Articles

Synthesis and Selective Cyclooxygenase-2 Inhibitory Activity of a Series of Novel, Nitric Oxide Donor-Containing Pyrazoles†

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The synthesis of a series of novel pyrazoles containing a nitrate (ONO_2) moiety as a nitric oxide (NO)-donor functionality is reported. Their COX-1 and COX-2 inhibitory activities in human whole blood are profiled. Our data demonstrate that pyrazole ring substituents play an important role in COX-2 selective inhibition, such that a cycloalkyl pyrazole (**6b**) was found to be a potent and selective COX-2 inhibitor. Other modifications at the 3 position of the central pyrazole ring (**17b**, **23b**, **26b-I**) enhanced COX-2 inhibitory potency. Among the pyrazoles synthesized, the oxime (**23b**) was identified as the most potent COX-2 selective inhibitor. Accordingly, **23b** was profiled pharmacologically in the rat after oral administration and shown to possess potent antiinflammatory activity in the carrageenan-induced air-pouch model and less gastric toxicity than a standard COX-2 inhibitor when administered with background aspirin treatment. We suggest that the enhanced gastric tolerance of an NO-donor COX-2 selective inhibitor has the potential to augment the clinical profile of this drug class.

Introduction

Nonsteroidal antiinflammatory drugs (NSAIDs) are widely used to treat the signs and symptoms of inflammation, particularly arthritic pain.[1,2] NSAIDs exert their antiinflammatory effect mainly through inhibition of cyclooxygenases (COXs), key enzymes in prostaglandin (PG) biosynthesis from arachidonic acid.[3−5] There are at least two mammalian COX isoforms, COX-1 and COX-2.[6,7] Constitutive COX-1 is responsible for the chronic, low-level production of cytoprotective PGs in the gastrointestinal (GI) tract, whereas the main function of inducible, short-lived COX-2 is to generate PGs in inflammatory cells. Traditional NSAIDs such as aspirin, indomethacin, and naproxen are nonselective in that they inhibit COX-2 and, with somewhat greater potency, COX-1.[8−11] Morbidity and mortality due to NSAID-induced GI toxicity are significant and frequent enough worldwide to limit the therapeutic use of this drug class.[12] Common NSAID clinical side-effects, including GI irritation, bleeding, and ulceration, are believed to reflect NSAID inhibition of "housekeeping" PG production by COX-1. Indeed, the first COX-2 selective inhibitors approved for human use, Celecoxib (Celebrex)[15a] and Rofecoxib (Vioxx),[15b] exert the beneficial antiinflammatory and analgesic properties of NSAIDs with enhanced—but not absolute—GI tolerance.[13,14]

Yet COX-2 selective inhibitors are not without limitations.[16a] At higher doses and/or with long-term use, COX-2 selective inhibitors may lose selectivity and inhibit COX-1 in vivo. Recent evidence points to a homeostatic role for at least some COX-2-generated PGs. Potential clinical limitations of long-term COX-2 inhibitor therapy include ulcer exacerbation in high-risk patients, delayed gastroduodenal ulcer healing, kidney toxicity, and a pro-thrombotic prostacyclin (PGI_2) deficiency.[16−19] Particularly noteworthy in light of the now routine use of low-dose aspirin in the prophylaxis of cardiovascular disease and acute coronary syndromes, the gastric tolerability of COX-2 selective inhibitors is compromised in patients taking aspirin.[19a]

Along with prostacyclin (PGI_2), nitric oxide (NO) plays an important cytoprotective role in GI homeostasis by helping maintain mucosal blood flow, by optimizing mucus secretion, and by inhibiting platelet and inflammatory-cell activation.[20−24] As an alternative to COX-2 selective inhibitors, we and others have developed a synthetic strategy toward safer, GI-sparing NASIDs involving the chemical coupling of a NO-donor moiety to a nonselective NSAID.[20−24] Structurally diverse NO-releasing NSAIDs (including nitrate and nitrosothiol derivatives of aspirin, naproxen, ketoprofen, diclofenac, and flurbiprofen) have been characterized.[20−26] Some NO-donor NSAIDs have antiinflammatory activity comparable to their respective parent NSAIDs in acute rodent models, but with less GI toxicity,[20−26] and may even promote ulcer healing.[22] The intrinsic tissue-protective and antiinflammatory properties of NO may help reduce further the GI irritation still associated with

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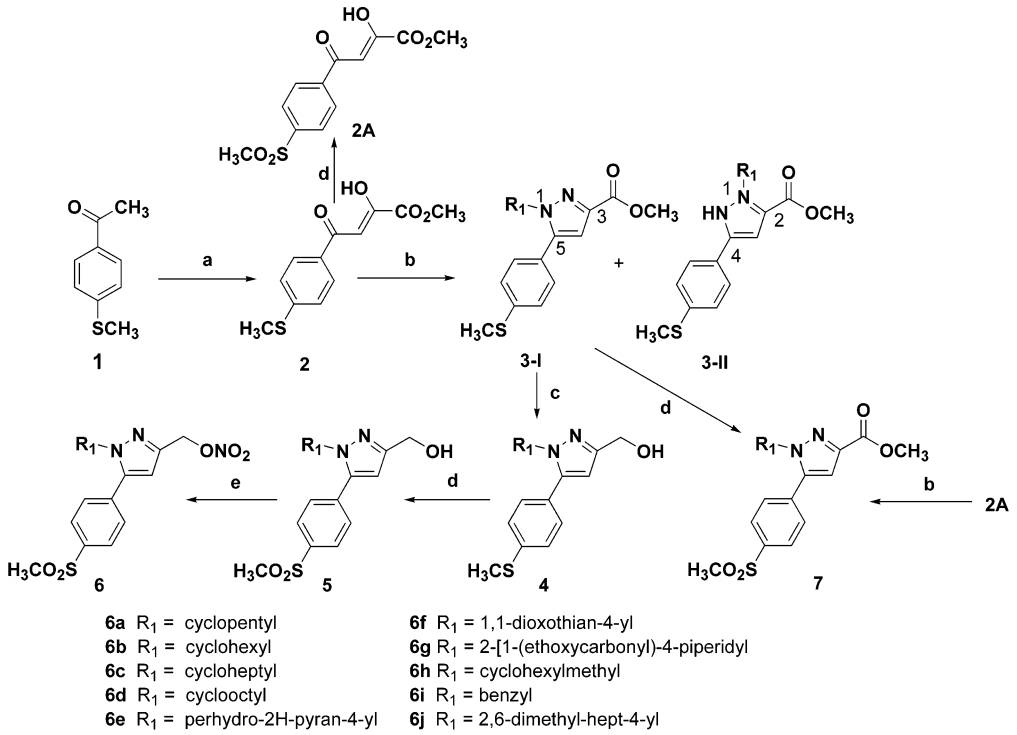
Scheme 1[a]



6a R_1 = cyclopentyl
6b R_1 = cyclohexyl
6c R_1 = cycloheptyl
6d R_1 = cyclooctyl
6e R_1 = perhydro-2H-pyran-4-yl
6f R_1 = 1,1-dioxothian-4-yl
6g R_1 = 2-[1-(ethoxycarbonyl)-4-piperidyl
6h R_1 = cyclohexylmethyl
6i R_1 = benzyl
6j R_1 = 2,6-dimethyl-hept-4-yl

[a] (a) $NaOCH_3$, dimethyl oxalate, toluene; (b) R_1NHNH_2, MeOH, H^+, 60 °C; (c) LAH, THF; (d) Oxone, MeOH/H_2O or *m*CPBA, CH_2Cl_2, 0 °C; (e) f.HNO_3/Ac_2O,$CHCl_3$, −10 °C.

COX-2 selective inhibitors, particularly in the setting of aspirin cardiovascular prophylaxis.[27,28]

We report herein the synthesis, COX inhibitory structure−activity relationship (SAR), and biological evaluation of a series of novel pyrazole COX-2 selective inhibitors containing a NO-donor group.[29] As compared to routine COX-2 selective inhibitors without NO-donating properties, the NO-donor COX-2 selective inhibitors possess additional biological activities that could enhance the overall clinical profile of this drug class.

Chemistry

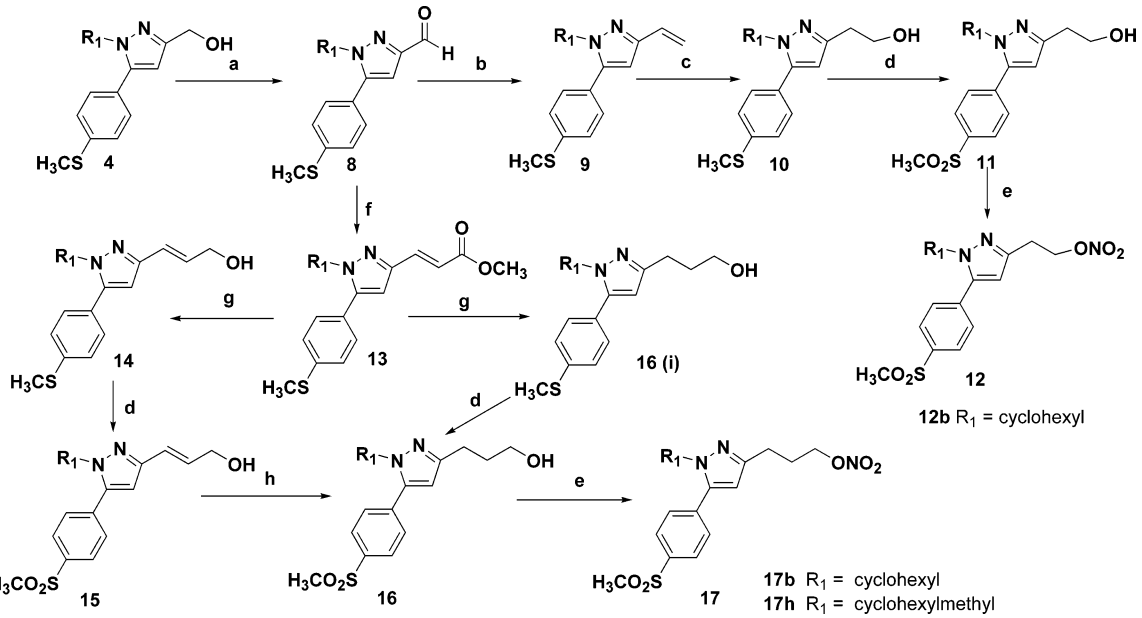
Pyrazole compounds have been identified as potent, selective COX-2 inhibitors with good pharmacokinetic profiles. From this knowledge base, we sought to develop COX-2 selective pyrazoles with NO-donating capabilities. In our case, incorporation of the NO-donor group requires that the pyrazole have an appropriate functionality that can be easily derivatized to a nitrate group. For this purpose, a hydroxyl group was deemed most appropriate for nitration. Generally, for COX-2 selective inhibitors, substitution at positions 1, 3, and 5 of the pyrazole is required. Substitution at position 4 dramatically diminishes COX-2 selectivity. Optimum selectivity is observed with an aryl sulfonamide or sulfone group at position 1 of the pyrazole ring, another substituted or nonsubstituted aryl group at position 5, and a small aliphatic moiety (such as a methyl or trifluoromethyl group) at position 3.

The clinically approved COX-2 inhibitor Celebrex has a 1,5- diaryl substitution and a trifluoromethyl group at position 3. However, SAR studies of pyrazoles with a cycloalkyl subtitution at position 1 and an aryl sulfone substitution at position 5 have not been previously reported**.** We have synthesized pyrazole analogues which incorporate this arrangement of functional groups. Furthermore, these compounds bear a nitrate group as NO donor. The nitrate group is linked to the pyrazole core either by a simple alkyl, alkenyl, keto, or keto derivative tether.

A series of 1-cycloalkyl-5-arylsufone pyrazoles was prepared from commercially available 4-methylthioacetophenone, as illustrated in Scheme 1. The reaction of dimethyl oxalate with the enolate derived from 4-methylthioacetophenone in toluene gave the diketoester **2** in high yield. This was condensed with cycloalkylhydrazines in the presence of a catalytic amount of concentrated HCl or trifluoroacetic acid to obtain pyrazoles **3** in high yield. In most cases, the 1,3,5-substituted pyrazole, **3-I**, was formed exclusively**.** In those cases where there was concurrent formation of the 1,2,4-regioisomer, **3-II**, the two products were readily separated by recrystallization. The ester group of **3-I** was reduced by lithium aluminum hydride (LAH) to obtain the alcohols **4**, which were oxidized to the sulfones **5** with Oxone in high yield. Introduction of the NO-donor (nitrate) group was achieved with a mixture of fuming nitric acid and acetic anhydride in chloroform or ethyl acetate at −10 °C to give **6** in moderate to high yield. Those nitrates unstable to flash chromatography were purified by recrystallization**.** Sulfones of pyrazole methyl esters **7** were prepared by oxidation of **3-I** with Oxone in quantitative yield or by condensaton of **2A** with a hydrazine.

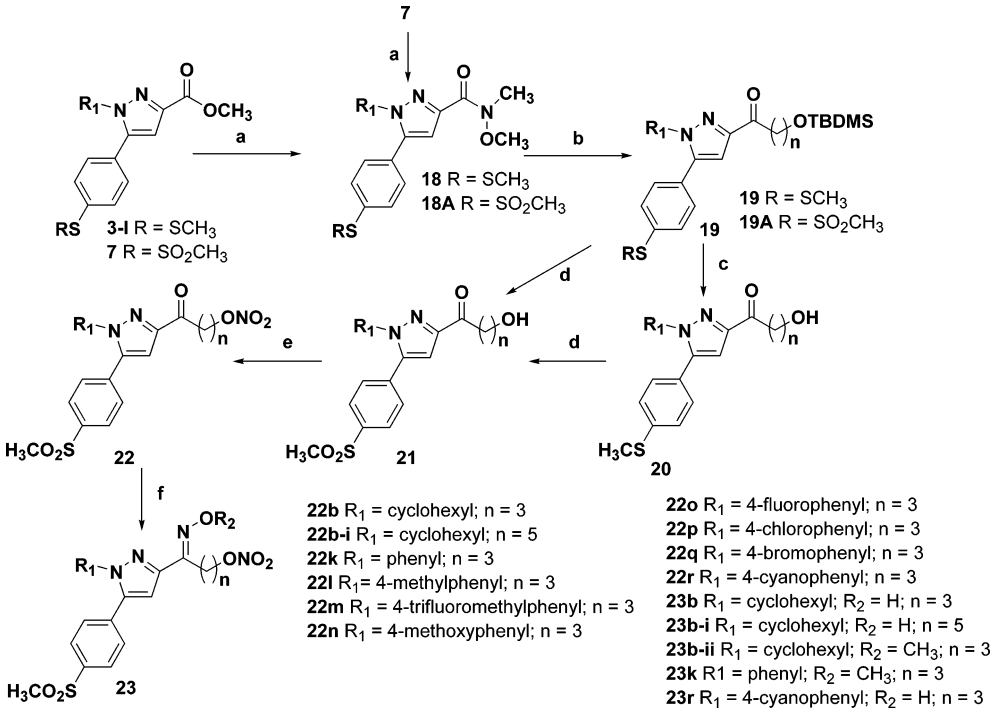
The two-carbon and three-carbon homologues of **6** were synthesized as shown in Scheme 2. The alcohol **4** (Scheme 1) was subjected to Swern oxidation followed by Wittig olefination to give **9** in good yield. Hydroboration[30,31] of the terminal alkene followed by selective

Scheme 2[a]



[a] (a) DMSO/$(COCl)_2$, Et_3N, CH_2Cl_2; (b) Ph_3PCH_3Br/BuLi; (c) BH_3·THF,H_2O_2,NaOH; (d) Oxone, MeOH, H_2O; (e) f. HNO_3/Ac_2O, $CHCl_3$; (f) BuLi/$(CH_3O)_2PCH_2CO_2CH_3$, THF; (g) LAH, THF; (h) Pd/H_2, 50 psi.

Scheme 3[a]

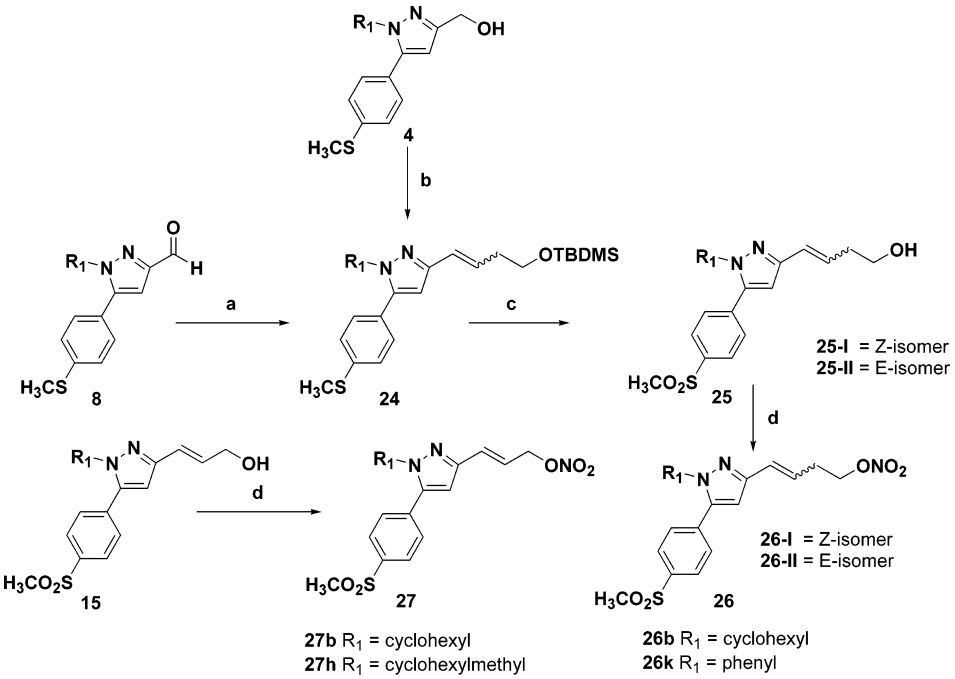


[a] (a) Me_3Al/$HN(OCH_3)CH_3$.HCl, CH_2Cl_2, 0 °C; (b) TBDMSO(CH_2)nMgBr, THF; (c) TBAF, THF; (d) Oxone, MeOH/H_2O; (e) f.HNO_3/Ac_2O, $CHCl_3$, −10 °C; (f) NH_2OR_2·HCl, 15 N NaOH/EtOH.

oxidation of the sulfide with Oxone gave **11** in high yield. Nitration of **11** was achieved as shown in Scheme 1 to afford the ethyl nitrate **12**. The propyl nitrates **17** were synthesized from aldehydes **8** in four or five steps. Horner−Wadsworth−Emmons olefination of **8** afforded **13** in high yield. Reduction of the ester group of **13** with LAH followed by oxidation of the methyl sulfide gave **15**. This was hydrogenated to afford **16,** which was nitrated to give **17**. Alternatively, reduction of **13** with excess LAH gave hydroxypropylpyrazole methyl sulfide **16(i)**, which was oxidized and then nitrated to give **17**.

The syntheses of pyrazole nitrates with carbonyl linkers are illustrated in Scheme 3. Weinreb amides **18** were synthesized from the reaction of **3-I** (Scheme 1) with *N*,*O*-dimethylhydroxylamine hydrochloride in the presence of trimethylaluminum.[32,33] Grignard reaction of **18** with a TBDMS-protected three- or five-carbon Grignard reagent gave **19** in good yield. The TBDMS group of **19** was readily removed by tetrabutylammonium fluoride (TBAF) to afford **20**, which was oxidized with Oxone to give sulfones **21**. **(**A more direct conversion of **19** to **21** can be achieved by simultaneous

Scheme 4[a]



[a] (a) $BrPh_3P(CH_2)_2CH_2OTBDMS$, BuLi, THF, −78 °C; (b) $BrPh_3P(CH_2)_2CH_2OTBDMS$, MnO_2, guanidine, $Ti(OPri)_4$, THF, 70 °C; (c) Oxone, $MeOH/H_2O$; (d) $f.HNO_3/Ac_2O$, $CHCl_3$, −10 °C or $f.HNO_3$, $CHCl_3$, 0 °C.

deprotection[34] and oxidation in a single step using Oxone.) Nitration of **21** afforded ketonitrates **22** in high yield.

Many alkyl and aryl oximes have the potential for in vivo NO release by an as yet unknown mechanism.[35] To generate a pyrazole COX-2 inhibitor with the potential to act as a bifunctional NO donor, the oximes **23** were prepared by the reaction of **22** with hydroxylamine hydrochloride or methoxylamine hydrochloride in the presence of 15 N NaOH (Scheme 3).

Nitrates attached by three- or four-carbon alkenyl linkers were prepared as outlined in Scheme 4. Aldehydes **8** (Scheme 2) were converted to a separable mixture of *Z* and *E* alkenes **24** using a Wittig reagent[36] in high yield. Alternatively, **24** could be synthesized by a one-pot reaction involving treatment of the alcohols **4** (Scheme 1) with the same Wittig reagent in the presence of manganese dioxide and guanidine.[37] Removal of the TBDMS group of **24** and oxidation of the sulfide to a sulfone with Oxone gave the hydroxy pyrazole **25**. Nitration of **25** in the usual manner gave the four-carbon chain alkenyl nitrates **26**. The three-carbon-containing alkenyl nitrate **27** can be prepared from alcohol **15** (Scheme 2) in a similar manner.

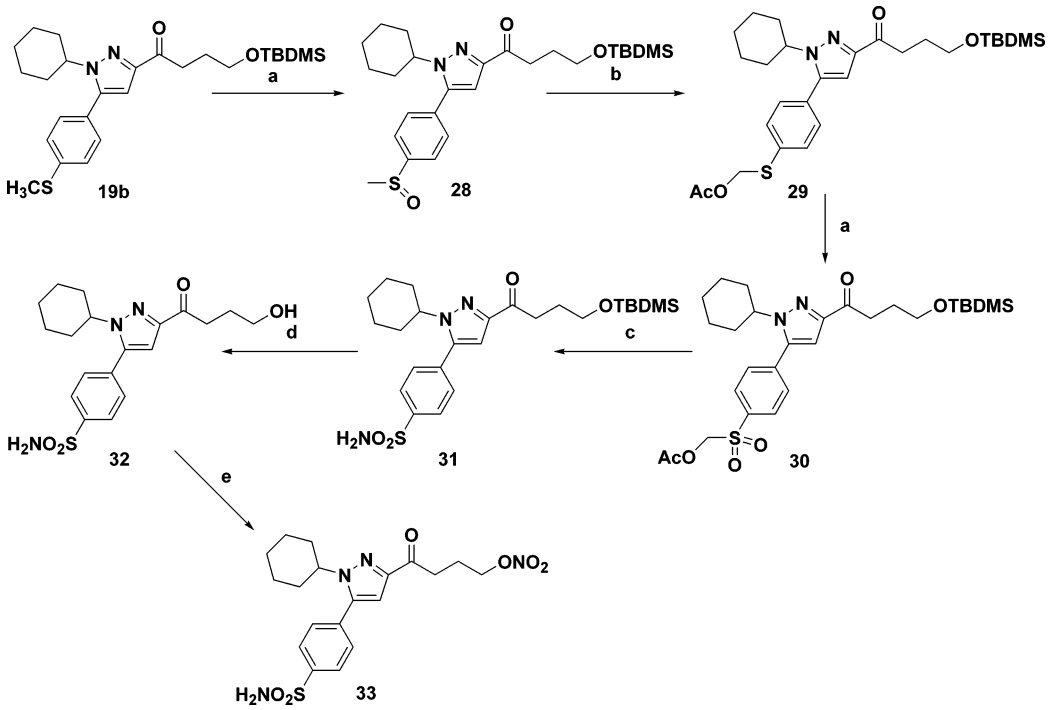
Generally, sulfonamides have slightly better affinities than sulfones for the COX-2 active site.[15b] Thus, we decided to prepare the sulfonamide analogue **33** of sulfone **22b** from its methyl sulfide, as described in Scheme 5.[38] The oxidation of **19b** with magnesium monoperoxyphthalate (MMPP) gave sulfoxide **28**. Treatment of **28** with acetic anhydride at 120 °C caused a Pummerer rearrangement to give the acetoxymethylthio compound **29**. Further oxidation of **29** with MMPP gave **30**. Compound **30** could be converted to **31** by treatment with NaOAc and K_2CO_3 followed by reaction with hydroxylamine-*O*-sulfonic acid. Removal of the TBDMS group by TBAF followed by nitration in a usual manner afforded **33**.

Results and Discussion

A few early compounds were evaluated as potential COX inhibitors by using human or ovine recombinant COX-1 and human COX-2. Subsequently, all compounds were tested for their ability to inhibit COX-1 and COX-2 activity in human whole blood (HWB).[39,40] For both of these in vitro assays, compounds were tested against COX-1 at 100 μM and against COX-2 at 10 and 1 μM (Tables 1−5). For the most potent, selective COX-2 inhibitors, IC_{50}'s were determined in the HWB assay (Table 6). All compounds that inhibited COX-2 with potency and high selectivity were tested in the rat carrageenan-induced air-pouch model[41,42] to index their in vivo antiinflammatory activity (i.e., suppression of white-cell infiltration and/or PG production) at a fixed oral dose (45 μmol/kg) (Table 7). The most selective COX-2 inhibitor with potent antiinflammatory activity (**23b**) was further profiled in a rat gastric injury model.

In Vitro Activity. A common feature among many previously described COX-2 selective inhibitors is 1,5-diaryl substitution of a central pyrazole ring. We explored replacing the aryl substitution at the 1 position with various cycloalkyl groups. The substitution at the 3 position, a nitroxymethyl group, was derived from the corresponding hydroxy derivative. In vitro profiles for these compounds as COX inhibitors are summarized in Table 1. Cyclopentyl-substituted nitrate **6a** slightly potentiated COX-2 activity, whereas the cyclohexyl nitrate **6b**, cycloheptyl nitrate **6c** or cyclooctyl nitrate **6d** showed selective COX-2 inhibition at both the 1 μM and 10 μM. Bulky and more lipophilic cycloalkyl groups (e.g., cyclooctyl) marginally enhanced COX-1 inhibitory activity at the 100 μM test concentration (% COX-1

Scheme 5[a]



[a] (a) MMPP, MeOH, CH_2Cl_2; (b) Ac_2O/NaOAc, 120 °C; (c) i. NaOAC, MeOH, ii. K_2CO_3, MeOH iii. NH_2OSO_3H; (d) TBAF, THF; (e) f.HNO_3/Ac_2O,$CHCl_3$, −10 °C.

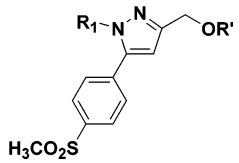
inhibition: **6a** = 0, **6b** = 35, **6c** = 35 and **6d** = 60). The COX-inhibitory $IC_{50's}$ of **6b** (COX-1 > 100 μM; COX-2 = 0.4 μM) show that it is a very potent, highly selective COX-2 inhibitor (Table 6).

Next, we introduced a heteroatom into the cyclohexyl ring of **6b** to examine its potential effect upon COX-2 inhibitory potency and selectivity. As seen in Table 1, introduction of oxygen or sulfur into the cyclohexyl ring markedly decreased COX-2 inhibition (% COX-2 inhibition: **6b** = 80 and **6e** = 30 at 10 μM). Likewise, a 4-carbethoxy substitutant (**6g)** reduced COX-2 inhibitory potency, as compared to **6e** (**6g** = 0% COX-2 inhibition at 10 μM). These results suggest that the lipophilic character of the cyclohexyl group at position 1 contributes to COX-2 inhibitory activity. Substitution of a spacer group (CH_2) between the pyrazole center and position 1 weakened the COX-2 inhibitory activity when compared to **6b** (e.g., % COX-2 inhibition for cyclohexylmethyl **6h** = 65; benzyl **6i** = 40 at 10 μM). These data show how important the lipophilic cyclohexyl ring is to COX-2 inhibitor potency as compared to aromatic ring substitution. Compound **6j**, in which the cycloalkyl ring was replaced by an open alkyl chain (2,6-dimethylhept-4-yl), did not inhibit COX-2 up to a 10 μM test concentration and marginally inhibited COX-1 (by 15%) at 100 μM. The lack of activity of **6e, 6f**, and **6j** suggests that the active site of COX-2 is very sensitive to both the electronic and steric properties of substitution at the 1 position.

The effect of the chain length at the 3 position of the pyrazole ring was next examined. Lengthening the chain from one to three carbons enhanced COX-2 inhibition (% COX-2 inhibition: **6b** = 80; **12b** = 95; and **17b** = 100 at 10 μM) (Table 2). Even at 1 μM, these compounds were appreciable COX-2 inhibitors (Table 2). However, **17b** showed limited selectivity in that it inhibited COX-1 by 90% at 100 μM, prompting the synthesis of **17h** with a cyclohexylmethyl group at position 1 and a three-carbon nitrate linker at position 3. The COX inhibitor profile of the cyclohexylmethyl compound, **17h**, is consistent with its corresponding one-carbon chain analogue, **6h** (% inhibition of COX-2 for **17h** = 75 and **6h** = 10 at 1 μM). This series suggests that COX-2 inhibitory potency might be enhanced by lengthening the carbon chain at position 3, perhaps at the expense of COX-2 selectivity.

With the aim of improving these COX-2 inhibitors and retaining the 3-position nitrated linker, we varied the nature of the carbon chain. First, we considered a series of pyrazole nitrates (**22b, 22k**−**r)** containing carbonyl linkers (Scheme 3). Synthesis and biological evaluation of such carbonyl pyrazoles have not been reported previously. Aryl substituted nitrates demonstrated very good COX-2 inhibition (Table 3). However, most of the phenyl or substituted phenyl pyrazoles (**22k**−**r**) showed somewhat greater COX-1 inhibitory activity compared with **22b**. Among these carbonyl-pyrazole derivatives, the *N*-cyclohexyl substituent (**22b**) was more potent and selective than the phenyl or substituted phenyl derivatives. Changing the 4-fluoro (**22o**) substituent to 4-chloro (**22p**) or 4-bromo (**22q**) compromised COX-2 selectivity, and a 4-cyano substituent (**22r**) clearly diminished COX-2 inhibitory potency. Replacing the 4-methyl (**22l**) substituent with a 4-trifluoromethyl group (**22m**) did not alter COX-2 selectivity but reduced potency. 4-Methoxy substitution yielded the more potent, less COX-2 selective compound **22n** (IC_{50} for COX-1 and COX-2, 1.5 μM and 2.5 μM, respectively) (Table 6). Elongation of the nitrate-containing carbonyl chain from three (**22b**) to five (**22b-i**) carbons did not significantly reduce COX-2 inhibitory potency (% inhibition of COX-2 for **22b** = 80 and **22b-i** = 75 at 10 μM).

Table 1. In Vitro Enzyme and Human Whole Blood COX-1 and COX-2 Inhibition by Pyrazole Nitrate and Alcohol Derivatives



			% inhibition HWB[a]		
			COX-1	COX-2	
compd	R_1	R′	100 μM	10 μM	1 μM
6a[b]	cyclopentyl	NO_2	0	−100	−125
5a		H	40	−75	−125
6b	cyclohexyl	NO_2	35	80	45
5b[b]		H	25	35	10
6c	cycloheptyl	NO_2	35	90	60
5c		H	40	25	10
6d	cyclooctyl	NO_2	60	90	50
5d		H	35	75	35
6e[b]	perhydro-2*H*-	NO_2	10	30	10
5e[b]	pyran-4-yl	H	10	10	0
6f[b]	1,1-dioxothian-4-yl	NO_2	nd	0	10
5f[b]		H	nd	10	0
6g	2-[1-(ethoxycarbonyl)-4-piperidyl]	NO_2	20	0	0
5g		H	0	10	10
6h[b]	cyclohexylmethyl	NO_2	25	65	10
5h[b]		H	65	40	0
6i	benzyl	NO_2	55	40	20
5i		H	25	15	10
6j	2,6-dimethylhept-4-yl	NO_2	15	0	15
5j		H	0	25	10
	Celecoxib		nd	100	50
	Celecoxib[b]		80	100	90
	Rofecoxib		75	100	75
	Rofecoxib[b]		0	100	40

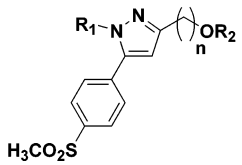
[a] Percent inhibition of COX-1 (100 μM) or COX-2 (10 and 1 μM) in human whole blood. Assays were performed in duplicate. Average % inhibition of two donors. [b] Percent inhibition of recombinant COX-1 (100 μM) or COX-2 (10 and 1 μM). nd, not determined.

On the basis of the COX-2 potency and selectivity demonstrated in the carbonyl series (Table 3), compound **22b** was selected for further modification. It has been reported that replacement of the methyl sulfone moiety with a sulfonamide group generated more potent COX-2 inhibitors with enhanced in vivo antiinflammatory activity, albeit with some loss of COX-2 selectivity.[15b] Accordingly, we synthesized the carbonyl pyrazole-sulfonamide, **33** (Scheme 5), which was found to be less potent (15% inhibition of COX-2 at 10 μM and 30% inhibition of COX-1 at 100 μM) than **22b** in the HWB COX assay. The corresponding alcohol analogue (**32**) of **33** had limited COX-2 inhibitory activity (10% inhibition of COX-2 at 10 μM and 30% inhibition of COX-1 at 100 μM).

Further modification in the pyrazole carbonyl series produced a series of pyrazole oxime nitrates (Table 4). The hydroxime **23b** and methoximes **23b**−**ii** showed good COX-2 inhibitory potency (% inhibition of COX-2 for **23b** = 100 and **23b**−**ii** = 90 at 10 μM) and selectivity. Lengthening the carbon chain from three (e.g., **23b**) to five (e.g., **23b-i**) carbons diminished COX-2 inhibitory activity.

Pyrazole nitrates containing an alkene linker at position 3 were next evaluated as COX inhibitors (Table 5). In the alkene series, both the *E* and *Z* isomers were synthesized in order to compare their potencies and

Table 2. In Vitro Enzyme and Human Whole Blood COX-1 and COX-2 Inhibition by Pyrazole Nitrate and Alcohol Derivatives



				% inhibition HWB[a]		
				COX-1	COX-2	
compd	R_1	R_2	*n*	100 μM	10 μM	1 μM
6b	cyclohexyl	NO_2	1	35	80	45
6b[b]		NO_2	1	40	100	45
5b		H	1	25	35	10
12b[b]	cyclohexyl	NO_2	2	0	95	45
11b[b]		H	2	35	35	0
17b	cyclohexyl	NO_2	3	90	100	75
16b		H	3	90	90	45
6h	cyclohexylmethyl	NO_2	1	25	65	10
5h		H	1	65	40	0
17h	cyclohexylmethyl	NO_2	3	90	100	75
16h		H	3	90	90	45
	Celecoxib			nd	100	50
	Celecoxib[b]			80	100	90
	Rofecoxib			75	100	75
	Rofecoxib[b]			0	100	40

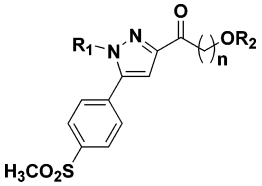
[a] Percent inhibition of COX-1 (100 μM) or COX-2 (10 and 1 μM) in human whole blood. Assays were performed in duplicate. Average % inhibition of two donors. [b] Percent inhibition of recombinant COX-1 (100 μM) or COX-2 (10 and 1 μM). nd, not determined.

selectivities. The *Z* isomers (e.g., **26b-I**, **26k-I**) were generally more potent and selective than the corresponding *E* series (e.g., **26b-II**, **26k-II**, **27b-II**, **27h-II**). Lengthening the carbon chain of **27b-II** by one carbon enhanced the COX-2 potency and selectivity of the *E* isomers (% inhibition of COX-2 for **26b-II** = 90 and **27b-II** = 45 at 10 μM). The compound **26b-I** emerged as the most potent and selective compound in the alkene series: its IC_{50}'s for COX-1 and COX-2 inhibition, 1000 μM and 0.5 μM, respectively, demonstrate a 2000-fold COX-2 selectivity (Table 6).

In Vivo Activity. Rat Carrageenan-Induced Air Pouch Model. As active compounds in the carbonyl series, we chose **22b**, **22l**, **22n**, and **22o** for in vivo pharmacological evaluation as antiinflammatory agents (Table 7). To this intent, we utilized the rat carrageenan-ionduced air-pouch model, since exudate PG production in this model is COX-2 driven. In this inflammation model, compound **22n** proved most potent, with 78% inhibition of PGE_2 formation and 43% inhibition of white-cell infiltration at an oral dose of 45 μmol/kg. However, **22n** showed poor selectivity ($IC_{50's}$ for COX-1/COX-2 = 1.5 μM/2.5 μM) (Table 6). Among selective pyrazole carbonyl derivatives, only compounds **22o** and **22b** showed good antiinflammatory activity. Both inhibited PGE_2 production by 45% at 45 μmol/kg. As the best COX-2 selective inhibitor in the pyrazole-alkene series, **26b-I** was also evaluated in the air pouch inflammation model. It showed moderate antiinflammatory activity, with 25% inhibition of PGE_2 formation and 17% inhibition of white-cell infiltration at an oral dose of 45 μmol/kg (Table 7).

Among the pyrazoles examined for antiinflammatory activity in vivo, the oxime **23b** proved to be the most potent, selective COX-2 inhibitor with 65% inhibition

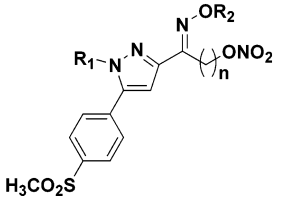
Table 3. In Vitro Human Whole Blood COX-1 and COX-2 Inhibition by Pyrazolecarbonyl Nitrate and Alcohol Derivatives



				% inhibition HWB[a]		
				COX-1	COX-2	
compd	R_1	R_2	*n*	100 μM	10 μM	1 μM
22b	cyclohexyl	NO_2	3	20	80	55
21b		H	3	0	90	80
22b-i	cyclohexyl	NO_2	5	25	75	80
21b-i		H	5	40	80	35
22k	phenyl	NO_2	3	60	95	35
21k		H	3	0	20	10
22l	4-methylphenyl	NO_2	3	55	95	70
21l		H	3	0	45	15
22m	4-trifluoromethylphenyl	NO_2	3	45	100	35
21m		H	3	−20	10	0
22n	4-methoxyphenyl	NO_2	3	100	100	95
21n		H	3	85	85	50
22o	4-fluorophenyl	NO_2	3	40	100	55
21o		H	3	0	25	25
22p	4-chlorophenyl	NO_2	3	60	100	30
21p		H	3	10	60	30
22q	4-bromophenyl	NO_2	3	90	95	70
21q		H	3	0	70	15
22r	4-cyanophenyl	NO_2	3	35	55	10
21r		H	3	0	10	0
	Celecoxib			nd	100	50
	Rofecoxib			75	100	75

[a] Percent inhibition of COX-1 (100 μM) or COX-2 (10 and 1 μM) in human whole blood. Assays were performed in duplicate. Average % inhibition of two donors.

Table 4. In Vitro Human Whole Blood COX-1 and COX-2 Inhibition by Pyrazole Oxime Nitrates



				% inhibition HWB[a]		
				COX-1	COX-2	
compd	R_1	R_2	*n*	100 μM	10 μM	1 μM
23b	cyclohexyl	H	3	10	100	55
23b-i	cyclohexyl	H	5	0	35	5
23b-ii	cyclohexyl	CH_3	3	0	90	55
23k	phenyl	H	3	50	85	25
23r	4-cyanophenyl	H	3	0	20	10
	Celecoxib			nd	100	50
	Rofecoxib			75	100	75

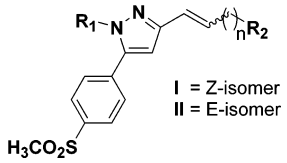
[a] Percent inhibition of COX-1 (100 μM) or COX-2 (10 and 1 μM) in human whole blood. Assays were performed in duplicate. Average % inhibition of two donors.

of PGE_2 formation at an oral dose of 45 μmol/kg in the air pouch model (Table 7).

Rat Gastric Damage Model. The gastric tolerance of a standard COX-2 inhibitor (valdecoxib) and the lead NO-donor COX-2 inhibitor (**23b**), alone and with a background of aspirin treatment, was studied. Figure 1 shows that the gastric lesions induced by valdecoxib and **23b** (GI lesion scores: 0.75 ± 0.18 mm and 0.38 ± 0.12 mm, respectively) at antiinflammatory doses were essentially as negligible as the lesions in the control vehicle group.

Aspirin induced 4.86 ± 1.27 mm of gastric lesion, which is significantly above control. This is consonant with prior demonstrations that COX-2 selective inhibitors have better gastrointestinal safety than traditional NSAIDs. A marked difference, however, was noted between valdecoxib and **23b** when they were administered with background aspirin treatment. In the setting of aspirin pretreatment, Valdecoxib potentiated gastric lesions when compared to either aspirin or valdecoxib alone. Yet the NO-donor COX-2 inhibitor **23b**, even at

Table 5. In Vitro Human Whole Blood COX-1 and COX-2 Inhibition by Alkenyl Pyrazole Nitrate and Alcohol Derivatives



				% inhibition HWB[a]		
				COX-1	COX-2	
compd	R_1	R_2	*n*	100 μM	10 μM	1 μM
26b-I	cyclohexyl	NO_2	2	20	95	70
25b-I		H	2	45	80	30
26k-I	phenyl	NO_2	2	90	100	95
25k-I		H	2	60	90	30
26b-II	cyclohexyl	NO_2	2	60	90	45
25b-II		H	2	15	35	5
26k-II	phenyl	NO_2	2	85	90	55
25k-II		H	2	25	30	0
27b-II	cyclohexyl	NO_2	1	40	45	0
15b-II		H	1	10	15	0
27h-II	cyclohexylmethyl	NO_2	1	50	75	35
15h-II		H	1	50	45	25
	Celecoxib			nd	100	50
	Rofecoxib			75	100	75

[a] Percent inhibition of COX-1 (100 μM) or COX-2 (10 and 1 μM) in human whole blood. Assays were performed in duplicate. Average % inhibtion of two donors.

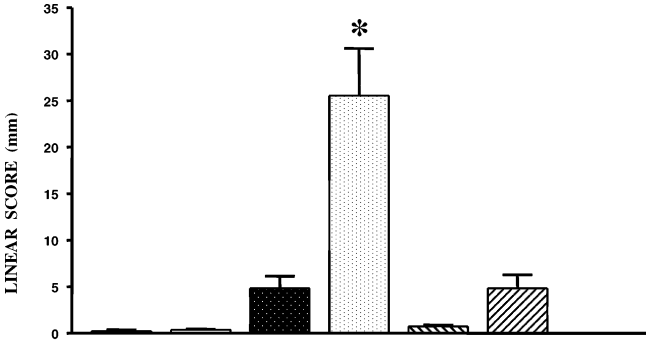
Table 6. IC_{50} Values of Some Pyrazole Compounds in Human Blood

	IC_{50} (μM)	
compd	COX-1	COX-2
Celecoxib	14	1.2
Rofecoxib	40	0.3
6b	>100	0.4
22n	1.5	2.5
26b-I	1000	0.5

Table 7. In Vivo Antiinflammatory Activity of Select Pyrazole Derivatives and Standarad COX-2 Inhibitors: Rat Air Pouch Model

	% inhibition	
compd[a]	white cell infiltrate	PGE_2
Celecoxib	60	97
Valdecoxib[b]	37	98
22b	42	45
22l	nd	20
22n	43	78
22o	23	45
23b	nd	65
26b−I	17	25

[a] All compounds dosed orally at 45 μmol/kg. [b] Valdecoxib dosed orally at 15 μmol/kg. nd, not determined.



A 1% Methocel – 0.5 % Methocel
B 1% Methocel – Valdecoxib 3 mg/kg (9.5 μmol/kg); n = 8
C Aspirin 25 mg/kg (139 μmol /kg) – 0.5 % Methocel; n = 9
D Aspirin 25 mg/kg (139 μmol /kg) – Valdecoxib 3 mg/kg (9.5 μmol/kg); n = 10
E 1% Methocel – Compound 23b 20.3 mg/kg (45 μmol/kg); n = 6
F Aspirin 25 mg/kg (139 μmol /kg) – Compound 23b 20.3 mg/kg (45 μmol/kg); n = 10

Figure 1. Aspirin-induced rat gastric lesion data for pyrazole-oxime **23b**, COX-2 inhibitors, and NSAIDs (male SD rats). Dose volume is 1 mL/kg. The ulcerogenicity was scored as given in the Experimental Section. Values are given as the arithmetic means ± SEM, Groups D and F were compared to group C for statistical significance by an ANOVA followed by Dunnett's Multiple Comparison Test. * $P < 0.01$.

higher doses relative to valdecoxib in combination with aspirin did not increase lesion scores compared to aspirin alone (Figure 1).

Conclusion

We have disclosed a series of novel pyrazole compounds that are selective, potent COX-2 inhibitors with promising oral activity as antiinflammatory agents in vivo. In most cases, hydroxy compounds were less potent COX-2 selective inhibitors than their corresponding nitrates. SAR studies indicated that the central pyrazole ring substituents play an important role in COX-2 potency such that 1-cycloalkyl and 5-aryl pyrazoles (e.g., **6b**) are potent COX-2 inhibitors. Replacement of the methyl sulfone moiety in **22b** with a sulfonamide group yielded **33**, which was inactive in this series. Other modifications at the 3-position of the central pyrazole ring (e.g., **17b**, **26b-I**, **23b**) enhanced COX-2 potency. Among the pyrazole examined, the oxime **23b** proved to be the most potent COX-2 inhibitor, with appreciable in vivo antiinflammatory activity and improved gastric tolerance. Further modifications of selective, orally active pyrazole-oxime COX-2 inhibitors, such as **23**, could provide a new generation of selective COX-2 inhibitors with improved gastrointestinal (if not overall) safety.

Experimental Section

COX Inhibition−Recombinant Enzyme Assay. A commercial kit with recombinant human or ovine COX-1 and human COX-2 enzymes was used to assess inhibition of each COX isoform. Manufacturer's (Cayman Chemical Company, Ann Arbor, MI) protocols were followed with the following modifications: enzymes were preincubated with heme for 2 min at 25 °C prior to incubation with the test compound at 25 °C for 20 min. Arachidonic acid substrate was then added and reacted with COX enzyme for 2 min at 37 °C. Prostaglandin production was quantified by an enzyme-linked immunoassay (Cayman) using a broadly specific antibody that binds to all the major prostaglandins and a prostaglandin acetylcholinesterase tracer in a microplate format with colorimetric readout. Compounds were tested at 100 μM against COX-1 and at 10 μM and 1 μM against COX-2. The % inhibition given in the tables represents average of two determinations with each enzyme.

COX Inhibition−Human Whole Blood Assay. Fresh heparinized human blood obtained by informed consent, from nonfasted, male or female donors who had not taken any asprin or NSAIDs for 14 days was collected in sodium heparin and distributed in 1 mL aliquots per well of a 24-well tissue culture plate. The plate was placed on a gently rotating platform shaker in a 5% CO_2 incubator at 37 °C for 15 min. Test compounds were dissolved and diluted in DMSO, and 1 μL of each dilution of the test compound was added per well in duplicate wells. To induce COX-2, lipopolysaccharide (LPS) from *E. coli* (Sigma Chemical Co., St. Louis, MO) was added at 10 μg/mL to appropriate wells 15 min after the addition of the test compounds. For the stimulation of COX-1, the calcium ionophore, A23187 (Sigma Chemical Co., St. Louis, MO) was added to a final concentration of 25 μM to separate wells 4.75 h after the addition of the test compounds. At 30 min after A23187 addition or 5 h after LPS addition, all incubations were terminated. Thromboxane B_2 in the blood samples were processed[39] and assayed in duplicate by EIA (Cayman Chemical Co., Ann Arbor, MI). The % inhibition given in the tables represents averages of two determinations on each blood sample from two donors. The results were not blood-donor dependent (data not shown).

Antiinflammatory Activity−Rat Air Pouch Model. A carageenan air pouch model was established essentially as described.[41,42] A pouch was formed in the intrascapular region of Male Sprague−Dawley rats (~250 g) by sterile air injection on days (−6) and (−3). On day 0, test compound or vehicle was dosed orally (0.5% methylcellulose vehicle) at 45 mg/kg, in blind fashion, 1 h prior to carrageenan injection (1.0 mL of a 1.0% solution) into the pouch. After 4 h, the inflammatory exudate was collected from the pouch for immunoassay of prostaglandin E_2 (PGE_2) formation (Cayman). The number of leukocytes in the exudate was determined by cell counting with a Beckman Coulter Particle Counter, the lower threshold set to exclude red blood cells. Twelve animals per treatment group were used. White cell counts were subjected to statistical analysis one-way ANOVA (Dunnett test), $P < 0.05$ defined as a statistical significance vs vehicle control group.

Rat Gastric Injury Model. Male Spraque-Dawley rats (180−200 g) purchased from Charles River. Animals were housed at 20−22 °C and 65−70% relative humidity on a 12/12 reverse light/dark cycle, with standard chow and water available ad libitum.

A minimum of 72 h was allowed for acclimatization of rats to their new environment prior to experimentation. Eighteen hours before an experiment, the animals were placed in cages with raised mesh bottoms and allowed free access to tap water, but no food. Compounds (including aspirin) were pulverized with a mortar and pestle and suspended with sufficient amount of vehicle. All compounds were prepared immediately before dosing. Aspirin was suspended in 1.0% Methocel, whereas test compounds were suspended in 0.5% Methocel, by vortexing in the presence of 2−3 layers of glass beads to obtain a homogeneous suspension. Compounds were administered intragastrically using gavage needles at a dose volume 1.0 mL/kg. Four groups of animals were dosed intragastrically with aspirin (25 mg/kg), and the test compounds were dosed 2 min later.

Three hours postdosing, rats were sacrificed, and their stomachs were removed, opened along the greater curvature, and digitally photographed. The images were analyzed using Image-J software for visible hemorrhagic lesions.

The total length of all lesions for each stomach was summed and reported as the total lesion score. Images were analyzed by investigators blinded as to treatment. Values are means ± SEM. The significance of differences between means was evaluated using a one-way analysis of variance (ANOVA), followed by Dunnett's Multiple Comparison Test. $P < 0.01$ was considered significant.

General Procedures. All reagents and anhydrous solvents were generally used as received from the commercial supplier. Reactions were routinely performed under a nitrogen atmosphere in oven-dried glassware. Melting points were determined with an electrothermal heating block (Metler) and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. NMR spectra were recorded in $CDCl_3$ unless otherwise specified, and chemical shifts are reported relative to tetramethylsilane as an internal standard. Low-resolution mass spectra were obtained using atmospheric pressure-turbo ion spray ionization. Elemental analyses were performed by Robertson Microlit Laboratories Inc., NJ. Gravity and flash column chromatographies were performed using EM Science silica gel 60 (230−400 mesh). TLC was performed on 250 μM precoated EM Science silica gel 60 F_{254} aluminum sheets. Preparative TLC was performed using 20 × 20 cm 1000 μM precoated silica gel plates (Whatman). Spots were visualized under 254 nm light or after staining with phosphomolybdate spray.

1-(1-Cyclopentyl-3-((nitrooxy)methyl)pyrazol-5-yl)-4-(methylsulfonyl)benzene (6a). *N*-(Azacyclopentylidenemethyl)(*tert*-butoxy)carboxamide (6a-a). Cyclopentanone (4 g, 47.6 mmol) and *tert*-butyl carbazate (6.28 g, 47.6 mmol) in methanol (150 mL) was stirred at room temperature for 2 h. The solvent was evaporated and the resulting solid dried under vacuo to give **6a-a** as a white solid in quantitative yield. Mp 119−120 °C. ^{1}H NMR δ 7.30−7.47 (bs, 1H), 2.48 (t, J = 7.3 Hz, 2H), 2.21 (t, J = 6.6 Hz, 2H), 1.67−1.95 (m, 4H), 1.53 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 162.2, 80.8, 33.2, 28.3, 26.9, 24.8, 24.7; MS m/z 199 (MH^+). Anal. ($C_{10}H_{18}N_2O_2$) C, H, N.

***tert*-Butoxy)-*N*-(cyclopentylamino)carboxamide (6a-b).** Sodium cyanoborohydride (2.96 g, 47.1 mmol) was added portionwise to a suspension of the product of **6a-a** (9.4 g, 47.6 mmol) in 50% acetic acid (137 mL) at room temperature. The resultant clear solution was stirred for 2 h at room temperature. The reaction mixture was neutralized with 1 N NaOH, extracted with CH_2Cl_2, washed with saturated $NaHCO_3$, dried, filtered, and evaporated to give the title compound as an oil (8.5 g, 90%). The crude product was used without further purification. ^{1}H NMR δ 6.25−6.51 (bs, 1H), 4.47−4.20 (bs, 1H), 3.35−3.55 (m, 1H), 1.27−1.80 (m, 8H), 1.53 (s, 9H); ^{13}C NMR δ 151.6, 75.1, 61.0, 56.2, 25.7, 23.1,18.8; MS m/z 201 (MH^+).

Cyclopentylhydrazine Trifluoroacetate (6a-c). Trifluoroacetic acid (25 mL) was added dropwise to a solution of the product **6a-b** (5.8 g, 29 mmol) in CH_2Cl_2 (25 mL). The reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated to give the trifluoroacetate salt of the title compound as a colorless oil in quantitative yield. ^{1}H NMR δ 3.63−3.72 (m, 1H), 1.92−2.2 (m, 2H), 1.60−1.90 (m, 4H); MS m/z 101 (MH^+).

Methyl (2*Z*)-2-Hydroxy-4-(4-methylthiophenyl)-4-oxobut-2-enoate (2). Dimethyl oxalate (26 g, 180.7 mmol) was added to a stirred suspension of sodium methoxide (9.75 g, 180.7 mmol) in dry toluene (200 mL) at 0 °C. The white suspension was stirred for 15 min at 0 °C. A solution of 4′-(methylthio)acetophenone (15 g, 90.4 mmol) in dry toluene (150 mL) was then added dropwise over 15 min, giving a yellow suspension which was stirred for 2 h at room temperature. The thick yellow suspension was transferred to a 2 L flask and stirred vigorously with 10% HCl (250 mL) and EtOAc (200 mL) to dissolve all the solids present. The organic layer was separated and the aqueous layer was extracted with EtOAc (100 mL). The combined organic extracts were washed with water (250 mL) and dried over Na_2SO_4, and the solvent was evaporated under reduced pressure to give a thick brown oil. The brown oil was dissolved in CH_2Cl_2 (25 mL) and hexane (125 mL) and left in a freezer at −20 °C for 16 h to give **2** (18 g, 79%) as orange solid. Mp 81 °C. ^{1}H NMR δ 7.83 (d, J = 8.6 Hz, 2H), 7.23 (d, J = 8.6 Hz, 2H), 6.97 (s, 1H), 3.89 (s, 3H), 2.47 (s, 3H); MS m/z 253 (MH^+). Anal. ($C_{12}H_{12}O_4S$) C, H, S.

Methyl 1-Cyclopentyl-5-(4-methylthiophenyl)pyrazol-3-carboxylate (3a-I). A mixture of **2** (2 g, 7.9 mmol) and **6a-c** (3.36 g, 10.3 mmol) in methanol (40 mL) was heated at 70 °C for 2 h and cooled to room temperature. The mixture was made basic with 5% Na_2CO_3 and extracted with EtOAc which was then washed with saturated $NaHCO_3$ and water. The organic extracts were dried over Na_2SO_4, and the solvent was evaporated under reduced pressure to give a thick oil, which was purified by chromatography over silica gel eluting with 1:2 EtOAc:Hex to give **3a-I** (1 g, 40%) as a colorless oil. Mp 76 °C. ^{1}H NMR δ 7.26−7.35 (m, 4H), 6.76 (s, 1H), 4.59−4.57 (m, 1H), 3.93 (s, 3H), 2.54 (s, 3H), 2.18−2.22 (m, 2H), 1.94−2.02 (m, 4H), 1.46−1.65 (m, 2H); ^{13}C NMR δ 163.2, 144.5, 142.5, 140.3, 129.6, 126.6, 126.4, 108.9, 60.4, 52.0, 33.4, 24.5, 15.5; MS m/z 317 (MH^+). Anal. ($C_{17}H_{20}N_2O_2S$) C, H, N.

(1-Cyclopentyl-5-(4-methylthiophenyl)pyrazol-3-yl)-methan-1-ol (4a). LAH (2.12 mL of 1 M solution in THF, 0.08 g, 2.12 mmol) was added dropwise to a solution of the product **3a-I** (0.67 g, 6.78 mmol) in THF (10 mL) at 0 °C. The yellow solution was stirred at room temperature for 1 h. Solid $Na_2SO_4 \cdot 10H_2O$ was added portionwise to the reaction mixture at 0 °C, followed by few drops of water and few drops of 0.1 N NaOH. The solid was filtered and washed with EtOAc. The residue, obtained after evaporation of the filtrate, was purified by chromatography over silica gel eluting with 1:1 EtOAc:Hex to give **4a** (0.61 g, ∼100%) as a white solid. Mp 98−99 °C. ^{1}H NMR δ 7.26−7.33 (m, 4H), 6.20 (s, 1H), 4.70 (s, 2H), 4.54−4.60 (m, 1H), 2.53 (s, 3H), 2.00−2.20 (m, 2H), 1.79−1.80 (m, 4H), 1.42−1.65 (m, 2H); ^{13}C NMR δ 151.2, 144.1, 139.5, 129.5, 127.8, 126.4, 104.2, 59.5, 59.3, 33.3, 24.8, 15.6; MS m/z 289 (MH^+), 271 (M − OH). Anal. ($C_{16}H_{20}N_2OS \bullet 0.6$ mol H_2O) C, H, N.

1-(1-Cyclopentyl-3-(hydroxymethyl)pyrazol-5-yl)-4-methylsulfonyl)benzene (5a). The product of **4a** (0.59 g, 2.04 mmol) was dissolved in MeOH (20 mL). Oxone (2.51 g, 4.09 mmol) in water (9 mL) was added at room temperature. The reaction mixture was stirred for 1 h, and the resulting solid was removed by filtration. CH_2Cl_2 was added to the filtrate, and it was washed with saturated $NaHCO_3$, water, dried over Na_2SO_4, and filtered. The residue after evaporation of the solvent was recrystallized from CH_2Cl_2/EtOAc/hexane to give **5a** (0.5 g, 76%) as white needles. Mp 145−146 °C. ^{1}H NMR δ 8.04 (dd, J = 1.74 and 6.7 Hz, 2H), 7.57 (dd, J = 1.8 and 6.7 Hz, 2H), 6.30 (s, 1H), 4.73 (d, J = 5.7 Hz, 2H), 4.45−4.60 (m, 1H), 3.11 (s, 3H), 2.03−2.20 (m, 2H), 1.85−2.02 (m, 4H), 1.48−1.65 (m, 2H); ^{13}C NMR δ 151.6, 142.6, 140.5, 136.7, 130.0, 128.0, 105.2, 59.8, 59.1, 44.6, 33.4, 24.8; MS m/z 321 (MH^+), 303 (M − OH), 343 (MNa^+). Anal. ($C_{16}H_{20}N_2O_3S$) C, H, N.

1-(1-Cyclopentyl-3-((nitrooxy)methyl)pyrazol-5-yl)-4-methylsulfonyl)benzene (6a). The product of **5a** (0.2 g, 0.63 mmol) in $CHCl_3$ (2.4 mL) was added to a mixture of fuming HNO_3 (0.13 mL, 0.2 g, 3.13 mmol) and Ac_2O (0.47 mL, 0.51 g, 5.0 mmol) at −10 °C and stirred at −10 °C for 20 min. The reaction mixture was quenched with ice cold water and extracted with CH_2Cl_2. The extracts were washed with ice cold saturated $NaHCO_3$ and water, dried over Na_2SO_4, and filtered, and the solvent was evaporated under reduced pressure. The residue obtained was recrystallized from CH_2Cl_2/EtOAc/Hex to give the **6a** (0.13 g, 58%) as a white solid. Mp 100−101 °C. ^{1}H NMR δ 8.05 (d, J = 8.3 Hz, 2H), 7.59 (d, J = 8.3 Hz, 2H), 6.40 (s, 1H), 5.50 (s, 2H), 4.50−4.65 (m, 1H), 3.12 (s, 3H), 1.82−2.20 (m, 6H), 1.52−1.70 (m, 2H); ^{13}C NMR δ 143.3, 142.8, 140.9, 136.2, 130.1, 128.0, 107.4, 68.8, 60.2, 44.6, 33.6, 24.9; MS m/z 366 (MH^+), 320 (M − NO_2). Anal. ($C_{16}H_{19}N_3O_5S$) C, H, N.

For compounds **6b**−**j** see Supporting Information.

4-{1-Cyclohexyl-3-[2-(nitrooxy)ethyl]pyrazol-5-yl}-1-(methylsulfonyl)benzene (12b). Methyl-1-cyclohexyl-5-(4-methylthiophenyl)pyrazol-3-carboxaldehyde (8b). To a stirred solution of oxalyl chloride (0.66 mL, 0.96 g, 6.1 mmol) in CH_2Cl_2 (2.5 mL) at −78 °C under nitrogen was added DMSO (1.08 mL, 1.19 g, 15.2 mmol) in CH_2Cl_2 (2 mL) dropwise over a period of 20 min. To this solution was added **4b** (1.84 g, 6.1 mmol) in CH_2Cl_2 (12 mL) dropwise over a period of 40 min at −78 °C. The mixture was stirred at −78 °C for 1.5 h. Triethylamine (4.25 mL, 3.08 g, 30.5 mmol) in CH_2Cl_2 (2.6 mL) was then added dropwise over a period of 45 min at −78 °C. The resultant mixture was stirred at 0°C for 20 min. To this

mixture was added water (2 mL) dropwise followed by CH_2Cl_2 (50 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with 5% HCl, dried over Na_2SO_4, and filtered. The residue after evaporation of the solvent was recrystallized from CH_2Cl_2/EtOAc/hexane to give **8b** (1.4 g, 77%) as a white solid. Mp 63 °C. ^{1}H NMR δ 9.97 (s, 1H), 7.32 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 8.3 Hz, 2H), 6.71 (s, 1H), 4.00−4.18 (m, 1H), 2.52 (s, 3H), 1.50−1.90 (m, 7H), 1.15−1.25 (m, 3H). ^{13}C NMR δ 186.8, 150.4, 144.4, 140.4, 129.3, 126.2, 105.4, 58.7, 33.2, 25.5, 24.5, 15.2. MS m/z 301 (MH^+).

4-(1-Cyclohexyl-3-vinylpyrazol-5-yl)-1-methylthiobenzene (9b). A solution of BuLi (5.07 mL of 1.6 M solution in hexane, 8.1 mmol) was added to a stirred solution of methyltriphenylphosphonium bromide (2.3 g, 6.5 mmol) in THF (20 mL) at −78 °C under nitrogen. The resulting solution was stirred for 30 min and then a solution of **8b** (1.3 g, 4.3 mmol) in THF (10 mL) was added. The cold bath was removed, and the mixture was stirred at room temperature for 2 h. Saturated NH_4Cl (50 mL) was added, and the mixture was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4 and filtered. The solvent was evaporated, and the crude product was chromatographed on silica gel eluting with 5% EtOAc /hexane to afford **9b** (0.92 g, 71%) as an oil. ^{1}H NMR δ 7.21 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.3 Hz, 2H), 6.68 (dd, J = 11 and 17.7 Hz, 1H), 6.25 (s, 1H), 5.58 (d, J = 17.7 Hz, 1H), 5.16 (d, J = 11 Hz, 1H), 3.85−3.96 (m, 1H), 2.42 (s, 3H), 1.50−2.00 (m, 7H), 1.05−1.20 (m, 3H); ^{13}C NMR δ 149.7, 143.1, 139.2, 129.5, 129.2, 127.4, 126.2, 114.4, 102.1, 57.6, 33.2, 25.5, 25.0, 15.3; MS m/z 299 (MH^+).

2-(1-Cyclohexyl-5-(4-methylthiophenyl)pyrazol-3-yl)-1-ethan-1-ol (10b). A solution of BH_3·THF complex (1 M solution in THF, 6 mL, 6 mmol) was added dropwise to a stirred solution of **9b** (0.9 g, 3 mmol) in THF at 0 °C and stirred for 45 min at 0 °C. 10% NaOH (6 mL) was added and followed by a 30% H_2O_2 solution (6 mL) dropwise. The product was extracted with EtOAc, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was chromatographed on silica gel eluting with (1:1) EtOAc/hexane to give **10b** (0.18 g, 19%) as an oil. ^{1}H NMR δ 7.23 (d, J = 8.3 Hz, 2H), 7.17 (d, J = 8.3 Hz, 2H), 5.95 (s, 1H), 3.82−3.96 (m, 1H), 3.84 (t, J = 5.7 Hz, 2H), 3.30 (bs, 1H), 2.80 (t, J = 5.7 Hz, 2H), 2.44 (s, 3H), 1.05−1.95 (m, 10H); ^{13}C NMR δ 149.5, 142.8, 139.2, 129.2, 127.5, 126.2, 104.7, 61.9, 57.5, 33.3, 30.9, 25.6, 25.1, 15.4; MS m/z 317 (MH^+).

2-(1-Cyclohexyl-3-(2-hydroxyethyl)pyrazol-5-yl)-1-(methylsulfonyl)benzene (11b). Compound **11b** was synthesized in a manner similar to the synthesis of **5a** using **10b** (0.17 g, 0.53 mmol) and Oxone (0.66 g, 1.07 mmol) to give **11b** (0.18 g, 96%) as a white solid. Mp 108 °C. ^{1}H NMR δ 7.95 (d, J = 8.1 Hz, 2H), 7.48 (d, J = 8.1 Hz, 2H), 6.07 (s, 1H), 3.81−3.94 (m, 1H), 3.83 (t, J = 5.9 Hz, 2H), 3.33 (bs, 1H), 3.05 (s, 3H), 2.81 (t, J = 5.9 Hz, 2H), 1.50−2.05 (m, 7H), 1.05−1.25 (m, 3H); ^{13}C NMR 149.8, 141.2, 140.1, 136.4, 129.5, 127.7, 105.6, 61.7, 57.9, 44.3, 33.2, 30.9, 25.4, 24.9; MS m/z 349 (MH^+). Anal. ($C_{18}H_{24}N_2O_3S$·0.25H_2O) C, H, N.

4-{1-Cyclohexyl-3-[2-(nitrooxy)ethyl]pyrazol-5-yl}-1-(methylsulfonyl)benzene (12b). Compound **12b** was synthesized in a manner similar to the synthesis of **6a** using **11b** (0.16 g, 0.45 mmol), fuming HNO_3 (94 μL, 0.14 g, 2.24 mmol), and Ac_2O (0.34 mL, 0.37 g, 3.58 mmol) to give **12b** (0.12 g, 66%) as a yellow solid. Mp 117 °C. ^{1}H NMR δ 7.98 (d, J = 8.3 Hz, 2H), 7.50 (d, J = 8.3 Hz, 2H), 6.15 (s, 1H), 4.70 (t, J = 6.7 Hz, 2H), 3.85−4.05 (m, 1H), 3.07 (s, 3H), 3.04−3.08 (m, 2H), 1.60−2.00 (m, 7H), 1.10−1.30 (m, 3H); ^{13}C NMR δ 146.5, 141.9, 140.6, 135.9, 129.7, 127.8, 106.0, 71.9, 58.4, 44.3, 33.1, 26.0, 25.5, 24.8; MS m/z 394 (MH^+).

4-{1-Cyclohexyl-3-[3-(nitrooxy)propyl]pyrazol-5-yl}-1-(methylsulfonyl)benzene (17b). Methyl (2*E*)-3-[1-Cyclohexyl-5-(4-methylthiophenyl)pyrazol-3-yl]prop-2-enoate (13b). A solution of BuLi (3.2 mL of 1.6 mol solution in hexane, 5.2 mmol) was added to a stirred solution of trimethylphosphonoacetate (0.92 g, 5.08 mmol) in THF (10 mL) at −78 °C under N_2. The resulting solution was stirred for 30 min, and a solution of **8b** (1.22 g, 4.06 mmol) in THF (10 mL) was added. The cold bath was removed, and the mixture was stirred at room temperature for 2 h. Water (50 mL) was added and the mixture was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4 and filtered. The solvent was evaporated and the crude product was chromatographed on silica gel eluting with (1:9) EtOAc:hexane to give **13b** (1.12 g, 77%) as an oil. ^{1}H NMR δ 7.71 (d, J = 16 Hz, 1H), 7.32 (d, J = 6.5 Hz, 2H), 7.23 (d, J = 6.8 Hz, 2H), 6.43 (s, 1H), 6.38 (d, J = 16 Hz, 1H), 4.03−4.08 (m, 1H), 3.93 (s, 3H), 2.52 (s, 3H), 1.55−2.00 (m, 7H), 1.22−1.28 (m, 3H); ^{13}C NMR δ 167.4, 146.8, 143.7, 139.8, 137.4, 129.3, 126.7, 126.2, 118.0, 104.6, 58.1, 51.4, 33.2, 25.5, 25.0, 15.3; MS m/z 357 (MH^+).

(2*E*)-3-[1-Cyclohexyl-5-(4-methylthiophenyl)pyrazol-3-yl]prop-2-en-1-ol (14b). Compound **14b** was synthesized in a manner similar to the synthesis of **4a** using **13b** (1.12 g, 3.4 mmol) and LAH (3.4 mL of 1M solution in THF, 0.13 g, 3.4 mmol) to give **14b** (0.62 g, 60%) as a white solid. Mp 90 °C. ^{1}H NMR δ 7.25−7.35 (m, 4H), 6.68 (d, J = 16 Hz, 1H), 6.32−6.39 (m, 1H), 6.31 (s, 1H), 4.30 (d, J = 5.5 Hz, 2H), 3.98−4.06 (m, 1H), 2.53 (s, 3H), 1.60−1.95 (m, 7H), 1.10−1.30 (m, 3H); ^{13}C NMR δ 148.8, 143.3, 139.4, 129.6 129.3, 127.5, 123.9, 102.6, 63.6, 57.7, 33.3, 25.6, 25.1, 15.4; MS m/z 329 (MH^+).

4-[3-((1*E*)-3-Hydroxyprop-1-enyl)-1-cyclohexylpyrazol-5-yl]-1-(methylsulfonyl)benzene (15b). Compound **15b** was synthesized in a manner similar to the synthesis of **5a** using **14b** (0.62 g, 1.89 mmol) and Oxone (1.45 g, 2.36 mmol) to give **15b** (0.52 g, 76%) as a white solid. Mp 121 °C. ^{1}H NMR δ 7.99 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 6.49 (d, J = 16 Hz, 1H), 6.35 (s, 1H), 6.29−6.38 (m, 1H), 4.27 (d, J = 5.5 Hz, 2H), 3.90−3.98 (m, 1H), 3.09 (s, 3H), 1.60−2.10 (m, 7H), 1.10−1.30 (m, 3H); ^{13}C NMR δ 149.1, 141.7, 140.4, 136.4, 130.3, 129.7, 127.8, 123.2, 103.6, 63.4, 58.2, 44.4, 33.3, 25.5, 24.9; MS m/z 361 (MH^+).

4-[1-Cyclohexyl-3-(3-hydroxypropyl)pyrazol-5-yl]-1-(methylsulfonyl)benzene (16b). Compound **15b** (0.52 g, 1.44 mmol) was dissolved in EtOH (20 mL) and degassed with N_2. 10% Pd/C (two spatulas) was added and hydrogenated at 20 psi for 3 h. The catalyst was removed by filtration, and the solvent was removed under reduced pressure. The crude material was chromatographed on silica gel eluting with (2:1) EtOAc:Hex to give **16b** (0.37 g, 71%) as a white solid. Mp 138 °C.^{1}H NMR δ 8.03 (d, J = 8.2 Hz, 2H), 7.54 (d, J = 8.1 Hz, 2H), 6.11 (s, 1H), 3.90−4.00 (m, 1H), 3.75 (t, J = 5.8 Hz, 2H), 3.30 (bs, 1H), 3.13 (s, 3H), 2.81 (t, J = 6.9 Hz, 2H), 1.60−2.10 (m, 9H), 1.15−1.30 (m, 3H); ^{13}C NMR δ 151.7, 141.4, 140.2, 136.6, 129.6, 127.8, 105.5, 62.7, 58.0, 44.4, 33.4, 31.5, 25.5, 24.9; MS m/z 363 (MH^+).

4-{1-Cyclohexyl-3-[3-(nitrooxy)propyl]pyrazol-5-yl}-1-(methylsulfonyl)benzene (17b). Compound **17b** was synthesized in a manner similar to the synthesis of **6a** using **16b** (0.14 g, 0.38 mmol), fuming HNO_3 (81 μL, 0.12 g, 1.93 mmol), and Ac_2O (0.29 mL, 0.31 g, 3.09 mmol) to give **17b** (0.11 g, 70%) as a yellow solid. Mp 77 °C. ^{1}H NMR δ 8.04 (d, J = 8.1 Hz, 2H), 7.55 (d, J = 8.1 Hz, 2H), 6.19 (s, 1H), 4.53 (t, J = 6.4 Hz, 2H), 3.95−4.07 (m, 1H), 3.11 (s, 3H), 2.85 (t, J = 7.45 Hz, 2H), 1.69−2.20 (m, 9H), 1.10−1.30 (m, 3H); ^{13}C NMR δ 150.1, 142.5, 140.9, 135.2, 129.7, 127.9, 105.7, 72.4, 58.8, 44.3, 32.8, 26.4, 25.4, 24.6, 23.7; MS m/z 408 (MH^+).

For compound **17h**, see Supporting Information.

1-(1-(Cyclohexyl-5-(4-(methylsulfonyl)phenyl)pyrazol-3-yl)-4-(nitrooxy)butan-1-one (22b). Methyl(2*Z*)-2-hydroxy-4-(4-(methylsulfonyl)phenyl)-4-oxobut-2-enoate (2A). Oxone (4.39 g, 7.1 mmol) in water (14 mL) was added dropwise to a solution of **2** (1.5 g, 6.0 mmol) in a mixture of MeOH (30 mL) and CH_2Cl_2 (2 mL) at 0 °C. The resultant suspension was gradually warmed to room temperature over a period of 1 h. The solid was filtered, and the filtrate was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ and water, dried (Na_2SO_4), and filtered. The solvent was evaporated to give **2A** (0.8 g, 47%). MS m/z 285 (MH^+), 302 (MNH_4^+).

Methyl-1-cyclohexyl-5-(4-methylsulfonylphenyl)pyrazole-3-carboxylate (7b). Compound **7b** was synthesized in a manner similar to the synthesis of **3a-I** using **2A** (7.4 g, 26

mmol) and cyclohexyl hydrazine hydrochloride (4.3 g, 29 mmol) in MeOH (100 mL) to give **7b** (8.3 g, 88%) as a tan solid. Mp 108 °C. ^{1}H NMR δ 8.09 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H), 6.88 (s, 1H), 4.06−4.10 (m, 1H), 3.97 (s, 3H), 3.16 (s, 3H), 1.26−2.19 (m, 10H). MS m/z 375 (MH^+). Anal. ($C_{19}H_{22}N_2O_4S$) C, H, N.

(1-Cyclohexyl-5-(4-methylsulfonyl)phenyl)pyrazol-3-yl)-*N*-methoxy-*N*-methylcarboxamide (18b-A). Trimethylaluminum (5.52 mL of 2 M solution in hexane, 0.80 g, 11.1 mmol,) was added dropwise to a suspension of dimethylhydroxylamine hydrochloride (1.11 g, 11.4 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The solution was stirred at 0 °C for 45 min and then at room temperature for 40 min. To this solution, **7b** (2.06 g, 5.7 mmol) in CH_2Cl_2 (4 mL) was added dropwise. Stirring was continued for 2 h at room temperature. The reaction mixture was cooled to 0 °C, and 10% HCl was carefully added dropwise. The aqueous phase was extracted with EtOAc, washed with water, brine, dried over Na_2SO_4, and filtered. The residue after evaporation of the solvent was dissolved in CH_2Cl_2 and filtered through a silica gel pad that was washed with EtOAc. The combined filtrate and washings were evaporated to give **18b-A** (1.48 g, 67%) as a white solid. Mp 53 °C. ^{1}H NMR δ 8.28 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 8.3 Hz, 2H), 6.81 (s, 1H), 4.00−4.20 (m, 1H), 3.85 (s, 3H), 3.48 (bs, 3H), 3.13 (s, 3H), 1.78−2.20 (m, 7H), 1.13−1.37 (m, 3H); ^{13}C NMR δ 144.6, 141.3, 140.9, 136.0, 130.0, 128.1, 109.5, 61.7, 59.0, 44.6, 33.5, 25.6, 25.1, 14.7, 14.2; MS m/z 392 (MH^+). Anal. ($C_{19}H_{25}N_3O_4S$) C, H, N.

1-(1-Cyclohexyl-5-(4-(methylsulfonyl)phenyl)pyrazol-3-yl)-4-(1,1,2,2-tetramethyl-1-silapropoxy)butan-1-one (19-A). To a solution of **18b-A** (1.0 g, 2.56 mmol) in THF (20 mL) was added dropwise the Grignard reagent prepared from 3-bromo-1-(1,1,2,2-tetramethyl-1-silapropoxy)propane (5 g, 19.8 mmol) and magnesium turnings (1.02 g, 42.5 mmol) in THF (50 mL) at 0 °C under nitrogen. The reaction mixture was gradually warmed to room temperature. After all the starting material had been consumed, saturated NH_4Cl was added dropwise at 0 °C. The reaction mixture was diluted with EtOAc, and the layers were separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with water, dried (Na_2SO_4), and filtered. The residue after evaporation of the solvent was chromatographed on silica gel, eluting with 1:10 to 2:10 to 1:2 to 1:1 to 2:1 EtOAc:Hex to give **19b-A** (1.27 g, 98%) as a white solid. Mp 131−133 °C. ^{1}H NMR δ 8.08 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 6.82 (s, 1H), 3.95−4.25 (m, 1H), 3.74 (t, J = 6.3 Hz, 2H), 3.16 (s, 3H), 3.13 (t, J = 7.4 Hz, 2H), 1.80−2.20 (m, 9H), 1.22−1.40 (m, 3H), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C NMR δ 196.5, 150.3, 142.4, 141.0, 135.9, 130.0, 128.1, 107.1, 62.7, 59.0, 44.6, 35.3, 33.4, 27.6, 26.1, 25.5, 25.1, 18.5, −5.2; MS m/z 505 (MH^+). Anal. ($C_{26}H_{40}N_2O_4SSi$) C, H, N.

1-(1-Cyclohexyl-5-(4-(methylsulfonyl)phenyl)pyrazol-3-yl)-4-hydoxybutan-1-one (21b). Tetrabutylammonium fluoride (2.57 mL of 1 M solution of THF, 0.67 g, 2.57 mmol) was added dropwise to a solution of **19b-A** (1.04 g, 2.06 mmol) in THF (24 mL) at 0 °C. The resultant solution was stirred at 0 °C for 2 h and then at room temperature for 3 h. The residue after evaporation of the solvent was chromatographed on silica gel, eluted with 1:1 to 2:1 EtOAc:Hex to give an oil which was recrystallized from CH_2Cl_2/EtOAc/Hex to give **21b** (0.64 g, 79%). Mp 112−114 °C. ^{1}H NMR δ 8.07 (d, J = 8.3 Hz, 2H), 7.57 (dd, J = 1.7 and 6.7 Hz, 2H), 6.83 (s, 1H), 4.00−4.20 (m, 1H), 3.65−3.80 (m, 2H), 3.19 (t, J = 6.9 Hz, 2H), 3.14 (s, 3H), 2.32 (t, J = 5.8 Hz, 1H), 2.03 (p, J = 6.8 Hz, 2H), 1.68−1.97 (m, 6H), 1.18−1.40 (m, 4H). ^{13}C NMR δ196.9, 150.4, 142.7, 141.1, 135.7, 130.0, 128.2, 107.3, 62.3, 59.2, 44.6, 35.4, 33.5, 27.8, 25.5, 25.1; MS m/z 391 (MH^+), 373 (M − OH). Anal. ($C_{20}H_{26}N_2O_4S$) C, H, N.

1-(1-(Cyclohexyl-5-(4-(methylsulfonyl)phenyl)pyrazol-3-yl)-4-(nitrooxy)butan-1-one (22b). Compound **22b** was synthesized in a manner similar to the synthesis of **6a** using **21b** (0.5 g, 1.28 mmol), fuming HNO_3 (0.27 mL, 0.40 g, 6.4 mmol), and Ac_2O (0.96 mL, 1.04 g, 10.3 mmol) to give **22b** (0.41 g, 74%). Mp 122−124 °C. ^{1}H NMR δ 8.07 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 8.2 Hz, 2H), 6.81 (s, 1H), 4.59 (t, J = 6.4 Hz, 2H), 4.04−4.09 (m, 1H), 3.21 (t, J = 7.1 Hz, 2H), 3.13 (s, 3H), 2.15−2.24 (m, 2H), 1.67−2.13 (m, 7H), 1.12−1.42 (m, 3H); ^{13}C NMR δ 194.7, 149.9, 142.6, 141.1, 135.7, 130.0, 128.2, 107.2, 72.8, 59.2, 44.6, 34.5, 33.4, 25.5, 25.1, 21.5; MS m/z 436 (MH^+). Anal. ($C_{20}H_{25}N_3O_6S$) C, H, N.

For compounds **22b-i**, **22k**−**r**, see Supporting Information.

1-(1-Cyclohexyl-3-(1-(hydroxyimino)-4-(nitrooxy)butyl)-pyrazol-5-yl)-4-(methylsulfonyl)benzene (23b). NaOH (49.8 mg, 1.24 mmol, 83 μL of 15 N solution) was added dropwise to a suspension of **22b** (0.22 g, 0.50 mmol) and hydroxylamine hydrochloride (87.9 mg, 1.26 mmol) in EtOH (4 mL) and CH_2Cl_2 (1 mL), and the reaction mixture was stirred at room temperature for 4 h. The residue after evaporation of the solvent was extracted into EtOAc, washed with water, dried Na_2SO_4, and filtered. The filtrate was evaporated in vacuo to give the crude product which was purified by preparative layer chromatography (elution with 1:1 EtOAc:hexane) to give **23b** as a mixture of isomers (0.11 g, 89% based on recovered starting material (0.1 g)) as a white solid. Mp 121−123 °C. ^{1}H NMR δ 8.07 (d, J = 14.2 Hz, 0.4H), 8.06 (d, J = 6.7 Hz, 2H), 7.58 (d, J = 14.1 Hz, 0.4H), 7.57 (d, J = 6.6 Hz, 2H), 6.84 (s, 0.2H), 6.57 (s, 1H), 4.58 (t, J = 6.4 Hz, 0.4H), 4.54 (t, J = 6.6 Hz, 2H), 3.95−4.08 (m, 1H), 3.14 (s, 0.6H), 3.13 (s, 3H), 3.03 (t, J = 7.2 Hz, 2H), 2.83 (t, J = 7.3 Hz, 0.4H), 2.12 (p, J = 6.8 Hz, 2H), 1.80−2.08 (m, 8H), 1.60−1.75 (m, 1H); MS m/z 451 (MH^+). Anal. ($C_{20}H_{26}N_4O_6S$) C, H, N.

For compounds **23b-i**, **23b-ii**, **23k**, and **23r**, see Supporting Information.

1-(3-((1*Z*)-4-(Nitrooxy)but-1-enyl)-1-cyclohexylpyrazol-5-yl)-4- (methylsulfonyl) benzene (26b-I). 1-((3*Z*)-4-(1-Cyclohexyl-5-(4-methylthiophenyl)pyrazol-3-yl)but-3-enyloxy)-1,1,2,2- tetramethyl-1-silapropane (24b-I). *n*-Butyllithium (2.5 M solution in hexane, 2.25 mL, 0.36 g, 5.6 mmol) was added dropwise to solution of (3-((1,1-dimethylethyl)-dimethylsilyl)oxy)propyl)triphenylphosphonium bromide (2.45 g, 4.76 mmol) in THF (13 mL) at −78 °C. The resultant solution was stirred at −78 °C for 1 h. To this solution was added **8b** (1.3 g, 4.3 mmol) in THF (13 mL) dropwise. The reaction mixture was stirred at −78 °C for 1 h. The reaction mixture was gradually allowed to warm to room temperature and stirred for 24 h. Water was added, and the reaction mixture was extracted with EtOAc. The organic layer was then washed with water, dried over Na_2SO_4, and filtered. The residue obtained after evaporation of the solvent was purified by chromatography on silica gel eluting with (0.5:10) EtOAc: Hex to give the pure *Z*-isomer, **24b-I** (1.2 g, 61%) as a colorless oil and minor E-isomer, **24b-II** (0.1 g, 5%). *Z*-isomer: ^{1}H NMR δ 7.33 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.5 Hz, 2H), 6.47 (d, J = 11.7 Hz, 1H), 6.28 (s, 1H), 5.65−5.77 (m, 1H), 3.98−4.12 (m, 1H), 3.76 (t, J = 6.9 Hz, 2H), 2.72 (q, J = 6.1 Hz, 2H), 2.54 (s, 3H), 1.60−2.18 (m, 7H), 1.15−1.40 (m, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR δ 148.4, 142.8, 139.3, 129.5, 128.7, 127.8, 126.4, 122.7, 105.9, 62.9, 57.8, 33.5, 33.1, 26.1, 25.8, 25.3, 18.5, 15.6, −5.0; MS m/z 457 (MH^+).

1-(3-((1*Z*)-4-(Hydroxy)but-1-enyl)-1-cyclohexylpyrazol-5-yl-4-methylsulfonyl)benzene (25b-I). The product of **24b-I** (1.17 g, 2.6 mmol) was dissolved in MeOH (51 mL). Oxone (4.73 g, 7.7 mmol) in water (11 mL) was added at room temperature. The reaction mixture was stirred for 1 h and then filtered to remove the solid. CH_2Cl_2 was added to the filtrate which was washed with saturated $NaHCO_3$, water, dried over Na_2SO_4, and filtered. The residue after evaporation of the solvent was recrystallized from CH_2Cl_2/EtOAc/hexane to give **25b-I** (0.88 g, 92%) as a white solid. Mp 170−172 °C. ^{1}H NMR δ 8.05 (d, J = 8.3 Hz, 2H), 7.56 (d, J = 8.3 Hz, 2H), 6.50 (d, J = 11.5 Hz, 1H), 6.27 (s, 1H), 5.80−5.94 (m, 1H), 3.90−4.10 (m, 1H), 3.87 (q, J = 5.7 Hz, 2H), 3.79 (t, J = 4.7 Hz, 1H), 3.13 (s, 3H), 2.75 (q, J = 5.9 Hz, 2H), 1.62−2.18 (m, 7H), 1.18−1.40 (m, 3H); ^{13}C NMR δ 148.1, 141.5, 140.7, 136.5, 130.4, 129.9, 128.1, 123.1, 107.1, 62.6, 58.5, 44.6, 33.6, 32.4, 25.7, 25.1. MS m/z 375 (MH^+). Anal. ($C_{20}H_{26}N_2O_3S$) C, H, N, S.

1-(3-((1*Z*)-4-(Nitrooxy)but-1-enyl)-1-cyclohexylpyrazol-5-yl)-4-(methylsulfonyl)benzene (26b-I). Compound **26b-I**

was synthesized in a manner similar to the synthesis of **6a** using **25b-I** (0.2 g, 0.53 mmol) in $CHCl_3$ (2.2 mL), fuming HNO_3 (0.11 mL, 0.17 g, 2.67 mmol), and Ac_2O (0.40 mL, 0.44 g, 4.27 mmol) to give **26b-I** (0.16 g, 71%) as a white solid. Mp 137−138 °C. ^{1}H NMR δ 8.05 (dd, J = 1.5 and 8.4 Hz, 2H), 7.57 (dd, J = 1.7 and 6.7 Hz, 2H), 6.48 (d, J = 10.2 Hz, 1H), 6.27 (s, 1H), 5.62−5.74 (m, 1H), 4.64 (t, J = 6.9 Hz, 2H), 3.93−4.10 (m, 1H), 3.13 (s, 3H), 3.00−3.05 (m, 2H), 1.78−2.14 (m, 6H), 1.62−1.77 (m, 1H), 1.19−1.38 (m, 3H); ^{13}C NMR δ 148.0, 141.3, 140.6, 136.6, 129.9, 128.1, 125.7, 124.1, 107.2, 72.7, 58.5, 44.6, 33.5, 27.3, 25.7, 25.2; MS *m/z* 420 (MH^+). Anal. ($C_{20}H_{25}N_3O_5S$•1/4 mol H_2O) C, H, N.

1-(3-((1*E*)-4-(Nitrooxy)but-1-enyl)-1-cyclohexylpyrazol-5-yl)-4-(methylsulfonyl)benzene (26b-II). 1-((3*E*)-4-(1-Cyclohexyl-5-(4-methylthiophenyl)pyrazol-3-yl)but-3-enyloxy)-1,1,2,2-tetramethyl-1-silapropane (24b-II). Compound **24b-II** was synthesized in a manner similar to the **24b-I** to give *Z*-isomer, **24b-I** (1.2 g, 61%) as a colorless oil and E-isomer, **24b-II** (0.1 g, 5%). *E*-isomer, **24b-II**: ^{1}H NMR δ 7.22−7.35 (m, 4H), 6.51 (d, J = 16.1 Hz, 1H), 6.26 (s, 1H), 6.12−6.25 (m, 1H), 3.92−4.08 (m, 1H), 3.72 (t, J = 7.10 Hz, 2H), 2.53 (s, 3H), 2.37−2.48 (m, 2H), 1.56−2.10 (m, 7H), 1.16−1.30 (m, 3H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR δ 149.8, 143.3, 139.3, 129.5, 128.1, 127.9, 126.5, 124.4, 102.1, 63.3, 57.8, 36.7, 33.5, 26.1, 25.8, 25.3, 18.5, 15.6, −5.0. MS *m/z* 457 (MH^+).

1-(3-((1*E*)-4-(Hydroxy)but-1-enyl)-1-cyclohexylpyrazol-5-yl)-4-methylsulfonyl)benzene (25b-II). Compound **25b-II** was synthesized in a manner similar to the synthesis of **25b-I** using **24b-II** (0.23 g, 0.67 mmol) in MeOH (14 mL) and Oxone (0.83 g, 13.4 mmol) in water (3 mL) to give **25b-II** (0.16 g, 64%) as a white solid. Mp 129−130 °C. ^{1}H NMR δ 8.04 (d, J = 8.2 Hz, 2H), 7.55 (d, J = 8.2 Hz, 2H), 6.07 (d, J = 16.0 Hz, 1H), 6.37 (s, 1H), 6.16−6.30 (m, 1H), 3.89−4.08 (m, 1H), 3.77 (q, J = 6.0 Hz, 2H), 3.13 (s, 3H), 2.49 (q, J = 6.5 Hz, 2H), 1.42−2.12 (m, 7H), 1.10−1.37 (m, 3H). ^{13}C NMR δ 149.9, 141.8, 140.6, 136.8, 129.9, 128.2, 128.1, 125.1, 103.4, 62.2, 58.4, 44.7, 36.5, 33.5, 25.8, 25.2. MS *m/z* 375 (MH^+). Anal. ($C_{20}H_{26}N_2O_3S$•0.25H_2O) C, H, N.

1-(3-((1*E*)-4-(Nitrooxy)but-1-enyl)-1-cyclohexylpyrazol-5-yl)-4-(methylsulfonyl)benzene (26b-II). Compound **26b-II** was synthesized in a manner similar to the synthesis of **6a** using **25b-II** (0.1 g, 0.27 mmol) in $CHCl_3$ (1.1 mL), fuming HNO_3 (56 μL, 84 mg, 1.34 mmol) and Ac_2O (0.20 mL, 0.22 g, 2.14 mmol) to give **26b-II** as a white foam. ^{1}H NMR δ 8.05 (dd, J = 1.5 and 8.4 Hz, 2H), 7.57 (dd, J = 1.7 and 6.7 Hz, 2H), 6.57 (d, J = 16.0 Hz, 1H), 6.37 (s, 1H), 6.09−6.23 (m, 1H), 4.57 (t, J = 6.7 Hz, 2H), 3.90−4.12 (m, 1H), 3.13 (s, 3H), 2.55−2.68 (m, 2H), 1.60−2.12 (m, 7H), 1.12−1.35 (m, 3H). ^{13}C NMR δ 149.3, 141.9, 140.6, 136.6, 129.9, 128.0, 125.9, 125.1, 103.5, 72.3, 58.4, 44.6, 33.5, 31.7, 30.5, 25.7, 25.1. MS *m/z* 420 (MH^+). Anal. ($C_{20}H_{25}N_3O_5S$) C, H, N.

For compounds **26k-I**, **26k-II**, and **27h-II**, see Supporting Information.

4-{1-Cyclohexyl-3-[4-(nitrooxy)butanoyl]pyrazol-5-yl}-benzenesulfonamide (33). 1-[1-Cyclohexyl-5-(4-methylthiophenyl)pyrazol-3-yl]-4-(1,1,2,2-tetramethyl-1-silapropoxy)-butan-1-one (19b). Compound **19b** was synthesized in a manner similar to the synthesis of **19b-A** using **18b** (3.9 g, 11.0 mmol) in THF (30 mL), the Grignard reagent prepared from 3-bromo-1-(1,1,2,2-tetramethyl-1-silapropoxy)propane (25 g, 98.8 mmol) and magnesium turnings (5.0 g, 20.8 mol) in THF (180 mL) to give **19b** (3.79 g, 48%) as a colorless oil. ^{1}H NMR δ 7.20−7.38 (m, 4H), 6.71 (s, 1H), 4.02−4.20 (m, 1H), 3.72 (t, J = 6.4 Hz, 2H), 3.10 (t, J = 7.3 Hz, 2H), 2.54 (s, 3H), 1.72−2.05 (m, 10H), 1.19−1.32 (m, 2H), 0.91 (s, 9H), 0.06 (s, 6H); MS *m/z* 473 (MH^+).

1-{1-Cyclohexyl-5-[4-(methylsulfinyl)phenyl]pyrazol-3-yl}-4-(1,1,2,2-tetramethyl-1-silapropoxy)butan-1-one (28). Compound **19b** (3.23 g, 6.84 mmol) was dissolved in CH_2Cl_2 (48 mL) and MeOH (15 mL). Magnesium monoperoxyphathalate hexahydrate (MMPP) (1.83 g, 3.69 mmol) was added in five equal portions at 1 min intervals. The resulting heterogeneous solution was stirred at room temperarture for 1 h. Saturated $NaHCO_3$ was added. The organic layer was separated, dried over Na_2SO_4, and the solvent was evaporated in vacuo to give the crude product. The crude product was chromatographed on silica gel eluting with 10% MeOH/CH_2Cl_2 to give **28** (1.5 g, 45%) as an oil. ^{1}H NMR δ 7.77 (d, J = 8.3 Hz, 2H), 7.51 (d, J = 8.3 Hz, 2H), 6.78 (s, 1H), 3.98−4.20 (m, 1H), 3.72 (t, J = 6.4 Hz, 2H), 3.12 (t, J = 7.3 Hz, 2H), 2.81 (s, 3H), 1.78−2.10 (m, 10H), 1.14−1.33 (m, 2H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR δ 196.6, 150.2, 146.7, 143.0, 133.3, 130.0, 124.3, 106.8, 62.7, 58.8, 44.0, 35.3, 33.4, 27.6, 26.1, 25.6, 25.1, 18.4, −5.3; MS *m/z* 488 (MH^+). Anal. ($C_{26}H_{39}N_2O_3SSi$) C, H, N.

(4-{1-Cyclohexyl-3-[4-(1,1,2,2-tetramethyl-1-silapropoxy)butanoyl]pyrazol-5-yl}phenylthio)methyl Acetate (29). Compound **28** (1.5 g, 3.1 mmol) was dissolved in acetic anhydride (12 mL). Powdered sodium acetate (1.1 g, 13.4 mmol) was added, and the solution was refluxed for 8 h. The solvent was evaporated in vacuo. The residue was taken up in (1:0.5) EtOAc:CH_2Cl_2, washed with sat. NH_4Cl and brine, and dried over Na_2SO_4. The solvent was removed under vacuo to give **29** (0.9 g, 56%) as an oil. ^{1}H NMR δ 7.54 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H), 6.73 (s, 1H), 5.49 (s, 2H), 4.00−4.18 (m, 1H), 3.73 (t, J = 6.4 Hz, 2H), 3.11 (t, J = 7.3 Hz, 2H), 2.15 (s, 3H), 1.83−2.00 (m, 10H), 1.12−1.32 (m, 2H), 0.91 (s, 9H), 0.06 (s, 6H); ^{13}C NMR δ 196.8, 170.3, 150.1, 143.5, 136.3, 129.8, 129.2, 106.5, 67.4, 62.8, 58.6, 35.3, 33.4, 27.7, 26.1, 25.6, 25.2, 21.2, 18.4, −5.2; MS *m/z* 531 (MH^+). Anal. ($C_{28}H_{42}N_2O_4SSi$) C, H, N.

[(4-{1-Cyclohexyl-3-[4-(1,1,2,2-tetramethyl-1-silapropoxy)butanoyl]pyrazol-5-yl}phenyl) sulfonyl]methyl Acetate (30). Compound **29** (0.9 g, 1.7 mmol) and MMPP (0.92 g, 1.86 mmol) were mixed in CH_2Cl_2 (16 mL) and MeOH (5 mL) and was stirred at room temperature for 16 h. The reaction mixture was neutralized with saturated $NaHCO_3$, and the solvent was evaporated to half of its volume. The residue was extracted into CH_2Cl_2, washed with saturated $NaHCO_3$ and water, dried over Na_2SO_4, filtered, and evaporated to give **30** (0.74 g, 78%) as an oil. ^{1}H NMR δ 8.05 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 8.3 Hz, 2H), 6.83 (s, 1H), 5.21 (s, 2H), 3.98−4.12 (m, 1H), 3.73 (t, J = 6.3 Hz, 2H), 3.12 (t, J = 7.4 Hz, 2H), 2.13 (s, 3H), 1.82−2.10 (m, 9H), 1.20−1.35 (m, 1H), 1.20−1.35 (m, 2H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR δ 196.4, 168.3, 150.4, 142.2, 137.3, 136.7, 130.0, 129.6, 107.3, 62.7, 59.1, 35.3, 34.8, 33.4, 31.7, 27.6, 26.1, 25.5, 25.1, 22.8, 20.4, 18.4, 14.2, −5.1; MS *m/z* 563 (MH^+). Anal. ($C_{28}H_{42}N_2O_6SSi$) C, H, N.

4-{1-Cyclohexyl-3-[4-(1,1,2,2-tetramethyl-1-silapropoxy)-butanoyl]pyrazol-5-yl}benzenesulfonamide (31). Sodium acetate (0.77 g, 9.4 mmol) was added to a solution of **30** (0.66 g, 1.17 mmol) in methanol (14 mL). The resultant mixture was stirred at room temperature for 15 min. K_2CO_3 (0.46 g, 3.3 mmol) was added, and the stirring was continued for 1.5 h. To this solution was added hydroxyaminosulfonic acid (0.53 g, 4.69 mmol). The mixture was stirred at room temperature for 2 h and diluted with EtOAc, and saturated $NaHCO_3$ was added. The solvent was evaporated to a small volume, and more EtOAc was added. The layers were separated, and the organic layer was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and filtered. The residue after evaporation of the solvent was chromatographed on silica gel eluting with 1:2 to 1:1 EtOAc:hexane to give **31** (0.38 g, 64%) as a white solid. Mp 151−153 °C. ^{1}H NMR δ 8.04 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 6.78 (s, 1H), 4.96 (s, 2H), 3.92−4.10 (m, 1H), 3.72 (t, J = 6.3 Hz, 2H), 3.12 (t, J = 7.3 Hz, 2H), 1.75−2.10 (m, 8H), 1.48−1.60 (m, 2H), 1.20−1.38 (m, 2H), 0.90 (s, 9H), 0.06 (s, 6H); MS *m/z* 506 (MH^+).

4-[1-Cyclohexyl-3-(4-hydroxybutanoyl)pyrazol-5-yl]benzenesulfonamide (32). Tetrabutylammonium fluoride (0.75 mL of 1 M solution in THF, 0.20 g, 0.75 mmol) was added dropwise to a solution of **31** (0.38 g, 0.75 mmol) in THF (9 mL). The reaction mixture was stirred at room temperature for 16 h. The residue after evaporation of the solvent was chromatographed on silica gel eluting with 1:1 EtOAc:CH_2Cl_2 to give **32** (0.23 g, 78%) as a white solid. Mp 152−154 °C. ^{1}H NMR (d^6-DMSO) δ 7.95 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 8.4 Hz, 2H), 6.84 (s, 1H), 4.48 (t, J = 5.2 Hz, 2H), 4.08−4.22 (m, 1H),

3.42−3.49 (m, 2H), 3.02 (t, J = 7.4 Hz, 2H), 1.82−2.00 (m, 4H), 1.70−1.82 (m, 4H), 1.19−1.38 (m, 2H); ^{13}C NMR (d_6-DMSO) δ 195.2, 149.5, 144.4, 143.0, 132.6, 129.6, 126.3, 106.6, 60.2, 58.1, 34.9, 32.9, 27.0, 24.8, 24.7; MS m/z 374 (M − OH), 392 (MH^+). LCMS (94.3%).

4-{1-Cyclohexyl-3-[4-(nitrooxy)butanoyl]pyrazol-5-yl}-benzenesulfonamide (33). Compound **33** was synthesized in a manner similar to the synthesis of **6a** using **32** (0.15 g, 0.38 mmol), fuming nitric acid (80 μL, 0.12 g, 1.92 mmol), and acetic anhydride (0.28 mL, 0.31 g, 3.1 mmol) to give **33** (0.12 g, 74%) as a white solid. Mp 45−47 °C. ^{1}H NMR (d_6-DMSO) δ 8.05 (d, J = 8.3 Hz, 2H), 7.51 (d, J = 8.2 Hz, 2H), 6.80 (s, 1H), 4.75−4.90 (m, 2H), 4.59 (t, J = 6.3 Hz, 2H), 3.90−4.20 (m, 1H), 3.21 (t, J = 7.1 Hz, 2H), 2.15−2.24 (m, 2H), 1.75−1.92 (m, 4H), 1.92−2.15 (m, 2H), 1.40−1.60 (m, 2H), 1.18−1.32 (m, 2H);^{13}C NMR (d_6-DMSO) δ 194.9, 149.9, 142.8, 142.6, 134.7, 129.8, 127.2, 107.1, 72.8, 59.1, 34.6, 33.4, 25.5, 25.1, 21.5; MS m/z 437 (MH^+). LCMS (94.6%).

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Supporting Information Available: Experimental details and spectroscopic data for the compounds **6b−j**, **17h**, **22b-i**, **22k−r**, **23b-i**, **23b-ii**, **23k**, **23r**, **26k-I**, **26k-II**, **27h-II**. This material is available free of charge via the Internet at http://pubs.acs.org.

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