JOC Article

Synthesis of 4,5-Diaryl-1*H*-pyrazole-3-ol Derivatives as Potential COX-2 Inhibitors

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4,5-Diaryl-*1H*-pyrazole-3-ol was utilized as a versatile template to synthesize several classes of compounds such as pyrazolo-oxazines **7**, pyrazolo-benzooxazines **9**, pyrazolo-oxazoles **10**, and its analogues **11a**−**c** as potential COX-2 inhibitors. Compounds **11b**,**c** were successfully synthesized with use of pyridinium *p*-toluenesulfonate mediated cyclization of the ketal intermediate. Diaryl-pyrazolo-benzooxazepine analogues were synthesized by using Cu-mediated cyclization of the *O*-alkylated arylbromide intermediate. Arylsulfonamides were synthesized efficiently on a large scale with 4-[4-(4-fluorophenyl)-5-hydroxy-2*H*-pyrazol-3-yl]benzenesulfonamide **31** template readily synthesized from commercially available 4-sulfamoyl benzoic acid **29**. The structure of a representative compound from each class was confirmed by X-ray crystallography. Selected compounds tested for inhibitory activity against COX-1 and COX-2 enzymes showed good selectivity for COX-2 versus COX-1 enzyme.

Introduction

Pyrazole derivatives have a long history of application in the agrochemical and the pharmaceutical industry[1] as herbicides and insecticides[2] and as part of biologically active pharmaceuticals.[1,3] Celebrex[3a] (**1**), a currently marketed selective COX-2 inhibitor, is a diaryl pyrazole derivative. 3-Hydroxy pyrazoles and 3-amino pyrazoles have been shown to be versatile intermediates to access a variety of biologically active heterocycles.[4]

Our quest for a novel COX-2 inhibitor[5] began with the discovery that diaryl hydrazone **2** showed high affinity for the COX-2 enzyme (Table 3). This compound, however, also showed high affinity for the COX-1 enzyme. To improve the COX-2 enzyme selectivity of compound **2**, we explored a series of conformationally restricted *N*-acyl hydrazones such as compound **3**. Acyl hydrazones have been reported[6] in the literature to exhibit antiinflammatory and analgesic activity. As we expected, compound **3** showed a 100-fold selectivity for COX-2 over COX-1 enzyme in the in vitro assay (Table 3). Cyclic aryl hydrazones such as 4,5-diaryl-*2H*-pyridazine-3-one and

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(1) (a) Elguero, J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon-Elsevier Science: Oxford, 1996; Vol. 3, pp 1−75. (b) Elguero, J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon-Elsevier Science: Oxford, 1984; Vol. 5, Part 4A, pp 167−304 (c) Attanasi, O. A.; De Crescentini, L.; Filippone, P.; Foresti, E.; Galeazzi, R.; Ghiviriga, I.; Katritzky, A. R. *Tetrahedron* **1997**, *53*, 5617−5640 and references therein. (d) Zimmermann, D.; Krogsgaard-Larsen, P.; Ehrhardt, J.-D.; Madsen, U.; Janin, Y. L. *Tetrahedron* **1998**, *54*, 9393−9400. (e) Jacobsen, N.; Kolind-Andersen, H.; Christensen, J. *Can. J. Chem.* **1984**, *62*, 1940. (f) Katritzky, A. R.; Maine, F. W. *Tetrahedron* **1964**, *20*, 299. (g) Krohs, W.; Hensel, O. Pyrazolone and Dioxopyrazolidine. In *Arzneim. Forsch., Beih.* **1961**. (h) Hamper, B. *J. Fluorine Chem.* **1990**, *48*, 123−131.

(2) (a) Schallner, O. Herbicides from pyrazole derivatives; Bayer, A. G., Fed. Rep. Ger., Ger. Offen., DE 3402308; *Chem Abstr.* **1986**, *104*, 34075j. (b) Boehner, B.; Hall, R. G. Preparation of Pyrazolylphosphonate pesticides; Ciba-Giegy A.-G., Switz., Ger. Offen., DE4139849; *Chem Abstr.* **1992**, *117*, 131386n. (c) Miller, P. C.; Molyneaux, J. M. *Org. Prep. Proced. Int.* **1999**, *31*, 295−304. (d) Eto, M. *Bioorganic Chemistry of Pesticide research abd Development* (*Japan*); Soft Science, Inc., Tokyo, Japan, 1985; pp 519−537. (e) Dewald, H. A.; Lobbestael, S.; Poschel, B. P. H. *J. Med. Chem.* **1981**, *24*, 982. (f) JP-A-63-122372, JP-A-63-122673, JP-A-63-170365, JP-A-2-173, JP-A-2-288866. (g) Moedritzer, K.; Rogers, M. D. United States Patent 4,964,895, 1990; *Chem. Abstr.* **1989**, *111*, 23509y. (h) Gaede, B. J.; McDermott, L. L. *J. Heterocycl. Chem.* **1993**, *30*, 295−304.

(3) (a) Penning, T. D.; Tally, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Doctor, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347. (b) Madsen, U.; Slok, F. A.; Stensbol, T. B.; Brauner-Osborn, H.; Lutzhoft, H. C. H.; Poulsen, M. V.; Eriksen, L.; Krogsgaard-Larsen, P. *Eur. J. Med. Chem.* **2000**, *35*, 69−76. (c) Zhang, J.; Didierlaurent, S.; Fortin, M.; Lefrançois, D.; Uridat, E.; Vevert, J. P. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1351−1355. (d) Selwood, D. L.; Brummell, D. G.; Glen, R. C.; Goggin, M. C.; Reynolds, K.; Tatlock, M. A.; Wishart, G. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1089−1092. (e) Zimmermann, D.; Janin, Y. L.; Brehm, L.; Bräuner-Osborne, H.; Ebert, B.; Johansen, T. N.; Madsen, U.; Krogsgaard-Larsen, P. *Eur. J. Med. Chem.* **1999**, *34*, 967−976. (f) Tanikawa, K.; Matsumota, T.; Nakamura, A.; Asada, Y.; Shudo, N. U.S. patent 5,968,967, 1999.

(4) (a) Teruo, O. EP0531901A2. (b) Faraci, W. S.; Welch, W. M. U.S. patent 6,005,109. (c) Rudiger, O. DD242044A1. (d) Selby, T. P.; Stevenson, T. M. U.S. patent 5,670,455. (e) Tietze, L. F.; Stteinmetz, A.; Balkenhohl, F. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1303−1306. (f) Flores, A. F. C.; Zanatta, N.; Rosa, A.; Brondani, S.; Martins, M. A. P. *Tetrahedron. Lett.* **2002**, *43*, 5005−5008. (g) Tietze, L.; Steinmetz, A. *Synlett* **1996**, 667−668. (h) Wiley, R. H.; Wiley, P. *Pyrazolones, Pyrazolidones and Derivatives*; Interscience Publishers, A Division of John Wiley and Sons: New York, 1964.

(5) (a) Griswold, D. E.; Adams, J. L. Constitutive Cyclooxygenase (COX-1) and Inducible Cyclooxygenase (COX-2): Rationale for selective Inhibition and Progress to date. *Med. Res. Rev.* **1996**, *16*, 181−206. (b) Hinz, B.; Brune, K. Cyclooxygenase-2−10 years later. *J. Pharmacol. Exp. Ther.* **2002**, *300*, 367−375.

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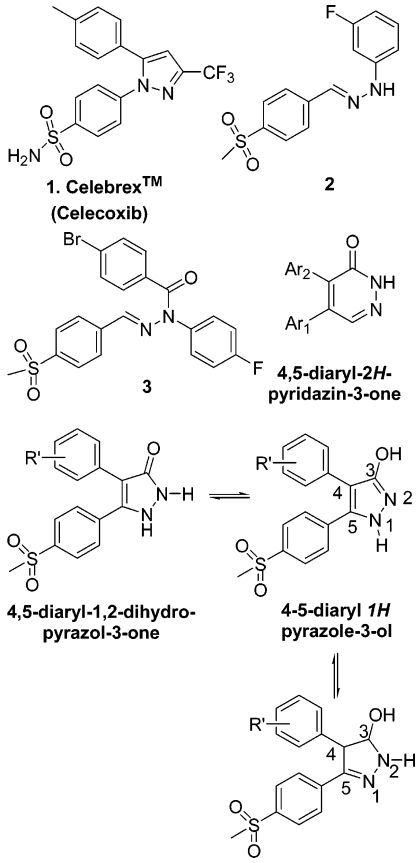
4, 5-diaryl-1*H*-pyrazol-3-one might provide even greater selectivity. Since the six-membered hydrazones, pyridazinones, had been elaborated by both Merck and Abbott,[7] we focused our research effort on five-membered cyclic acyl hydrazone, **4**, 5-diaryl-1*H*-pyrazol-3-one.[8] There are several reports[1,9] in the literature on the nature of the tautomerism of unsubstituted *1H*-pyrazol-3-ones and 4,5 mono or dialkyl *1H*-pyrazol-3-ones showing the existence of the keto as well as enol tautomers as a function of the solvent and the mode of substitution. Therefore, we decided to examine if 4,5-diaryl analogues such as the intermediate 4-(4-fluorophenyl)-5-(4-methylsulfonyl)-*1H* pyrazole-3-one, **4**, would exist as a pyrazol-3-one or pyrazole-3-ol. On the basis of the information in the literature[1,9] regarding the nature of the dipolar repulsion between contiguous NH's or lone pair repulsion between contiguous imino nitrogens, compound **4** could potentially exist mainly in the enolic form. In addition, the second aryl group on the C4 position would be expected to increase the acidity of the benzylic proton and promote population of the enolic tautomeric form. Indeed, the X-ray crystal structure of compound **4** demonstrated that the molecule exists exclusively in the enolic form.



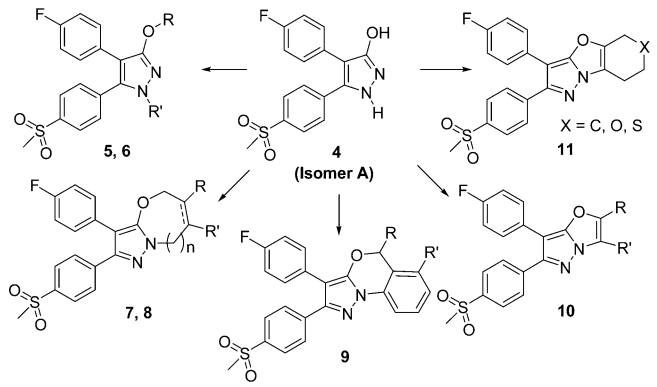


FIGURE 1. Isomer A derivatives.

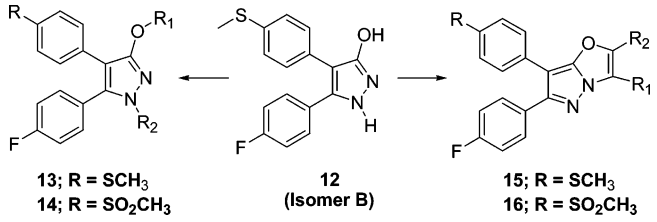


FIGURE 2. Isomer B derivatives.

Two regioisomeric hydroxypyrazoles were possible depending on the position of the sulfanylmethyl pharmacophore (Figures 1 and 2). To determine which isomer would show higher affinity and selectivity for the COX-2 enzyme, we synthesized both 4-(4-fluorophenyl)-5-(4-methylsulfonyl)-*1H* pyrazole-3-ol (**4**) (isomer A) and 5-(4-fluorophenyl)-4-(4-methylthio)-*1H* pyrazole-3-ol (**12**) (isomer B). The presence of the hydroxy functionality in **4** could provide access to a 1,3 or 2,3 substitution pattern, leading to several structurally diverse classes of compounds such as 1,3-dialkyl pyrazoles **5** and **6**, pyrazolo-oxazines[10] **7**, dihydro-oxa-1,8a-diaza-azulene **8**, pyrazolo-benzooxazines **9**, and pyrazolo-oxazoles **10** and its analogues **11a**−**c** (Figures 1 and 2). The synthetic methodology to prepare these various pyrazolo derivatives and the biological activity of selected compounds is described herein.

Results and Discussion

Schemes 1 and 2 depict the synthetic methodologies utilized to obtain diaryl-*1H*-pyrazole-3-ols **4** and **12**. The starting *β*-keto ester, 2-(4-fluorophenyl)-3-(4-(methylsulfanyl)phenyl)-3-oxo-propionic acid ethyl ester (**22**), was synthesized by two methods. In the first approach (Method 1, Scheme 1), known methodology for the

(6) (a) Matheus, M. E.; Oliveira, L. F.; Freitas, A. C. C.; Carvalho, A. M. M. S. P.; Barreiro, E. J. *Braz. J. Med. Biol. Res.* **1991**, *24*, 1291−1222. (b) *Chem. Abstr.* **1992**, *116*, 187490. (c) Sui, Z.; Guan, J.; Ferro, M. P.; McCoy, K.; Wachter, M. P.; Murray, W. V.; Singer, M.; Steber, M.; Ritchie, D. M.; Argentieri, D. C. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 601−604. (d) Murineddu, G.; Loriga, G.; Gavini, E.; Peana, A. T.; Mule, A. C.; Pinna, G. *Arch. Pharm. Pharm. Med. Chem.* **2001**, *334*, 393−398. (e) Reddy, E.; Reddy, M. V. patent WO 03/049698 A2.

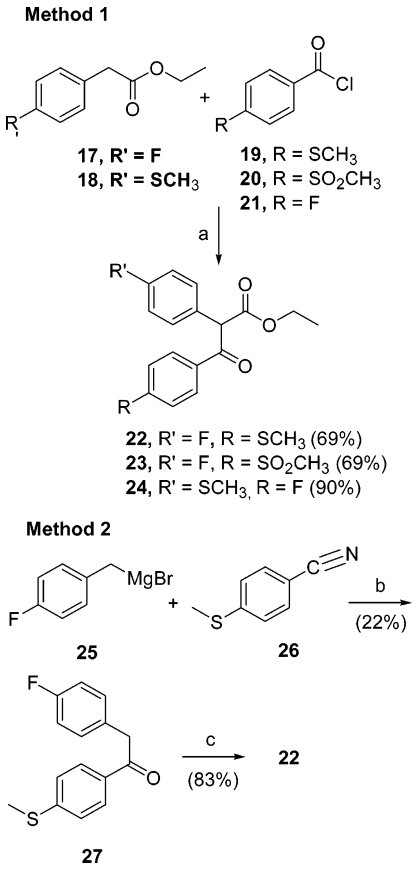
(7) (a) Li, C. S.; Brideau, C.; Chan, C. C.; Savoie, C.; Claveau, D.; Charleson, S.; Gordon, R.; Greig, G.; Gaunthier, J. Y.; Lau, C.; Riendeau, D.; Therien, M.; Wong, E.; Prasit, P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 597−600. (b) Black, L. A.; Basha, A.; Kolasa, T.; Kort, M. E.; Liu, H.; McCarty, C. M.; Patel, M. V.; Rohde, J. J. WO9910331, U.S. patent 6,307,047B1, 2001 (Abbott).

(8) (a) Kolasa, T.; Patel, M. V. U.S. patent 6,472,416B1, 2002 (Abbott). (b) This work was presented in part at the 28th National Medicinal Chemistry Symposium in San Diego, CA, on June 8−12, 2002; Poster No. 70.

(9) Parchment, O. G.; Green, D. V. S.; Taylor, P. J.; Hillier, I. H. *J. Am. Chem. Soc.* **1993**, *115*, 2352−2356 and the references therein.

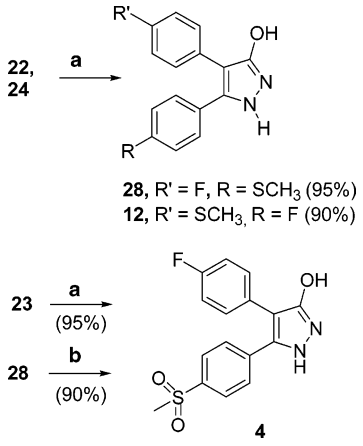
(10) During preparation of this manuscript, a publication by Ranatunge et al. (Ranatunge, R.; Garvey, D. S.; Janero, D. R.; Letts, L. G.; Martino, A. M.; Murty, M. G.; Richardson, S. K.; Young, D. V.; Zemetseva, I. S. *Bioorg. Med. Chem.* **2004**, *12*, 1357−1366) appeared that describes some compounds from this class.

SCHEME 1[a]



[a] Reagents and conditions: (a) LHMDS, THF, −78 °C; (b) Et_2O, 0 °C to room temperature, 14 h; (c) LHMDS, THF, −78 °C, ethyl cyanoformate.

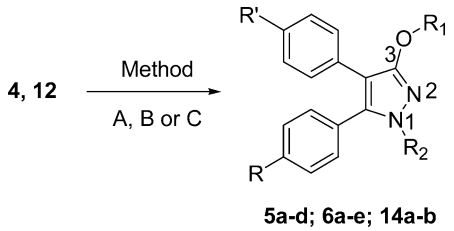
SCHEME 2[a]



[a] Reagents and conditions: (a) $NH_2NH_2{\cdot}H_2O$, CH_3CO_2H, dioxane/H_2O, reflux, 24 h; (b) 32% CH_3CO_3H, 0 °C, 1.15h.

synthesis of monoaryl β-keto-esters[11] was used to synthesize the diaryl β-ketoesters. (4-Fluorophenyl)acetic acid ethyl ester (**17**) or (4-(methylsulfanyl)phenyl)acetic acid ethyl ester (**18**) undergo acylation with the benzoyl chlorides **19**, **20**, and **21** to give diaryl β-ketoesters **22**, **23**, and **24** in good yield. In the second approach (Method 2, Scheme 1), compound **22** was synthesized via a Grignard reaction between 4-fluorobenzylmagnesium bromide (**25**) and 4-methylsulfanyl-benzonitrile (**26**) to give 2-(4-fluorophenyl)-1-(4-(methylsulfanyl)phenyl)ethanone[11] (**27**), which upon condensation with ethyl cyano formate[12] in the presence of LHMDS gave the desired product **22** in good yield. Cyclocondensation of **23** with hydrazine hydrate in the presence of acetic acid provided the key intermediate **4** in essentially quantitative yield. Similarly, cyclocondensation of the thiomethyl analogue **22** with hydrazine followed by oxidation of the thiomethyl group to the methyl sulfone gave the desired compound **4** in 90% yield.

SCHEME 3



Compound **12** was synthesized similarly from compounds **18** and **21** in excellent yield.

Alkylation of **4** could lead to the mono- or dialkylated product. When 1 equiv of alkylating reagent, e.g., phenacyl bromides, benzyl bromides, or bromopinacolone, etc., was used, the 3-*O*-alkylated analogue was formed exclusively in high yield. This product can then be alkylated at the 1 position with a different alkyl group. When two or more equivalents of the alkylating reagent mentioned earlier was used, 1,3-dialkylated product was isolated as the major product and not the 2,3-dialkylation product. This was confirmed by X-ray crystal structure of the dialkyl product (compound **5a**). A series of 1,3-dialkylated derivatives of **4** were synthesized with an excess of alkyl halide and K_2CO_3 in an aprotic solvent, such as DMF (**5a**−**d**, Scheme 3, Table 1). Compounds **6a**−**e** were synthesized by alkylation of **4** with a stoichiometric amount of one alkyl halide, R-X, to give the *O*-alkylation product followed by reaction with a second alkylating agent R′-X in acetone with K_2CO_3 (Scheme 4, Table 1). The structure assignment of compound **6c** was supported by X-ray crystallography. In the case of dibromoalkyl reagents where the *O*-alkylated product can undergo an intramolecular alkylation, alkylation occurs on the nitrogen at position 2 and not on the nitrogen at position 1 (Scheme 4). For example, reaction of **4** with the requisite dibromo alkyl group in DMF at 50 °C afforded pyrazolo-oxazine compounds **7a**−**c** (Scheme 4). For n = 0, the cyclization occurred in excellent yield and moderate yields were obtained for larger ring sizes (n = 1, 2). Alkylation of **4** with commercially available 1,4-dibromobutene (tech. grade) under the same reaction conditions provided compound **8a** in low yield presumably because the commercially available 1,4-dibromobutene was predominantly the trans isomer. On the other hand, reaction of **4** with dibromo-*o*-xylene afforded 3-(4-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)pyrazolo[1,5-*c*][1,3]-benzooxazepine (**8b**) in high yield.

(11) (a) Logue, M. W. *J. Org. Chem.* **1974**, *39*, 3455−3456. (b) Scheibler: Stein: JPCEAO *J. Prakt. Chem.* **1934**, *139*, 105−107. (c) Demopoulos, V. J.; Rekka, E.; Retsas, S. *Pharmazie* **1990**, *45*, 403−407.

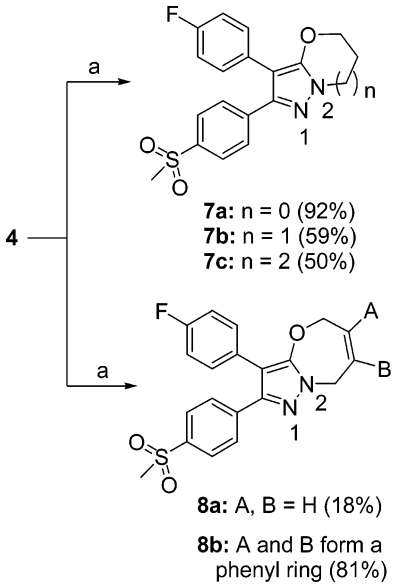
(12) Otter, R. R.; Shriner, R. L. *J. Am. Chem. Soc.* **1951**, *73*, 887−891.

TABLE 1. 1-Alkyl-3-alkoxy-4,5-diaryl Pyrazoles

C no.	R	R′	R_1	R_2	method[a]	yield (%)
5a	SO_2CH_3	F	$CH_2COC(CH_3)_3$	$CH_2COC(CH_3)_3$	A	81
5b	SO_2CH_3	F	CH_2(4-F-Ph)	CH_2(4-F-Ph)	A	60
5c	SO_2CH_3	F	CH_2CO(4-F-Ph)	CH_2CO(4-F-Ph)	A	51
5d	SO_2CH_3	F	CH_2CO(2-thienyl)	CH_2CO(2-thienyl)	A	60
6a	SO_2CH_3	F	CH_2CO(4-F-Ph)	ethyl	B	71
6b	SO_2CH_3	F	CH_2CO(2-thienyl)	ethyl	B	67
6c	SO_2CH_3	F	$CH_2COC(CH_3)_3$	ethyl	B	85
6d	SO_2CH_3	F	$CH_2COC(CH_3)_3$	CH_2CN	B	78
6e	SO_2CH_3	F	$CH_2COC(CH_3)_3$	$CH_2CH{=}C(Cl_2)_3$	B	87
14a	F	SO_2CH_3	CH_2CO(4-F-Ph)	CH_2CO(4-F-Ph)	C	85
14b	F	SO_2CH_3	$CH_2COC(CH_3)_3$	ethyl	C	12

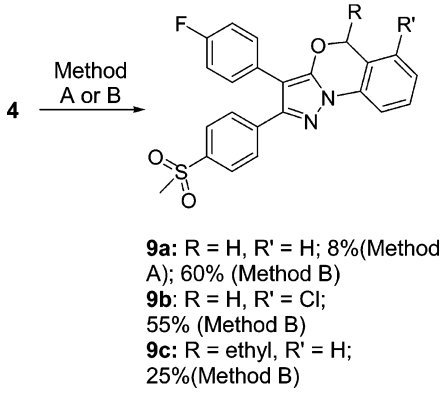
[a] Method A: excess R_1-X, K_2CO_3, DMF, 50 °C. Method B: (1) 1 equiv of R_1-X, K_2CO_3, DMF; (2) 1 equiv of R_2-X, acetone or DMF, K_2CO_3, 50 °C. Method C: (1) 1equiv of R_1-X, K_2CO_3, DMF; (2) 1 equiv of R_2-X, acetone or DMF, K_2CO_3, 50 °C; (3) CH_2Cl_2, CH_3CO_3H, 0 °C, 2 h. Alkylating agents R_1-X, R_2-X: (**5a**) bromopinacolone; (**5b**) 4-fluorobenzyl bromide; (**5c**) 4-fluorophenacylbromide; (**5d**) bromomethyl-2-thienyl-ketone; (**6a**) (1) 4-fluorophenacyl bromide, (2) ethyl iodide, DMF; (**6b**) (1) bromomethyl-2-thienyl-ketone, (2) ethyl iodide, acetone; (**6c**) (1) bromopinacolone; (2) ethyl iodide, acetone; **6d**: (1) bromopinacolone; (2) bromoacetonitrile, acetone; (**6e**) (1) bromopinacolone, (2) 1,1,3-trichloroprop-1-ene, acetone; (**14a**) (1) 4-fluorophenacyl bromide; (**14b**) (1) 4-fluorophenacyl bromide, (2) ethyl iodide, DMF.

SCHEME 4[a]



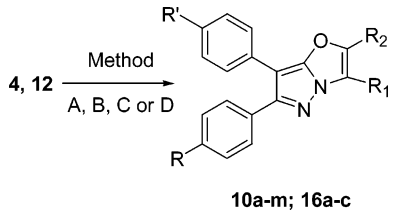
[a] Reagents and conditions: (a) alkylating agent, K_2CO_3, DMF, 50 °C, 7 h. Alkylating agents: (**7a**) 1,3-dibromoethane, (**7b**) 1,3-dibromopropane, (**7c**) 1,4-dibromobutane, (**8a**) 1,4-dibromo-2-butene, (**8b**) α,α′-dibromo-*o*-xylene.

SCHEME 5[a]



[a] Method A: alkylating agent, K_2CO_3, Cu, pyridine, rt. Method B: alkylating agent, K_2CO_3, 50 °C then CuI, K_2CO_3, DMF, 150 °C. Alkylating agents: (**9a**) 2-bromobenzylbromide, (**9b**) 2-chloro-6-fluorobenzyl chloride, (**9c**) 1-(2-bromophenyl)-1-propylmesylate.

SCHEME 6



In the case of bromoalkyl-bromoaryl alkylating agents, the first step, as seen in previous cases, leads to an *O*-alkylated bromoaryl product. This bromoaryl compound can then be cyclized on the nitrogen at the 2 position under Ullman coupling conditions to give compounds such as **9a**−**c** (Scheme 5). A stoichiometric amount of 2-bromobenzyl bromide was reacted with **4** to achieve complete *O*-alkylation. The reaction mixture was then treated with Cu powder to afford the cyclization product, pyrazolo-benzooxazines **9a**, in 8% yield. When CuI was used instead of Cu powder (Method B), a better yield (60%) was obtained, therefore method B was used to synthesize **9b** in moderate yield (55%). Alkylation of **4** with the mesylate of 1-(2-bromophenyl)-1-propanol followed by CuI-mediated cyclization at high temperature yielded compound **9c** in low yield (25%).

In the case of α-halo ketones as alkylating agents, the intramolecular cyclization of the *O*-alkylated keto compound was accomplished under acidic condition (Scheme 6, Table 2). The *O*-alkylated derivatives were formed by alkylation of **4** and **12** with the appropriate α-halo ketones. Cyclization of *O*-alkylated keto derivatives in the presence of *p*-toluenesulfonic acid monohydrate in toluene and acetic acid afforded pyrazolo[5,1-*b*]oxazole compounds **10a**−**m**. The structure of a representative member of this series, compound **10m**, was confirmed by X-ray crystallography. Compounds **16a**−**c** were obtained by oxidation of the thiomethyl compounds to the sulfones with peracetic acid in CH_2Cl_2. Scheme 7 depicts the synthesis of substituted pyrazolo-oxazole derivatives **11a**−**c**. Compound **11a** was synthesized by *O*-alkylation of **4** with 2-chlorocyclohexanone in DMF and K_2CO_3, as described earlier. Cyclization with standard conditions involving TsOH failed to give **11a**; however, under mildly acidic conditions with pyridinium-*p*-toluenesulfonate compound **11a** was obtained in 70% yield. For the synthesis

TABLE 2. Diarylpyrazolo[5,1-*b*]oxazoles

C no.	R	R′	R_1	R_2	method[a]	yield (%)
10a	SO_2CH_3	F	H	H	A	10
10b	SO_2CH_3	F	4-F-Ph	H	A	89
10c	SO_2CH_3	F	Ph	H	A	49
10d	SO_2CH_3	F	Ph	CH_3	A	78
10e	SO_2CH_3	F	$C(CH_3)_3$	H	A	58
10f	SO_2CH_3	F	$CH_2(C_6H_{12})$	H	A	70
10g	SO_2CH_3	F	CH_3	4-F-Ph	A	65
10h	SO_2CH_3	F	2-thienyl	CH_3	A	71
10i	SO_2CH_3	F	CH_3	CH_3	A	36
10j	SO_2CH_3	F	H	CF_3	B	28
10k	SO_2CH_3	F	CH_3	COOEt	A	90
10*l*	SO_2CH_3	F	CH_3	CN	C	37
10m	SO_2CH_3	F	CH_2CH_3	H	A	38
16a	F	SO_2CH_3	4-F-Ph	H	D	59
16b	F	SO_2CH_3	CH_3	4-F-Ph	D	71
16c	F	SO_2CH_3	CH_2CH_3	H	D	12

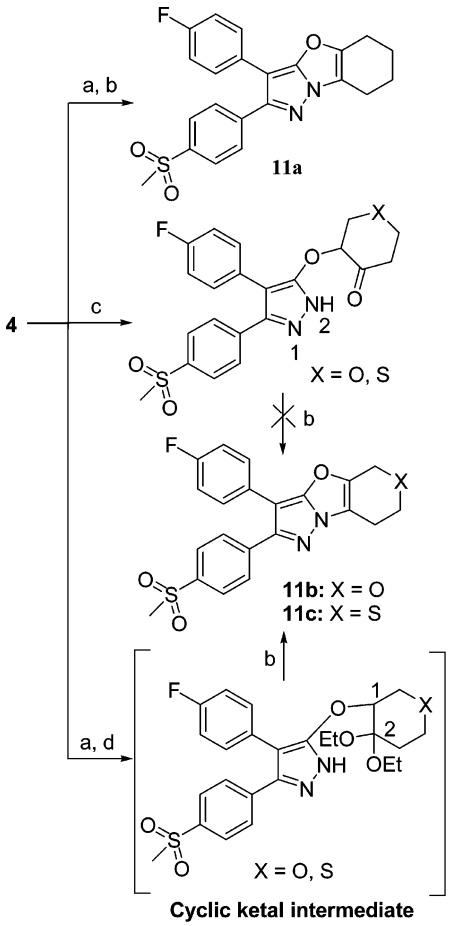
[a] Method A: (1) alkylating agent, K_2CO_3, DMF, 50 °C; (2) TsOH·H_2O, toluene/AcOH, reflux. Method B: (1) alkylating agent, K_2CO_3, DMF, 50 °C; (2) PPA, toluene, reflux. Method C: (1) alkylating agent, K_2CO_3, DMF, 50 °C; (2) TsOH·H_2O, toluene/AcOH, reflux; (3) 1 N NaOH in dioxane/EtOH; (4) *N*-hydroxysuccinimide, DCC, THF; (5) cyanuric chloride 50 °C. Method D: (1) alkylating agent, K_2CO_3, DMF, 50 °C; (2) TsOH·H_2O, toluene/CH_3CO_2H, reflux; (3) CH_2Cl_2, 32% CH_3CO_3H, 0 °C, 2 h. Alkylating agents: (**10a**) 2-bromomethyldioxolane; (**10b**) 4-fluorophenacyl bromide; (**10c**) phenacyl bromide; (**10d**) 2-bromopropiophenone; (**10e**) 1-bromopinacolone; (**10f**) (a) bromomethyl cyclohexyl ketone; (**10g**) 1-chloro-1-(4-fluorophenyl)acetone; (**10h**) 2-chloropropio-2′-thiophene; (**10i**) 2-bromo-3-butanone; (**10j**) 3-bromo-1,1,1-trifluoroacetone; (**10k**) 2-chloro-3-ketobutyrate; (**10*l***) 2-chloro-3-ketobutyrate; (**10m**) 1-bromo-2-butanone; (**16a**) 4-fluorophenacyl bromide; (**16b**) 3-chloro-3-(4-fluorophenyl)-2-propanone; (**16c**) 1-bromo-2-butanone.

of compounds **11b** and **11c**, the *O*-alkylation product was obtained in high yield, but the intramolecular cyclization of the *O*-alkylated ketone under the same reaction conditions as **11a** failed. It can be argued that the interaction of the pyrazole oxygen with the heteroatom in the 4 position of the tetrahydropyran or thiopyran ring put the carbonyl group away from the 2 position nitrogen of the pyrazole. Therefore we decided to convert the carbonyl carbon into a conformationally more flexible ketal (sp^3 carbon) and indeed, cyclization of the ketal in the presence of pyridinium-*p*-toluenesulfonate gave the desired products **11b** and **11c**.

Since a sulfonamide group is present in CelebrexTM, we decided to synthesize sulfonamide analogues of some selected sulfones to evaluate the effect of this pharmacophore on COX-2 activity. An efficient synthesis was developed starting with commercially available 4-sulfamoylbenzoic acid **31** (Scheme 8). Acid chloride formation and protection of the sulfonamide was achieved in a single step with use of oxalyl chloride and DMF in dichloromethane. *β*-Keto ester formation followed by condensation with hydrazine as described earlier gave compound **31** in excellent yield. This intermediate was then utilized to synthesize final sulfonamide analogues such as **32**, **33**, **34**, and **35** (Scheme 9) via the synthetic methodology described earlier.

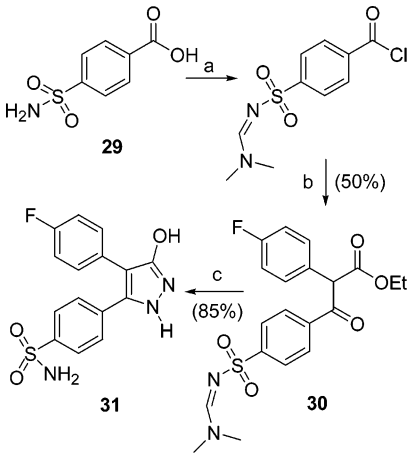
All the compounds synthesized from **4** (isomer A) and **12** (isomer B) were tested for their inhibitory activity against recombinant human COX-1 (r-hu COX-1) and COX-2 (r-hu COX-2) enzymes as a primary screen as described in ref 7a. The data on selected compounds are shown in Table 3. In general, isomer A derivatives were more potent and selective for the COX-2 enzyme than for isomer B derivatives.

SCHEME 7[a]



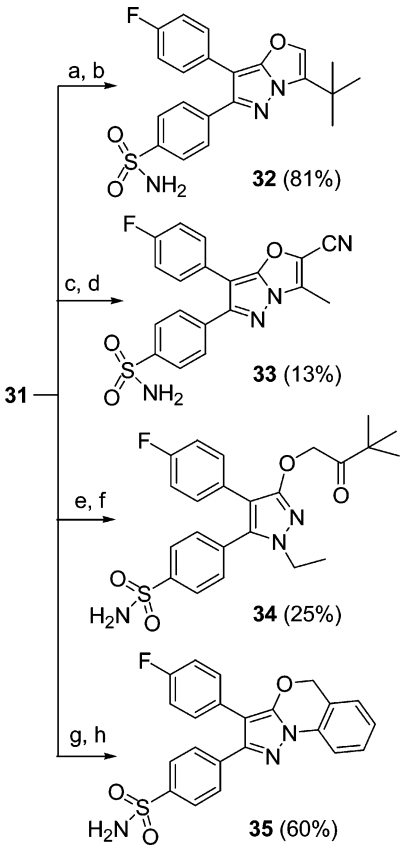
[a] Reagents and conditions: (**11a**) (a) 2-chloro cyclohexanone, K_2CO_3, DMF, (b) pyridinium-*p*-toluenesulfonate, 70%; (**11b**) (c) 3-bromo-tetrahydro-4*H*-pyran-4-one, K_2CO_3, DMF; (**11c**) (c) 3-bromo-tetrahydro-4*H*-thiopyran-4-one, K_2CO_3, DMF, (d) pyridinium-*p*-toluenesulfonate, EtOH, reflux, 12 h.

SCHEME 8[a]



[a] Reagents and conditions:: (a) 2 M oxalyl chloride, CH_2Cl_2, DMF, 40 °C, 12 h; (b) 4-fluorophenylacetate, LHMDS, THF, −78 °C; (c) NH_2NH_2·H_2O, CH_3CO_2H, dioxane/H_2O, reflux, 24 h.

SCHEME 9[a]



[a] Reagents and conditions: (**32**) (a) 1-bromopinacolone, K_2CO_3, DMF, 50 °C, (b) *p*-TsOH·H_2O, CH_3CO_2H, toluene, reflux, 4 h; (**33**) (c) (1) 2-chloro-3-ketobutyrate, K_2CO_3, DMF, 50 °C, (2) TsOH·H_2O, toluene/CH_3CO_2H, reflux, (d) (1) 1 N NaOH in dioxane/EtOH, (2) *N*-hydroxysuccinimide, DCC, THF, (3) cyanuric chloride, 50 °C; (**34**) (e) 1-bromopinacolone, K_2CO_3, DMF, 40 °C, 1 h, (f) ethyl iodide, acetone, K_2CO_3, 50 °C; (**35**) (g) 2-bromo benzyl bromide, K_2CO_3, DMF, 50 °C, 40 min, (h) CuI, K_2CO_3, 150 °C, 2 h.

TABLE 3. In Vitro COX-1 and COX-2 Activity of Selected Compounds

C no.	r-hu COX-1, % inhib.	r-hu COX-2, % inhib. or IC_{50}
2	95% at 1 μM	84% at 1 μM
3	72% at 100 μM	76 nM
5b	17% at 100 μM	90% at 100 nM
6c	0% at 100 μM	5 nM
6c	3% at 100 μM	31 nM
6d	0% at 100 μM	5 nM
7b	4% at 100 μM	720 nM
8a	20% at 100 μM	90% at 100 nM
9a	25% at 100 μM	82% at 100 nM
10f	51% at 100 μM	94% at 100 nM
10k	61% at 100 μM	12 nM
10l	38% at 100 μM	4 nM
10m	23% at 100 μM	75% at 10 nM
11b	4% at 100 μM	213 nM
11c	20% at 100 μM	55 nM
32	99% at 100 μM	88% at 100 nM
33	96% at 100 μM	69 nM

In summary, we have demonstrated the use of a 4,5-diaryl-1*H*-pyrazole-3-ol intermediate to synthesize several novel classes of compounds in moderate to good yields. In addition, the structures of representative compounds from each class were confirmed by X-ray crystallography. Several compounds demonstrated in vitro activity and selectivity for the COX-2 enzyme. Compounds **6c**, **6d**, and **10*l*** demonstrated single digit nanomolar potency for the COX-2 enzyme.

Experimental Section

2-(4-Fluorophenyl)-2-(4-methylsulfonylphenyl)acetic Acid Methyl Ester (23). To a solution of ethyl (4-fluoro)-phenylacetate (**17**) (2.35 g, 14 mmol) in THF (15 mL) at −78 °C was added dropwise 1 N lithium bis(trimethylsilyl)amide (14 mL, 14 mmol) and after 15 min a suspension of 4-methylsulfonylbenzoyl chloride (**20**) (3.3 g, 15 mmol) in THF (25 mL) was added in portions. The reaction was then continued for the next 60 min at −78 °C and for 12 h at 0 to 5 °C. The mixture was quenched with 10% citric acid, the THF was removed in vacuom and the residue was triturated with hexane to provide 3.4 g (69%) of solid product **23**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.27 (s, 3 H), 3.69 (s, 3 H), 6.35 (s, 1 H), 7.21 (m, 2 H), 7.44 (m, 2 H), 8.06 (d, J = 9 Hz, 2 H), 8.25 (d, J = 9 Hz, 2 H); MS (DCI-NH_3) m/z 368 $(M + H)^+$.

4-(4-Fluorophenyl)-5-(4-methylsulfonylphenyl)-3-hydroxypyrazole (4). A mixture of 2-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)acetic acid methyl ester (**23**) (2.09 g, 5.74 mmol), hydrazine hydrate (0.36 mL, 6 mmol), and CH_3CO_2H (0.36 mL, 6 mmol) in dioxane (100 mL) and H_2O (10 mL) was refluxed for 24 h. The dioxane was removed in vacuo, and the residue was diluted with water (50 mL), then the solid was filtered and dried in vacuo to provide 1.8 g (95%) of **4**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.26 (s, 3 H), 7.17 (m, 2 H), 7.27 (m, 2 H), 7.57 (m, 2 H), 7.93 (d, J = 9 Hz, 2 H); MS (DCI-NH_3) m/z 333 $(M + H)^+$, 350 $(M + NH_4)^+$. $C_{16}H_{13}FN_2O_3S$·0.5 H_2O: C, 57.51; H, 3.98; N, 8.38. Found: C, 57.71; H, 4.13; N, 7.85.

Ethyl 2-(4-Fluorophenyl)-2-((4-methylthio)benzoyl)acetate (22). Method A: To a solution of 4-methylthiobenzoic acid (3.36 g, 20 mmol) and a few drops of DMF in anhydrous CH_2Cl_2 (50 mL) at 0 °C was added dropwise oxalyl chloride (4.4 mL, 50 mmol) and the resulting mixture was stirred at 0 °C for 6 h. The mixture was then concentrated in vacuo to obtain 3.7 g (∼100%) of crude 4-methylthiobenzoyl chloride (**19**).

A mixture of 4-fluorophenylacetic acid (10.8 g, 70 mmol) and concentrated H_2SO_4 (1 mL) in ethanol (150 mL) was refluxed for 8 h. The reaction mixture was then concentrated in vacuo and the residue was dissolved in ethyl ether. The ether solution was washed with 10% $NaHCO_3$ and brine, dried with anhydrous $MgSO_4$, and concentrated in vacuo to give 12.2 g (96%) of ethyl (4-fluorophenyl)acetate, **17**.

Lithium bis(trimethylsilyl)amide (1 N, 20 mL, 20 mmol) was added dropwise to a solution of ethyl (4-flluorophenyl)acetate (**17**) (3.84 g, 20 mmol) in THF (20 mL) at −78 °C. After 15 min a suspension of crude 4-methylthiobenzoyl chloride (**19**) (3.7 g, 20 mmol) in THF (50 mL) was added dropwise to this mixture and the resulting mixture was stirred at −78 °C for 60 min. The mixture was quenched with saturated NH_4Cl and extracted with EtOAc. The acetate layer was washed with water and brine, dried with anhydrous $MgSO_4$, and concentrated in vacuo. The residue was chromatographed (silica gel, 19:1 CH_2Cl_2−EtOAc) to provide 4.55 g (69%) of the title compound **22**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (m, 3 H), 2.50 (s, 3 H), 4.20 (m, 2 H), 5.53 (s, 1 H), 7.03 (t, J = 9 Hz, 2 H), 7.22 (d, J = 9 Hz, 2 H), 7.38 (m, 2 H), 7.85 (d, J = 9 Hz, 2 H); MS (DCI-NH_3) m/z 333 $(M + H)^+$, 350 $(M + NH_4)^+$.

Method B: To a suspension of Mg turnings (2.4 g, 100 mmol) in anhydrous Et_2O (200 mL) was added a few drops of *p*-fluorobenzyl bromide and the mixture was warmed to initiate the reaction. The remaining amount of *p*-fluorobenzyl bromide (6.4 mL, 50 mmol) in Et_2O (50 mL) was added slowly at such rate as to maintain gentle boiling. Upon completion of addition the mixture was refluxed for the next 2 h and then cooled to 0 °C. The mixture was then slowly cannulated to a solution of 4-methylthiobenzonitrile (7.46 g, 50 mmol). The reaction mixture was allowed to warm to room temperature

and was left at ambient temperature for 14 h. The mixture was quenched with saturated NH_4Cl, and the ethyl layer was washed with water and brine, dried with anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography (silica gel, 5:4:1 hexane−CH_2Cl_2−EtOAc) to provide 2.8 g (22%) of 4-fluorobenzyl 4-methythiophenyl ketone (**27**). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.55 (s, 3 H), 4.36 (s, 2 H), 7.14 (t, J = 9 Hz, 2 H), 7.29 (m, 2 H), 7.38 (d, J = 9 Hz, 2 H), 7.98 (d, J = 9 Hz, 2 H); MS (DCI-NH_3) m/z 261 $(M + H)^+$, 278 $(M + NH_4)^+$.

Lithium bis(trimethylsilyl)amide (1 N, 3.9 mL, 3.9 mmol) in anhydrous THF (10 mL) at −78 °C was treated dropwise with a solution of 4-fluorobenzyl 4-methythiophenyl ketone (**27**) (1.03 g, 3.9 mmol) in THF (25 mL). The mixture was stirred at −78 °C for 30 min and then ethyl cyanoformate (0.39 mL, 3.9 mmol) was added. The reaction mixture was stirred at −78 °C for 3 h and then at room temperature for 3 h. After the mixture was quenched with saturated NH_4Cl and extracted with ethyl acetate, the acetate layer was washed with water and brine, dried with anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography (silica gel, 5:4:1 hexane−CH_2Cl_2−EtOAc) to provide 1.1 g (83%) of ethyl 2-(4-fluorophenyl)-2-((4-methylthio)benzoyl)acetate (**22**). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (m, 3 H), 2.50 (s, 3 H), 4.20 (m, 2 H), 5.53 (s, 1 H), 7.03 (t, J = 9 Hz, 2 H), 7.22 (d, J = 9 Hz, 2 H), 7.38 (m, 2 H), 7.85 (d, J = 9 Hz, 2 H); MS (DCI-NH_3) m/z 333 $(M + H)^+$, 350 $(M + NH_4)^+$.

A mixture of ethyl 2-(4-fluorophenyl)-2-(4-methylthiobenzoyl)acetate (**22**) (1.33 g, 4 mmol), hydrazine hydrate (0.25 mL, 4.2 mmol), and CH_3CO_2H (0.25 mL, 4.2 mmol) in dioxane (50 mL) and H_2O (5 mL) was refluxed for 24 h and then concentrated in vacuo. To the residue was added water and the solid was filtered and dried in vacuo to afford 1.15 g (95%) of crude product **28**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.47 (s, 3 H), 7.12 (t, J = 9 Hz, 2 H), 7.26 (m, 6 H); MS (DCI-NH_3) m/z 301 $(M + H)^+$, 318 $(M + NH_4)^+$.

To a solution of **28** (200 mg, 0.48 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added 32% peracetic acid (0.22 mL) and the mixture was stirred at 0 °C for 4 h. The mixture was then washed with water, saturated $NaHCO_3$, and brine, dried with anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography (silica gel, EtOAc) to afford compound **4** (194 mg, 90%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.26 (s, 3 H), 7.17 (m, 2 H), 7.27 (m, 2 H), 7.57 (m, 2 H), 7.93 (d, J = 9 Hz, 2 H); MS (DCI-NH_3) m/z 333 $(M + H)^+$, 350 $(M + NH_4)^+$.

1-[1-(3,3-Dimethyl-2-oxo-butyl)-4-(4-fluorophenyl)-5-(4-(methanesulfonyl)phenyl)-1*H*-pyrazol-3-yloxy]-3,3-dimethylbutan-2-one (5a). A mixture of **4** (90 mg, 0.3 mmol), bromopinacolone (0.21 mL, 0.6 mmol), and anhydrous K_2CO_3 (1.1 g, 0.8 mmol) in DMF (40 mL) was refluxed at 50 °C for 7 h. The mixture was poured into water and extracted with EtOAc. The organic solvent was removed in vacuo and the residue was purified by chromatography (silica gel, EtOAc) to provide 250 mg (81%) of product **5a**. Mp 180−182 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.95 (s, 9 H), 1.14 (s, 9 H), 3.23 (s, 3 H), 5.00 (s, 2 H), 5.22 (s, 2 H), 7.10 (m, 2 H), 7.22 (m, 2 H), 7.49 (d, J = 9 Hz, 2 H), 7.97 (d, J = 9 Hz, 2 H); MS $(APCI^+)$ m/z 529 $(M + H)^+$, $(APCI^-)$ m/z 527 $(M - H)^-$, 563 $(M + Cl)^-$. Anal. Calcd for $C_{28}H_{33}FN_2O_5S\cdot0.25H_2O$: C, 63.08; H, 6.33; N, 5.25. Found: C, 62.95; H, 6.39; N, 5.14.

2-[1-Ethyl-4-(4-fluorophenyl)-5-(4-(methanesulfonyl)-phenyl)-1*H*-pyrazol-3-yloxy]-1-(4-fluorophenyl)ethanone (6a). To a mixture of **4** (200 mg, 0.6 mmol) and K_2CO_3 (83 mg, 0.6 mmol) in DMF (30 mL) at 50 °C was added dropwise a solution of *p*-fluorophenacyl bromide (130 mg, 0.6 mmol) in DMF (10 mL) and the resulting mixture was stirred at 50 °C for 50 min. The mixture was then poured into water and extracted with ethyl acetate. The acetate layer was washed with water and brine, dried with anhydrous $MgSO_4$, and concentrated in vacuo to provide 280 mg (99%) of 3-(4-fluorophenacyloxy)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)pyrazole. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.23 (s, 3 H), 5.64 (s, 2 H), 7.22 (m, 2 H), 7.39 (m, 4 H), 7.60 (d, J = 9 Hz, 2 H), 7.95 (d, J = 9 Hz, 2 H), 8.12 (m, 2 H), 12.60 (s, 1 H); MS (APCI + Q1) m/z 469 $(M + H)^+$, (APCI − Q1) m/z 467 $(M - H)^+$. Anal. Calcd for $C_{24}H_{18}F_2N_2O_4S\cdot0.25H_2O$: C, 60.95; H, 3.94; N, 5.92; Found: C, 61.28; H, 4.28; N, 5.45.

To a mixture of 3-(4-fluorophenacyloxy)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)pyrazole (117 mg, 0.25 mmol) and K_2CO_3 (41 mg, 0.3 mmol) in DMF (20 mL) was added dropwise ethyl iodide (0.04 mL, 0.5 mmol) and the mixture was refluxed for 8 h at 50 °C. The mixture was then poured into water and extracted with EtOAc, The organic layer was washed with water and brine, dried with anhydrous $MgSO_4$, and concentrated in vacuo. The residue was chromatographed (silica gel, 1:1 hexanes−EtOAc) to provide 90 mg (72%) of the desired product **6a**. Mp 170−171 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.15 (t, J = 7 Hz, 3 H), 3.31 (s, 3 H), 3.78 (q, J = 7 Hz, 2 H), 5.70 (s, 2 H), 7.11 (t, J = 9 Hz, 2 H), 7.22 (m, 2 H), 7.42 (t, J = 9 Hz, 2 H), 7.63 (d, J = 9 Hz, 2 H), 8.01 (d, J = 9 Hz, 2 H), 8.10 (m, 2 H); MS $(APCI^+)$ m/z 497 $(M + H)^+$, $(APCI^-)$ m/z 495 $(M - H)^-$, 531 $(M + Cl)^-$. Anal. Calcd for $C_{26}H_{22}F_2N_2O_4S\cdot0.5H_2O$: C, 61.77; H, 4.58; N, 5.54. Found: C, 61.90; H, 4.41; N, 5.47.

3-(4-Fluorophenyl)-2-(4-(methanesulfonyl)phenyl)-5*H*-benzo[*d*]pyrazolo[5,1-*b*][1,3]oxazine (9a). Method A: To a mixture of **4** (133 mg, 0.4 mmol) and anhydrous K_2CO_3 (69 mg, 0.5 mmol) in pyridine (25 mL) were added 2-bromobenzyl bromide (100 mg, 0.4 mmol) and copper powder (20 mg) and the resulting mixture was stirred at room temperature for 14 h. The mixture was then poured into 10% citric acid and extracted with EtOAc. The acetate layer was washed with water and brine, dried with anhydrous $MgSO_4$, and concentrated in vacuo. The residue was chromatographed (silica gel, 3:2 hexanes−EtOAc) to afford 12 mg (8%) of the title product. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.25 (s, 3 H), 5.51 (s, 2 H), 7.30 (m, 5 H), 7.43 (d, J = 8 Hz, 1 H), 7.53 (m, 1 H), 7.74 (t, J = 9 Hz, 3 H), 7.96 (d, J = 9 Hz, 2 H); MS (APCI + Q1) m/z 421 $(M + H)^+$, (APCI − Q1) m/z 420 $(M)^+$. Anal. Calcd for $C_{23}H_{17}FN_2O_3S\cdot0.25H_2O$: C, 65.01; H, 4.15; N, 6.59. Found: C, 65.08; H, 3.99; N, 6.47.

Method B: To a solution of **4** (200 mg, 0.6 mmol) and K_2CO_3 (97 mg, 0.7 mmol) in DMF (25 mL) at 50 °C was added dropwise a solution of 2-bromobenzyl bromide (175 mg, 0.7 mmol) in DMF (5 mL). The mixture was stirred until the starting material disappeared (∼40 min). To this mixture was added K_2CO_3 (200 mg, 1.5 mmol) and CuI (30 mg) and the resulting mixture was heated at 150 °C until starting material was gone (∼2 h). The reaction mixture was then cooled to room temperature, poured into 10% citric acid, and extracted with EtOAc. The EtOAc extract was concentrated in vacuo and the residue was purified to provide 150 mg (60%) of the desired product. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.26 (s, 3 H), 5.51 (s, 2 H), 7.30 (m, 5 H), 7.43 (d, J = 8 Hz, 1 H), 7.53 (m, 1 H), 7.74 (t, J = 9 Hz, 3 H), 7.95 (d, J = 9 Hz, 2 H); MS $(APCI^+)$ m/z 421 $(M + H)^+$, $(APCI^-)$ m/z 420 $(M)^+$. Anal. Calcd for $C_{23}H_{17}FN_2O_3S\cdot0.5H_2O$: C, 64.32; H, 4.22; N, 6.59. Found: C, 64.25; H, 4.26; N, 6.25.

3,7-Bis(4-fluorophenyl)-6-(4-(methanesulfonyl)phenyl)-pyrazolo[5,1-*b*]oxazole (10b). A mixture of the *O*-alkylated derivative from compound **5b** (47 mg, 0.1 mmol), *p*-TsOH × H_2O (19 mg, 0.1 mmol) in toluene (20 mL), and CH_3CO_2H (7 mL) was refluxed for 4 h with use of a Dean−Stark trap. The mixture was then concentrated in vacuo and the residue was dissolved in EtOAc. The acetate solution was washed with 10% bicarbonate and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed (silica gel, 1:1 hexanes−EtOAc) to provide 40 mg (89%) of the desired product. Mp 200−202 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.25 (s, 3 H), 7.26 (t, J = 9 Hz, 2 H), 7.45 (m, 4 H), 7.80 (d, J = 9 Hz, 2 H), 8.00 (d, J = 9 Hz, 2 H), 8.30 (m, 2 H), 8.83 (s, 1 H); MS $(APCI^+)$ m/z 451 $(M + H)^+$, $(APCI^-)$ m/z 449 $(M - H)^-$,

485 $(M + Cl)^-$. Anal. Calcd for $C_{24}H_{16}F_2N_2O_3S \cdot 0.6H_2O$: C, 62.49; H, 3.76; N, 6.07. Found: C, 62.62; H, 3.62; N, 5.68.

1-(4-Fluorophenyl)-2-(4-(methanesulfonyl)phenyl)-4,7-dihydro-5*H*-6,8-dioxa-3,3a-diaza-cyclopenta[*a*]indene (11b). To a solution of 4-(4-fluorophenyl)-5-(4-methylsulfonyl)-3-(tetrahydro-4*H*-pyran-4-on-3-yloxy)pyrazole, prepared according to the procedure for compound **6a** substituting 3-bromotetrahydro-*4H*-pyran-4-one for *p*-fluorophenacyl bromide (340 mg, 0.8 mmol), in ethanol (120 mL) was added pyridinium *p*-toluenesulfonate (30 mg) and the resulting mixture was refluxed at 75 °C for 12 h. The mixture was then concentrated in vacuo and the residue was chromatographed (silica gel, 1:2 hexanes−EtOAc) to provide 230 mg of cyclic ketal intermediate.

This ketal intermediate was dissolved in toluene (30 mL) and AcOH (5 mL) and treated with pyridinium *p*-toluenesulfonate (10 mg) at reflux for 6 h. The mixture was then concentrated in vacuo and purified by chromatography (silica gel, 1:2 hexanes−EtOAc) to provide 100 mg (31%) of the title compound. Mp 200−201 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.98 (m, 2 H), 3.25 (s, 3 H), 4.03 (t, J = 6 Hz, 2 H), 4.75 (s, 2 H), 7.26 (t, J = 9 Hz, 2 H), 7.37 (m, 2 H), 7.74 (d, J = 9 Hz, 2 H), 7.95 (d, J = 9 Hz, 2H); MS $(APCI^+)$ m/z 413 $(M + H)^+$, $(APCI^-)$ m/z 447 $(M + Cl)^-$. Anal. Calcd for $C_{21}H_{17}FN_2O_4S \cdot 0.5H_2O$: C, 59.84; H, 4.30; N, 6.64. Found: C, 60.02; H, 4.22; N, 6.53.

3-Ethyl-7-(4-fluorophenyl)-6-(4-(methanesulfonyl)phenyl)pyrazolo[5,1-*b*]oxazole (10m). The title compound was prepared according to the procedure of compound **10b**, substituting 1-bromo-2-butanone for phenacyl bromide. Mp 177−179 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.35 (t, J = 7 Hz, 3 H), 2.85 (q, J = 7 Hz, 2 H), 3.25 (s, 3 H), 7.25 (m, 2 H), 7.35 (m, 2 H), 7.73 (d, J = 9 Hz, 2 H), 7.95 (d, J = 9 Hz, 2 H), 8.9 (s, 1 H); MS (DCI-NH_3) m/z 357 $(M + H)^+$, m/z 374 $(M + NH_4)^+$. Anal. Calcd for $C_{20}H_{17}FN_2O_3S$: C, 62.49; H, 4.46; N, 7.29. Found C, 62.28; H, 4.36; N, 6.95.

4-[4-(4-Fluorophenyl)-5-hydroxy-2*H*-pyrazol-3-yl]benzenesulfonamide (31). To a suspension of 4-aminosulfonylbenzoic acid (**29**) (5.03 g, 25 mmol) in 2 M oxalyl chloride in CH_2Cl_2 (30 mL, 60 mmol) at room temperature was added dropwise DMF (2.1 mL, 26 mmol) and the resulting mixture was refluxed at 40 °C for 12 h. The mixture was then concentrated in vacuo to provide crude 4-(*N*′,*N*′-dimethylaminomethyleneaminosulfonyl)benzoyl chloride, which was used directly in the next step. To a solution of commercially available ethyl 4-fluorophenylacetate (4.5 g, 25 mmol) in THF (50 mL) at −78 °C was added 1 N LHMDS (26 mL, 26 mmol). After 20 min the 4-(*N*′,*N*′-dimethylaminomethyleneaminosulfonyl)benzoyl chloride was added in portions and the reaction mixture was stirred at this temperature for the next 3 h. The mixture was then concentrated in vacuo, 10% citric acid was added, and the solution was extracted with EtOAc. The acetate layer was washed with water and brine, dried with anhydrous $MgSO_4$, and concentrated in vacuo. Purification by column chromatography (silica gel, EtOAc) afforded 5 g (50%) of ethyl 2-(4-(*N*′,*N*′-dimethylaminomethyleneaminosulfonyl)-benzoyl)(4-fluorophenyl) acetate (**30**). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.15 (t, J = 7 Hz, 3 H), 2.90 (s, 3 H), 3.14 (s, 3 H), 4.14 (q, J = 7 Hz, 2 H), 6.25 (s, 1 H), 7.20 (t, J = 9 Hz, 2 H), 7.43 (m, 2 H), 7.90 (d, J = 9 Hz, 2 H), 8.14 (d, J = 9 Hz, 2 H), 8.23 (s, 1 H); MS $(APCI^+)$ m/z 421 $(M + H)^+$, $(APCI^-)$ m/z 419 $(M - H)^-$, 455 $(M + Cl)^-$. A mixture of the keto ester **30**, hydrazine hydrate (1.5 mL, 25 mmol), and acetic acid (1.8 mL, 30 mmol) in dioxane (120 mL) was refluxed for 4 h. The mixture was then concentrated; the residue was dissolved in EtOAc, and washed with water and brine. Removal of acetate in vacuo and purification of the residue by chromatography (silica gel, CH_2Cl_2−EtOH 4:1) gave 3.4 g (∼85%) of 5-(4-aminosulfonylphenyl)-4-(4-fluorophenyl)-3-hydroxypyrazole (**31**). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.15 (t, J = 9 Hz, 2 H), 7.35 (m, 2 H), 7.40 (s, 2 H), 7.49 (d, J = 9 Hz, 2 H), 7.80 (d, J = 9 Hz, 2 H); MS $(APCI^+)$ m/z 334 $(M + H)^+$, $(APCI^-)$ m/z 332 $(M - H)^-$, 368 $(M + Cl)^-$.

2-(4-Aminosulfonylphenyl)-6-*tert*-butyl-3-(4-fluorophenyl)pyrazolo[5,1-*b*]oxazole (32). To a solution of **31** (666 mg, 2 mmol) and K_2CO_3 (276 mg, 2 mmol) in DMF (25 mL) at 50 °C was added dropwise bromopinacolone (0.28 mL, 2 mmol) in DMF (5 mL). The mixture was stirred at 50 °C for 30 min and then poured into 10% citric acid and extracted with EtOAc. The extract was concentrated in vacuo to provide 758 mg of crude 5-(4-aminosulfonylphenyl)-4-(4-fluorophenyl)-3-pivaloyl methoxypyrazole, MS $(APCI^+)$ m/z 432 $(M + H)^+$, $(APCI^-)$ m/z 430 $(M - H)^-$, 466 $(M + Cl)$. A mixture of the above *O*-alkylated derivative (216 mg, 0.5 mmol), *p*-TsOH·H_2O (30 mg) in CH_3CO_2H (20 mL), and toluene (80 mL) was refluxed with use of a Dean−Stark trap for 4 h. The mixture was then concentrated in vacuo, The residue was dissolved in EtOAc and washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed (silica gel, 1:1 hexanes−EtOAc) to provide **32** (168 mg, 80%). Mp 196−200 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.50 (s, 9 H), 7.25 (t, J = 9 Hz, 2 H), 7.33 (m, 2 H), 7.43 (s, 2 H), 7.65 (d, J = 9 Hz, 2 H), 7.83 (d, J = 9 Hz, 2 H), 7.95 (s, 1 H); MS $(APCI^+)$ m/z 414 $(M + H)^+$, $(APCI^-)$ m/z 412 $(M - H)^-$, 448 $(M + Cl)^-$. Anal. Calcd for $C_{21}H_{20}FN_3O_3S \cdot 0.25H_2O$: C, 60.34; H, 4.94; N, 10.05. Found: C, 60.47; H, 5.14; N, 9.45.

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Supporting Information Available: Characterization data and procedures for the preparation of compounds **5b**−**d**, **6b**−**e**, **14a**,**b**, **7a**−**c**, **8a**,**b**, **9b**,**c**, **10a**, **10c**−**m**, **16a**−**c**, **11a**, **11c**, **33**, **34**, **35** and CIF files containing complete details supporting the X-ray crystallographic determination of compounds **4**, **5a**, **6b**, **6c**, and **10m**. This material is available free of charge via the Internet at http://pubs.acs.org.

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