (d, J = 8.7 Hz, 2H), 7.36−7.24 (m, 9H), 7.83 (d, J = 8.7 Hz, 2H).

4-[5-(4-Chlorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (9a). Step 1: Preparation of 3-(4-Chlorophenyl)-2,3-epoxy-4′-methoxypropiophenone. To a solution of 2 g of 4-chloro-4′-methoxychalcone in 15 mL of EtOH and 5 mL of acetone at 50°C was added 2 mL of 30 wt % H_2O_2 and 1.5 mL of 4 N NaOH. After stirring for 3 h, the resulting precipitate was filtered and dried to obtain 1.3 g of a white solid: ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H), 4.05 (d, 1H), 4.21 (d, 1H), 6.96 (d, 2H), 7.31 (d, 2H), 7.38 (d, 2H), 8.01 (d, 2H).

Step 2: 4-[5-(4-Chlorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrazol-1-yl]benzenesulfonamide. A solution of 500 mg of the product from step 1 and 390 mg of (4-sulfamoylphenyl)hydrazine hydrochloride in 5 mL of EtOH with 3 drops of acetic acid was stirred at reflux for 3 h. The reaction mixture was partitioned between water (50 mL) and EtOAc (100 mL) and the aqueous layer extracted with EtOAc (3×). The combined extracts were dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on silica gel with 30:70 EtOAc/hexane as eluant to obtain 198 mg (30% overall yield) of **9a**: ^{1}H NMR (acetone-d_6) δ 3.86 (s, 3H), 7.03 (d, 2H), 7.06 (s, 1H), 7.39 (d, 2H), 7.48 (d, 2H), 7.66 (d, 2H), 7.99 (d, 2H), 7.95 (d, 2H).

4-[5-(4-Chlorophenyl)-3-(5-chloro-2-thienyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (9b). The title compound was prepared from 3-(4-chlorophenyl)-1-(5-chlorothien-2-yl)prop-2-en-1-one using the procedure described above for **9a** to furnish **9b**: ^{1}H NMR (acetone-d_6) δ 7.08 (d, J = 8 Hz, 2H), 7.40 (d, J = 8 Hz, 2H), 7.42 (s, 1H), 7.48 (d, J = 8 Hz, 2H), 7.54 (d, J = 8 Hz, 2H), 7.95 (d, J = 8 Hz, 2H).

Methyl 1-[4-(Aminosulfonyl)phenyl]-5-(4-fluorophenyl)-1*H*-pyrazole-3-carboxylate (3a). Step 1: Preparation of Methyl 4-(4-Fluorophenyl)-2,4-diketobutyrate. Dimethyl oxalate (18.80 g, 0.159 mol) and 4′-fluoroacetophenone (20.0 g, 0.145 mol) were stirred in 400 mL of MeOH. The reaction flask was placed in a sonication bath (Bransonic 1200), and 70 mL of 25% NaOMe in MeOH was added over 25 min. The reaction mixture was sonicated at 45°C for 16 h. The reaction mixture became an insoluble mass during this time. The solid was broken up and poured into 500 mL of 1 N HCl and the white suspension stirred vigorously at room temperature for 1 h. The suspension was cooled to 0°C and stirred for 30 min. The solid was filtered, washed with 100 mL of cold water, and dried to give 22.91 g (70.6%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 3.95 (s, 3H), 7.04 (s, 1H), 7.19 (dd, J = 8.9, 8.7 Hz, 2H), 8.03 (ddd, J = 8.9, 8.7, 5.0 Hz, 2H); ^{19}F NMR ($CDCl_3$) δ −103.9 (m).

Step 2: Preparation of Methyl 1-[4-(Aminosulfonyl)-phenyl]-5-(4-fluorophenyl)-1*H*-pyrazole-3-carboxylate. The product of step 1 (10.0 g, 44.61 mmol) and (4-sulfamoylphenyl)hydrazine hydrochloride (10.98 g, 49.07 mmol) were stirred in 200 mL of MeOH at reflux for 3 h. After cooling to room temperature, the suspension was stirred at 0°C for 30 min, filtered, washed with water (100 mL), and dried to yield 14.4 g (86%) of **3a** as a white solid: ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H), 6.28 (s, 1H), 7.00 (dd, J = 8.7, 8.5 Hz, 2H), 7.18 (ddd, J = 8.7, 8.5 Hz, 4.9 Hz, 2H), 7.36 (d, J = 8.7 Hz, 2H), 7.85 (d, J = 8.7 Hz, 2H); ^{19}F NMR ($CDCl_3$) δ −111.4 (m).

1-[4-(Aminosulfonyl)phenyl]-5-(4-fluorophenyl)-1*H*-pyrazole-3-carboxylic Acid (10a). To a solution of 10.0 g (26.64 mmol) of **3a** in 200 mL of THF were added 27 mL of 2.5 N NaOH and 25 mL of water, and the suspension was refluxed for 16 h. The mixture was cooled to room temperature, and 110 mL of 1 N HCl was added. The suspension was extracted with CH_2Cl_2 (2 × 200 mL), and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to an oil. Trituration with 300 mL of CH_2Cl_2 yielded, upon filtration and drying, 9.0 g (94%) of **10a** as a white solid: ^{1}H NMR (CD_3OD) δ 7.06 (s, 1H), 7.11 (dd, J = 8.9, 8.7 Hz, 2H), 7.31 (ddd, J = 8.9, 8.7, 4.8 Hz, 2H), 7.51 (d, J = 8.7 Hz, 2H), 7.93 (d, J = 8.7 Hz, 2H); ^{19}F NMR (CD_3OD) δ −114.01 (m).

1-[4-(Aminosulfonyl)phenyl]-5-(4-fluorophenyl)-1*H*-pyrazole-3-carboxamide (11a). To a solution of **10a** (3.0 g, 7.99 mmol) in 100 mL of MeOH was added a catalytic amount of sodium cyanide. Anhydrous ammonia was sparged through the reaction vessel for 16 h without temperature control, during which time the suspension turned a deep red color. The solution was sparged with anhydrous nitrogen at room temperature for 20 min and stirred at 0°C for 30 min. The solid was filtered, washed with 50 mL of cold water, and dried to yield 1.87 g (65%) of **11a** as a white solid: ^{1}H NMR ($CDCl_3$/CD_3OD) δ 6.39 (s, 1H), 6.82−6.67 (m, 6H), 6.95 (m, 2H), 7.14 (d, J = 8.7 Hz, 2H), 7.64 (d, J = 8.7 Hz, 2H); ^{19}F NMR ($CDCl_3$/CD_3OD) δ −112.00 (m).

4-[3-Cyano-5-(4-fluorophenyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (13a). To 20 mL of anhydrous DMF at 0°C was added 0.530 mL (6.105 mmol) of oxalyl chloride. The mixture was stirred at 0°C for 10 min, and a solution of **11a** in DMF was added to the vigorously stirring solution over 2 min. After 15 min, pyridine (1.0 mL, 12.21 mmol) was added to quench the reaction. The mixture was poured into 1 N HCl (100 mL) and extracted with EtOAc (2 × 75 mL). The combined organic extracts were washed with 1 N HCl (2 × 100 mL) and brine (3 × 100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to a crude oil. Flash chromatography on silica gel using 40% EtOAc/hexane furnished 0.66 g (69%) of **13a** as a white solid: ^{1}H NMR ($CDCl_3$) δ 4.88 (br s, 2H), 6.87 (s, 1H), 7.23−7.07 (m, 4H), 7.44 (d, J = 8.9 Hz, 2H), 7.94 (d, J = 8.9 Hz, 2H); ^{19}F NMR ($CDCl_3$) δ −109.90 (m).

***N*-(3-Chlorophenyl)-1-[4-(aminosulfonyl)phenyl]-5-(4-fluorophenyl)-1*H*-pyrazole-3-carboxamide (12a).** A solution of 0.50 g (1.38 mmol) of **10a**, 0.206 g (1.522 mmol) of 1-hydroxybenzotriazole hydrate (HOBT), and 0.318 g (1.66 mmol) of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) in 30 mL of DMF was stirred at room temperature for 40 min. 3-Chloroaniline (0.154 mL, 1.453 mmol) was added and the mixture stirred at room temperature for 16 h. The mixture was poured into 100 mL of 5 wt % aqueous citric acid and the solution extracted with EtOAc (2 × 60 mL). The combined organic extracts were washed with aqueous citric acid (60 mL), saturated $NaHCO_3$ (2 × 60 mL) and brine (2 × 60 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to an oil. Trituration with 20 mL of CH_2Cl_2 yielded, upon filtration and drying, 0.439 g (67%) of **12a** as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.02−6.94 (m, 4H), 7.21−7.11 (m, 3H), 7.33 (d, J = 8.9 Hz, 2H), 7.46 (dd, J = 7.0, 2.0 Hz, 1H), 7.79 (t, J = 2.0 Hz, 1H), 7.86 (d, J = 8.7 Hz, 2H), 8.90 (s, 1H); ^{19}F NMR ($CDCl_3$/CD_3OD) δ −111.38 (m).

4-(3-Methoxy-5-phenyl-1*H*-pyrazol-1-yl)benzenesulfonamide (19). Step 1: Preparation of 4-(3-Hydroxy-5-phenyl-1H-pyrazol-1-yl)benzenesulfonamide (18). To 0.5 N NaOH (100 mL, 50 mmol) at 0°C was added ethyl benzoylacetate (9.6 g, 50 mmol), and the reaction was stirred at 0°C for 3 h and at room temperature for 16 h. The mixture was slowly poured into cold concentrated HCl, producing a white precipitate which was collected and washed with water and cold carbon tetrachloride to provide 6.9 g of the keto acid. The keto acid and 1 equiv of (4-sulfamoylphenyl)hydrazine hydrochloride were heated neat at 90°C for 4 h. The mixture was cooled and the crude product purified by flash chromatography on silica gel using a gradient of 50% EtOAc/hexane to 80% EtOAc/hexane as eluant to afford hydroxypyrazole **18** (23% yield): ^{1}H NMR (DMSO-d_6) δ 6.03 (s, 1H), 7.39 (m, 6H), 7.82 (d, J = 8 Hz, 2H), 7.90 (d, J = 8 Hz, 2H), 8.05 (d, J = 8 Hz, 2H).

Step 2: Preparation of 4-(3-Methoxy-5-phenyl-1*H*-pyrazol-1-yl)benzenesulfonamide (19). Excess MeI (0.5 g), **18** (100 mg, 0.32 mmol), and 60 wt % NaH (9 mg, 0.64 mmol) were stirred in 5 mL of DMF for 6 h. The mixture was poured into EtOAc and water, and the organic layer was separated, dried over Na_2SO_4, and concentrated. Purification by silica gel flash chromatography yielded 55 mg (52%) of **19**: ^{1}H NMR ($CDCl_3$) δ 4.04 (s, 3H), 6.05 (s, 1H), 7.40 (m, 3H), 7.86 (d, J = 8 Hz, 2H), 7.97 (m, 5H).

4-[4-Chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (20a). A solution of **1f** (500 mg, 1.2 mmol) in 50 mL of glacial acetic acid at room temperature was treated with chlorine gas for a period of 15 min. After stirring at room temperature for 1.25 h, the solution was diluted with 100 mL of water and extracted three times with ether. The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a white solid. Recrystallization from ether/petroleum ether provided 390 mg (75%) of **20a**: ^{1}H NMR ($CDCl_3$) δ 5.78 (br s, 2H), 7.25 (d, J = 6.6 Hz, 2H), 7.45 (d, J = 6.3 Hz, 2H), 7.49 (d, J = 6.3 Hz, 2H), 7.97 (d, J = 6.6 Hz, 2H).

4-[4-Fluoro-5-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (24). Step 1: Preparation of 2-Fluoroacetophenone. To a solution of 2-hydroxyacetophenone (2.5 g, 18.4 mmol) in 100 mL of CH_2Cl_2 at −78 °C, was added triflic anhydride (10 g, 35.4 mmol) followed by 2,6-lutidine (4.1 mL, 35.4 mmol), and the mixture was stirred at −78 °C for 50 min. The mixture was poured into CH_2Cl_2 and water, and the CH_2Cl_2 layer was separated, washed with brine, dried over Na_2SO_4 and concentrated to a pale orange solid. To a solution of the crude triflate in 100 mL of THF was added 35 mL of 1 N tetrabutylammonium fluoride in THF. The mixture was refluxed for 15 min, cooled, and poured into ether and water. The ether layer was separated, washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel using 20:1 hexane/EtOAc furnished the α-fluoro ketone (0.852 g, 33.5%): ^{1}H NMR ($CDCl_3$) δ 5.54 (d, J = 46.7 Hz, 2H), 7.49 (t, J = 7 Hz, 2H), 7.63 (t, J = 7 Hz, 1H), 7.90 (d, J = 7 Hz, 2H).

Step 2: Preparation of 2,4,4,4-Tetrafluoro-1-phenylbutane-1,3-dione. To a solution of 2-fluoroacetophenone (0.48 g, 3.4 mmol) in 25 mL of THF at −78 °C was added 4 mL of 1 N lithium bis(trimethylsilyl)amide (LiHMDS), and the mixture was stirred at −78 °C for 45 min. 1-(Trifluoroacetyl)-imidazole (0.65 mL, 5.7 mmol) was added and the mixture stirred at −78 °C for 30 min and at 0 °C for 30 min. The reaction was quenched with 0.5 N HCl, the mixture was poured into ether and water, and the ether layer was separated, washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel using a gradient of 10:1−4:1 hexane/EtOAc furnished the 1,3-diketone (0.34 g, 43%).

Step 3: Preparation of 4-[4-Fluoro-5-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide. The diketone from step 2 (0.34 g, 1.45 mmol) was treated with (4-sulfamoylphenyl)hydrazine hydrochloride (0.35 g, 1.56 mmol) in 15 mL of EtOH at reflux for 15 h. The mixture was cooled and filtered and the filtrate concentrated to a yellow gum. Flash chromatography using 3:1 hexane/EtOAc provided 0.28 g of a yellow solid. Recrystallization from CH_2Cl_2/hexane gave **24** as a pale yellow solid in 32% overall yield: ^{1}H NMR ($CDCl_3$) δ 5.04 (s, 2H), 7.26 (m, 2H), 7.47 (m, 5H), 7.91 (d, J = 7.8 Hz, 2H).

4-[5-(4-Chlorophenyl)-4-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (25a). To a solution of 4-chloropropiophenone (1.82 g, 10.8 mmol) in THF (25 mL) at −78 °C was added 1.0 M NaHMDS in THF (10.8 mL). The solution was kept at −78 °C for 45 min, warmed to −20 °C, and cooled back to −78 °C. To this solution was added 1-(trifluoroacetyl)imidazole (2.0 g, 12.0 mmol) in 5 mL of THF. The mixture was warmed to ambient temperature and stirred for 16 h. The mixture was diluted with ether and washed with 1 N HCl solution. The organic layer was separated, dried

(Na_2SO_4), and concentrated. To the crude product was added (4-sulfamoylphenyl)hydrazine hydrochloride (2.5 g, 11.2 mmol) in 30 mL of EtOH, and the mixture was refluxed for 19 h. The mixture was cooled and partitioned between EtOAc and water and the organic layer separated, dried, and concentrated *in vacuo*. The residue was purified by flash chromatography (2:1 hexane/EtOAc) to give **25a** as a crystalline solid (2.2 g, 49%): ^{1}H NMR (acetone-d_6) δ 2.17 (s, 3H), 6.70 (s, 2H), 7.36 (d, J = 8 Hz, 2H), 7.49 (d, J = 8 Hz, 2H), 7.51 (d, J = 8 Hz, 2H), 7.92 (d, J = 8 Hz, 2H).

4-[5-(4-Chlorophenyl)-4-ethyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (25b). The title compound was prepared from 4′-chlorobutyrophenone using the procedure described above for **25a** to provide **25b** in 21% yield: ^{1}H NMR (acetone-d_6) δ 1.11 (t, J = 8 Hz, 3H), 2.56 (q, J = 8 Hz, 2H), 6.69 (s, 2H), 7.40 (d, J = 8 Hz, 2H), 7.48 (d, J = 8 Hz, 2H), 7.50 (d, J = 8 Hz, 2H), 7.90 (d, J = 8 Hz, 2H).

4-[5-(4-Fluorophenyl)-4-*n*-propyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (25c). The title compound was prepared from 4′-fluorovalerophenone using the procedure described above for **25a** to provide **25c** in 36% yield: ^{1}H NMR ($CDCl_3$) δ 0.84 (t, J = 6 Hz, 3H), 1.50 (m, 2H), 2.52 (t, J = 6 Hz, 2H), 5.66 (s, 2H), 7.08 (t, J = 8 Hz, 2H), 7.21 (m, 2H), 7.30 (d, J = 8 Hz, 2H), 7.77 (d, J = 8 Hz, 2H).

4-[4-Hydroxy-5-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (26). To a solution of **25d** (475 mg, 1.2 mmol) in DMF (6 mL) was added sodium thiomethoxide (420 mg, 6.0 mmol), and the mixture was heated at 120 °C for 3 h. The mixture was cooled and diluted with EtOAc and the organic layer separated, washed with water, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash chromatography (1:1 hexane/EtOAc) to give 226 mg (49%) of **26**: ^{1}H NMR (acetone-d_6) δ 6.69 (s, 2H), 7.33−7.42 (m, 5H), 7.48 (d, J = 8 Hz, 2H), 7.90 (d, J = 8 Hz, 2H), 8.26 (br s, 1H).

4-[5-(4-Hydroxyphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (1m). Demethylation of **1o** using the conditions described for **26** provided **1m** in 29% yield: ^{1}H NMR (CD_3OD) δ 6.95 (dd, J = 8 Hz, 2H), 7.03 (s, 1H), 7.30 (d, J = 8 Hz, 2H), 7.69 (d, J = 8 Hz, 2H), 8.14 (d, J = 8 Hz, 2H); HRMS m/z 383.0546 (calcd for $C_{16}H_{12}F_3N_3O_3S$, 383.0551).

4-(4-Chloro-5-phenyl-1*H*-pyrazol-1-yl)benzenesulfonamide (21a). Step 1: Preparation of Methyl 4-Phenyl-2,4-diketobutyrate. To a mixture of 65.9 g of acetophenone (0.55 mol) and 103.6 g of dimethyl oxalate (0.88 mol) in 1 L of MeOH was added 25 wt % NaOMe in MeOH (230 mL, 1.0 mol). The mixture was stirred at room temperature for 16 h, acidified with concentrated HCl, and extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a solid which was recrystallized from aqueous MeOH to afford 73.2 g (65%) of the title compound as a white solid: mp 57−60 °C; ^{1}H NMR ($CDCl_3$) δ 3.95 (s, 3H), 7.09 (s, 1H), 7.66−7.46 (m, 3H), 8.00 (d, J = 8.66 Hz, 2H), 15.25 (br s, 1H). Anal. ($C_{11}H_{10}O_4$) C, H.

Step 2: Preparation of Methyl 1-[4-(Aminosulfonyl)-phenyl]-5-phenyl-1*H*-pyrazole-3-carboxylate. The product from step 1 (5.34 g, 25.9 mmol) and (4-sulfamoylphenyl)-hydrazine hydrochloride (6.08 g, 27.2 mmol) were heated in 30 mL of MeOH at reflux for 16 h. The solution was cooled and diluted with water, and the resulting solid was filtered, washed with water, dried *in vacuo*, and recrystallized from MeOH to afford 5.35 g (58%) of the title compound as a white solid: mp 197−198 °C; ^{1}H NMR ($CDCl_3$) δ 3.82 (s, 3H), 6.45 (br s, 2H), 6.89 (s, 1H), 7.10−7.06 (m, 2H), 7.26−7.21 (m, 3H), 7.30 (d, J = 8.86 Hz, 2H), 7.76 (d, J = 8.86 Hz, 2H). Anal. ($C_{17}H_{15}N_3O_4S$) C, H, N.

Step 3: Preparation of 1-[4-(Aminosulfonyl)phenyl]-4-chloro-5-phenyl-1*H*-pyrazole-3-carboxylic Acid. A solution of the product from step 2 (1.87 g, 5.23 mmol) in 20% aqueous dioxane was treated with 2.5 N NaOH (5.2 mL) and refluxed for 16 h. The solution was acidified with HCl and extracted with CH_2Cl_2, and the combined extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the crude product. A portion of the solid (0.50 g, 1.46 mmol) was dissolved in acetic acid and treated with chlorine in acetic acid (1.2 N, 1.8 mL). The reaction mixture was stirred at room temperature for 16 h and treated with aqueous $NaHSO_3$. The resulting solid was filtered and dried *in vacuo* to afford 0.389 g (71%) of the title compound as a white solid: ^{1}H NMR (CD_3OD) δ 7.32−7.39 (m, 2H), 7.47−7.40 (m, 3H), 7.46 (d, J = 8.7 Hz, 2H), 7.87 (d, J = 8.7 Hz, 2H); HRMS (FAB) m/z 377.0249 (calcd for $C_{16}H_{12}ClN_3O_4S$, 377.0237).

Step 4: Preparation of 4-(4-Chloro-5-phenyl-1*H*-pyrazol-1-yl)benzenesulfonamide. The product from step 3 (0.30 g, 0.794 mmol) was heated in a stream of nitrogen to 260 °C for 10 min. After cooling to room temperature, the crude solid was crystallized from aqueous EtOH to afford 251 mg (95%) of **21a** as a white solid: ^{1}H NMR ($CDCl_3$) δ 4.78 (br s, 2H), 7.30−7.25 (m, 2H), 7.38 (d, J = 8.7 Hz, 2H), 7.44−7.40 (m, 3H), 7.77 (s, 1H), 7.85 (d, J = 8.7 Hz, 2H).

4-[4-Bromo-5-(4-chlorophenyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (21b). Step 1: Preparation of 3-(4-Chlorophenyl)-3-oxopropanal. A solution of 4′-chloroacetophenone (15.4 g, 0.1 mol), ethyl formate (8.15 g, 0.11 mol), and 25% NaOMe in MeOH (23.77 g, 0.11 mol) in 150 mL of Et_2O was stirred at room temperature for 16 h; 1 N HCl (150 mL) was added, and the mixture was extracted with ether. The ether extract was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to afford a clear oil which was used without further purification.

Step 2: Preparation of 4-[5-(4-Chlorophenyl)-1*H*-pyrazol-1-yl]benzenesulfonamide. A solution of the crude product from step 1 (18.3 g, 100 mmol) and (4-sulfamoylphenyl)hydrazine hydrochloride (11.18 g, 50 mmol) in EtOH was heated at reflux for 16 h. After cooling to room temperature, water was added to precipitate a white solid (4.3 g, 13%): mp 185−187 °C; ^{1}H NMR ($CDCl_3$/400 MHz) δ 4.93 (br s, 2H), 6.53 (d, J = 1.8 Hz, 1H), 7.17 (d, J = 8.7 Hz, 2H), 7.34 (d, J = 8.7 Hz, 2H), 7.43 (d, J = 8.7 Hz, 2H), 7.76 (d, J = 1.8 Hz, 1H), 7.89 (d, J = 8.7 Hz, 2H). Anal. ($C_{15}H_{12}ClN_3O_2S$) C, H, N.

Step 3: Preparation of 4-[5-(4-Chlorophenyl)-4-bromo-1H-pyrazol-1-yl]benzenesulfonamide. To a solution of the product from step 2 (3.34 g, 10 mmol) in acetic acid (150 mL) was added bromine (1.76 g, 11 mmol). After stirring at room temperature for 4 h, dilute $NaHCO_3$ was added and the mixture extracted with EtOAc. The extracts were washed with saturated $NaHCO_3$ and water, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by reverse phase HPLC using acetonitrile and water as eluant, followed by recrystallization, yielded **21b** as a white solid (200 mg, 5%): ^{1}H NMR (DMSO-d_6/400 MHz) δ 4.15 (s, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.43 (s, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 8.8 Hz, 2H), 8.04 (s, 1H).

4-(4-Fluoro-5-phenyl-1*H*-pyrazol-1-yl)benzenesulfonamide (22b). A solution of 2-fluoroacetophenone (200 mg, 1.45 mmol) in 2 mL of DMF dimethyl acetal was refluxed for 18 h. The mixture was cooled and concentrated to give the crude enamine: ^{1}H NMR ($CDCl_3$) δ 3.10 (s, 6H), 6.67 (d, J = 27 Hz, 1H), 7.42 (m, 3H), 7.64 (d, 2H).

Without further purification, the enamine was treated with (4-sulfamoylphenyl)hydrazine hydrochloride (0.34 g, 1.52 mmol) in 10 mL of EtOH and the mixture refluxed for 17 h. The mixture was cooled and filtered and the filtrate concentrated to a yellow gum. Flash chromatography using a gradient of 5:1−2:1 hexane/EtOAc provided 0.11 g of a yellow solid. Recrystallization from ether/hexane gave **22b** as a pale yellow solid in 24% overall yield: ^{1}H NMR ($CDCl_3$) δ 4.83 (s, 2H), 7.27 (s, 2H), 7.43 (m, 5H), 7.72 (d, J = 4.4 Hz, 1H), 7.88 (d, J = 8.7 Hz, 2H).

4-(4-Methyl-5-phenyl-1*H*-pyrazol-1-yl)benzenesulfonamide (22c). The title compound was synthesized from propiophenone using the procedure described above for **22b** to furnish **22c** in 12% overall yield: ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3H), 6.71 (s, 2H), 7.22 (m, 2H), 7.33−7.45 (m, 5H), 7.64 (s, 1H), 7.82 (d, J = 8 Hz, 2H).

4-[4-Cyano-5-(4-methylphenyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (22d). To a solution of 4-toluoylacetonitrile (1.0 g, 6.3 mmol) in 20 mL of THF were added 750 mg of DMF dimethyl acetal and a catalytic amount of *p*-toluenesulfonic acid, and the mixture was refluxed for 6 h. The mixture was

cooled, concentrated, and purified by flash chromatography on silica gel using a gradient of 30% EtOAc/hexane to 50% EtOAc/hexane as eluant to afford 1.0 g (75%) of the enamine intermediate. To a solution of this enamine in 10 mL of EtOH was added (4-sulfamoylphenyl)hydrazine hydrochloride (0.966 g), and the mixture was refluxed for 16 h. The mixture was cooled and concentrated and the crude solid recrystallized from EtOAc/hexane to give **22d** (250 mg, 16%): ^{1}H NMR (acetone-d_6) δ 2.35 (s, 3H), 6.71 (br s, 2H), 7.32 (s, 4H), 7.54 (d, J = 8 Hz, 2H), 7.94 (d, J = 8 Hz, 2H), 8.24 (s, 1H). The regiochemistry was assigned using an NOE experiment.

4-(4-Nitro-5-phenyl-1*H*-pyrazol-1-yl)benzenesulfonamide (22e). The title compound was prepared from benzoylnitromethane using the procedure described above for **22d** to provide **22e** in 38% overall yield: ^{1}H NMR ($CDCl_3$/acetone-d_6) δ 5.67 (br s, 2H), 7.33 (d, J = 8 Hz, 2H), 7.35 (d, J = 8 Hz, 2H), 7.46 (m, 3H), 7.88 (d, J = 8 Hz, 2H), 8.43 (s, 1H).

4-[4-(Methylsulfonyl)-5-(4-chlorophenyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (22f). Step 1: Preparation of 2-(Methylsulfonyl)-4′-chloroacetophenone. A suspension of 2-bromo-4′-chloroacetophenone (8.09 g, 34.6 mmol) and sodium methanesulfinate (3.89 g, 38.1 mmol) in THF (100 mL) was heated to reflux for 4 h. The solution was cooled and concentrated *in vacuo*. The residue was dissolved in EtOAc, washed with aqueous 0.25 N $KHSO_4$, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and filtered. Addition of isooctane to the filtrate, followed by filtration of the resulting solid, afforded 4.24 g (53%) of the title compound as a white solid: mp 147−148 °C; ^{1}H NMR ($CDCl_3$) δ 3.14 (s, 3H), 4.57 (s, 2H), 7.51 (d, J = 8.7 Hz, 2H), 7.96 (d, J = 8.9 Hz, 2H). Anal. ($C_9H_9ClO_3S$) C, H.

Step 2: Preparation of 4-[4-(Methylsulfonyl)-5-(4-chlorophenyl)-1*H*-pyrazol-1-yl]benzenesulfonamide. The product from step 1 (3.84 g, 16.50 mmol), DMF dimethyl acetal (5.50 mL, 41.30 mmol), and toluene (40 mL) were heated to reflux for 20 h. The solution was cooled, concentrated *in vacuo*, and recrystallized from EtOH. The resulting yellow solid was stirred with (4-sulfamoylphenyl)hydrazine hydrochloride (7.38 g, 33.0 mmol), Na_2CO_3 (1.75 g, 16.5 mmol), EtOH (100 mL), and H_2O (10 mL) and heated at reflux for 3 h. The solution was cooled and filtered and the filtrate concentrated *in vacuo* to afford a yellow semisolid. Flash chromatography on silica gel using 2:1 CH_2Cl_2/EtOAc as eluant followed by recrystallization from CH_2Cl_2/isooctane afforded 4.61 g (68%) of the **22f** as yellow-orange needles: ^{1}H NMR ($CDCl_3$) δ 2.83 (s, 3H), 3.50 (br s, 2H), 7.36−7.29 (m, 4 H), 7.41 (d, J = 8.66 Hz, 2H), 7.88 (d, J = 8.66 Hz, 2H), 8.17 (s, 1H).

4-(4-Amino-5-phenyl-1*H*-pyrazol-1-yl)benzenesulfonamide (23). To a solution of **22e** (300 mg, 0.87 mmol) in 10 mL of EtOH were added a catalytic amount of 10% Pd/C and 0.19 mL (6.1 mmol) of hydrazine hydrate. The mixture was refluxed for 16 h, cooled, filtered, and concentrated to afford **23** (270 mg, 100%): ^{1}H NMR (acetone-d_6) δ 3.86 (br s, 2H), 6.57 (br s, 2H), 7.26 (d, 2H), 7.38 (m, 6H), 7.79 (d, 2H).

4-(4-Chloro-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)benzenesulfonamide (20b). To a solution of **8a** (150 mg) in 10 mL of CH_2Cl_2 at room temperature was slowly added excess sulfuryl chloride. The reaction mixture was stirred at room temperature for 2 h, the reaction quenched with water, and the solution extracted with CH_2Cl_2 (3×). The combined extracts were dried and concentrated to give an oil which was purified by flash chromatography on silica gel using 30/70 EtOAc/hexane as eluant to give **20b** as a white solid: ^{1}H NMR (CD_3OD) δ 2.52 (s, 3H), 7.45 (m, 2H), 7.54 (d, J = 8 Hz, 2H), 7.58 (m, 3H), 8.02 (d, J = 8 Hz, 2H).

Methyl 1-[4-(Aminosulfonyl)phenyl]-4-chloro-5-(4-chlorophenyl)-1*H*-pyrazole-3-carboxylate (20f). Step 1: Preparation of 4-(4-Chlorophenyl)-3-ketobutyrate. To a solution of dimethyl oxalate (60.0 g, 0.51 mol) and 4′-chloroacetophenone (46.4 g, 0.3 mol) in 750 mL of MeOH was added 25 wt % NaOMe in MeOH (130 mL), and the mixture was stirred at room temperature for 16 h. The reaction mixture formed an insoluble mass which was acidified with excess 3 N HCl followed by extraction with ethyl acetate. The extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude solid was recrystallized from EtOAc/isooctane to afford 54.6 g (76%) of the title compound: mp 110−112 °C; ^{1}H NMR ($CDCl_3$) δ 3.48 (s, 1H), 3.95 (s, 3H), 7.04 (s, 1H), 7.48 (d, J = 8.66 Hz, 2H), 7.94 (d, J = 8.66 Hz, 2H).

Step 2: Preparation of Methyl 1-[4-(Aminosulfonyl)-phenyl]-5-(4-chlorophenyl)-1*H*-pyrazole-3-carboxylate. A solution of the product from step 1 (18.0 g, 0.75 mol) and (4-sulfamoylphenyl)hydrazine hydrochloride (21.8 g, 0.97 mol) in MeOH was heated to reflux for 30 min. The solution was cooled to 0 °C, and the resulting solid was filtered and dried *in vacuo* to afford 27.0 g (92%) of the title compound as a white solid: mp 227°C; ^{1}H NMR ($CDCl_3$) δ 3.96 (s, 3H), 7.03 (s, 1H), 7.14 (d, J = 8.66 Hz, 2H), 7.33 (d, J = 8.66 Hz, 2H), 7.44 (d, J = 8.86 Hz, 2H), 7.91 (d, J = 8.86 Hz, 2H). Anal. ($C_{17}H_{14}ClN_3O_4S$) C, H, N, S, Cl.

Step 3: Preparation of Methyl 1-[4-(Aminosulfonyl)-phenyl]-4-chloro-5-(4-chlorophenyl)-1*H*-pyrazole-3-carboxylate. The product from step 2 (0.79 g, 2.21 mmol) was dissolved in glacial acetic acid and treated with 2.7 mL of a 0.85 M solution of chlorine in acetic acid. After stirring at room temperature for 16 h, the solution was diluted with aqueous $NaHCO_3$ and the product isolated by filtration. The solid was washed with water and dried *in vacuo* to afford 800 mg (92%) of **20f** as a white solid: ^{1}H NMR ($CDCl_3$) δ 4.01 (s, 3H), 4.94 (br s, 2H), 7.45−7.42 (m, 5H), 7.87 (d, J = 8.86 Hz, 2H); HRMS m/z 426.0128 (calcd for $C_{17}H_{13}Cl_2N_3O_4S$ (M + 1), 426.0082).

1-[4-(Aminosulfonyl)phenyl]-4-chloro-5-(4-chlorophenyl)-1*H*-pyrazole-3-carboxylic Acid (20e). To a solution of 1.00 g (2.35 mmol) of **20f** in 30% aqueous dioxane was added 2.5 N NaOH (2.8 mL, 6.72 mmol), and the mixture was stirred at room temperature for 16 h. The mixture was acidified with 1 N HCl, and the resulting solid was filtered, washed with water, and dried *in vacuo* to afford **20e** (653 mg, 67%) as a white solid: ^{1}H NMR (CD_3OD) δ 7.44 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.7 Hz, 2H), 7.91 (d, J = 8.7 Hz, 2H).

4-[4-Chloro-5-(4-chlorophenyl)-3-(hydroxymethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (20c). To a solution of **20e** (4.14 g, 10 mmol) in 100 mL of THF at room temperature was added 40 mL of 1 M borane−THF complex dropwise, and the mixture was heated to reflux for 16 h. MeOH (10 mL) was added dropwise, and the mixture was extracted with EtOAc. The extracts were washed with 1 N HCl, water, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was recrystallized from EtOH/water to afford **20c** (3.3 g, 83%) as a white solid: ^{1}H NMR (DMSO-d_6/400 MHz) δ 4.52 (d, J = 8.0 Hz, 2H), 5.65 (t, J = 8.0 Hz, 1H), 7.32 (d, J = 8.8 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 7.43 (br s, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 8.4 Hz, 2H).

1-[4-(Aminosulfonyl)phenyl]-4-chloro-5-(4-chlorophenyl)-1*H*-pyrazole-3-carboxamide (20g). A solution of **20f** (900 mg, 2.11 mmol) and NaCN (10 mg) in MeOH was treated with anhydrous NH_3 for 20 min and allowed to stand at room temperature for 7.5 h. The solution was concentrated *in vacuo* to afford a solid that was recrystallized from MeOH/water to afford **20g** (801 mg, 92%) as a white solid: ^{1}H NMR (CD_3OD) δ 7.19 (d, J = 8.7 Hz, 2H), 7.36 (d, J = 8.7 Hz, 2H), 7.39 (d, J = 8.7 Hz, 2H), 7.89 (d, J = 8.7 Hz, 2H); HRMS m/z 411.0115 (calcd for $C_{16}H_{12}Cl_2N_4O_3S$ (M + 1), 411.0085).

4-[4-Chloro-5-(4-chlorophenyl)-3-cyano-1*H*-pyrazol-1-yl]benzenesulfonamide (20d). DMF (20 mL) was cooled to 0 °C and treated with oxalyl chloride (0.31 mL, 3.57 mmol) followed by a solution of **20g** (700 mg, 1.70 mmol) in 5 mL of DMF. The solution was stirred at 0 °C for 30 min and treated with pyridine (0.58 mL, 7.25 mmol). The solution was stirred at room temperature for 1 h, poured into 1 N HCl, and extracted with EtOAc. The extracts were washed with water, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 1:1.5 EtOAc/hexane as eluant to afford **20d** (386 mg, 55%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 5.00 (br s, 2H), 7.16 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 8.7 Hz, 2H), 7.40 (d, J = 8.5 Hz, 2H), 7.90 (d, J = 8.7 Hz, 2H).

***N*-Methyl-4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (29) and *N*,*N*-Dimethyl-4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (30).** To a solution of 100 mg (0.26 mmol) of **1d** in 2 mL of DMSO was added 60 wt % NaH (3.6 mg, 0.26 mmol) and the reaction mixture was stirred at ambient temperature for 1.5 h. To this mixture was added methyl iodide (0.025 mL, 0.4 mmol), and the mixture was stirred at room temperature for 16 h. The mixture was diluted with EtOAc (15 mL) and washed with water (3 × 10 mL) and the organic layer collected, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (3:1 hexane/EtOAc) to give **29** (22 mg, 21%): ^{1}H NMR ($CDCl_3$) δ 2.68 (d, J = 6 Hz, 3H), 4.50 (q, J = 6 Hz, 1H), 6.78 (s, 1H), 6.99 (t, J = 8 Hz, 2H), 7.23 (m, 2H), 7.49 (d, J = 8 Hz, 2H), 7.88 (d, J = 8 Hz, 2H); HRMS m/z 399.0662 (calcd for $C_{17}H_{13}F_4N_3O_2S$, 399.0665). Also obtained was **30** (31 mg, 29%): ^{1}H NMR ($CDCl_3$) δ 2.71 (s, 6H), 6.78 (s, 1H), 7.09 (t, J = 8 Hz, 2H), 7.22 (m, 2H), 7.50 (d, J = 8 Hz, 2H), 7.90 (d, J = 8 Hz, 2H); HRMS m/z 413.0814 (calcd for $C_{18}H_{15}F_4N_3O_2S$, 413.0821).

***N*-[4-[5-(4-Fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]phenyl]methanesulfonamide (31). Step 1: Preparation of 1-(4-Aminophenyl)-5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole.** To a solution of **32** (0.5 g, 1.4 mmol) and catalytic 10% Pd/C in 5 mL of EtOH at 50 °C was added 0.3 mL of hydrazine hydrate dropwise and the mixture was refluxed for 30 min. The mixture was filtered and concentrated to give 0.44 g (98%) of the title compound as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 3.88 (br s, 2H), 6.61 (d, 2H), 6.72 (s, 1H), 7.06 (m, 4H), 7.21 (dd, 2H).

Step 2: Preparation of *N*-[4-[5-(4-Fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]phenyl]methanesulfonamide. To a solution of 0.22 g (0.68 mmol) of the amine prepared in step 1 in 5 mL of CH_2Cl_2 were added 0.08 mL (1.0 mmol) of pyridine and 0.06 mL (0.77 mL) of methanesulfonyl chloride. After stirring at room temperature for 4.5 h, the mixture was poured into CH_2Cl_2 and 0.5 M HCl, and the organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated. Recrystallization from Et_2O/hexane provided **31** (0.17 g, 63%) as a tan solid: ^{1}H NMR ($CDCl_3$) δ 3.04 (s, 3H), 6.75 (s, 1H), 7.05 (t, J = 8.4 Hz, 2H), 7.15 (s, 1H), 7.24 (m, 6H).

2,2,2-Trifluoro-1-[4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]phenyl]ethanone (33). Step 1: Preparation of 1-(4-Bromophenyl)-5-(4-fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazole. Condensation of 4,4,4-trifluoro-1-(4-fluorophenyl)-1,3-butanedione and 4-(bromophenyl)-hydrazine hydrochloride using the conditions of step 2 of the 2-step procedure described above yielded the title compound in 52% yield: ^{1}H NMR ($CDCl_3$) δ 6.73 (s, 1H), 7.05 (t, J = 8.6 Hz, 2H), 7.19 (m, 4H), 7.49 (d, J = 8.6 Hz, 2H).

Step 2: Preparation of 2,2,2-Trifluoro-1-[4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]phenyl]-ethanone. To a solution of 1.09 g (2.83 mmol) of the bromide prepared above in 15 mL of THF at −78 °C was added 1.7 M *t*-BuLi in pentane (3.5 mL, 5.95 mmol), and the mixture was stirred at −78 °C for 30 min; 7 mL of this deep purple solution was added to a solution of 0.18 mL (1.5 mmol) of ethyl trifluoroacetate in 2 mL of THF at −78 °C and the mixture stirred at −78 °C for 10 min and at room temperature for 1 h. The mixture was poured into ether and water, and the organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel using a gradient of 400:1:2−200:2:1 CH_2Cl_2/MeOH/NH_4OH provided **33** (300 mg): ^{1}H NMR ($CDCl_3$) δ 6.78 (s, 1H), 7.11 (t, J = 8.6 Hz, 2H), 7.26 (2d, J = 8.6 Hz, 2H), 7.52 (d, J = 8.6 Hz, 2H), 8.08 (d, J = 8.6 Hz, 2H).

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