Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters 14 (2004) 6049–6052
Bioorganic & Medicinal Chemistry Letters

3-(2-Methoxytetrahydrofuran-2-yl)pyrazoles: a novel class of potent, selective cyclooxygenase-2 (COX-2) inhibitors

Ramani R. Ranatunge,*,† Richard A. Earl, David S. Garvey, David R. Janero, L. Gordon Letts, Allison M. Martino, Madhavi G. Murty, Stewart K. Richardson, David J. Schwalb, Delano V. Young and Irina S. Zemtseva

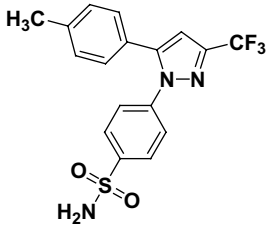
NitroMed Inc., 125 Spring St., Lexington, MA 02421, USA

Received 16 March 2004; revised 22 September 2004; accepted 24 September 2004
Available online 14 October 2004

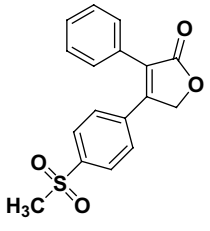
Abstract—A series of 3-(2-methoxytetrahydrofuran-2-yl)pyrazoles (**4**–**10**) was synthesized. The compounds were evaluated for their ability to inhibit cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) activity in human whole blood (HWB). The compound, 5-(4-methanesulfonylphenyl)-3-(2-methoxytetrahydrofuran-2-yl)-1-*p*-tolyl-1H-pyrazole **5** showed potent and selective COX-2 inhibition (IC_{50} for COX-1: >100 μM and COX-2: 1.2 μM).

1. Introduction

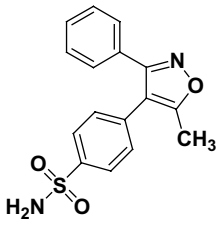
A new generation of anti-inflammatory drugs, celecoxib (Celebrex™),[1] rofecoxib (Vioxx®),[2] and valdecoxib (Bextra®),[3] is being widely prescribed to treat acute or chronic inflammation by providing symptomatic pain relief. The high cyclooxygenase-2 (COX-2) versus cyclooxygenase-1 (COX-1) selectivity demonstrated by these compounds explains their superiority over other NSAIDs in reducing gastrointestinal (GI) side effects.[4,5] However, emerging evidence suggests that adverse reactions such as GI irritation or ulceration and renal liabilities are associated with prolonged use of COX-2 selective inhibitors. These adverse reactions have been attributed, at least in part, to COX-1 inhibition occurring with long-term exposure or at higher doses.[6] COX-2 selective inhibitors are also known to suppress synthesis of prostacyclin, a potent vasodilator, gastroprotectant, and platelet inhibitor, via inhibition of endothelial COX-2. COX-2 selective inhibitors do not inhibit production of thromboxane, a vasoconstrictor, and promoter of platelet aggregation, which is synthesized in platelets by COX-1.[7,8] Therefore, COX-2 selective inhibitors intrinsically lack anti-thrombotic activity, and some cardiovascular liabilities have been associated preclinically with them.[9] Thus, there is still a need for novel, selective, and potent COX-2 inhibitors with an improved profile compared to current COX-2 inhibitors. Here we report the synthesis and COX inhibitory profile of a novel series of pyrazoles (**I**) containing a five-membered cyclic ether, some of which potently and selectively inhibit COX-2.



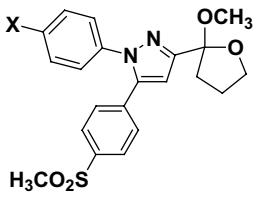
Celecoxib



Rofecoxib



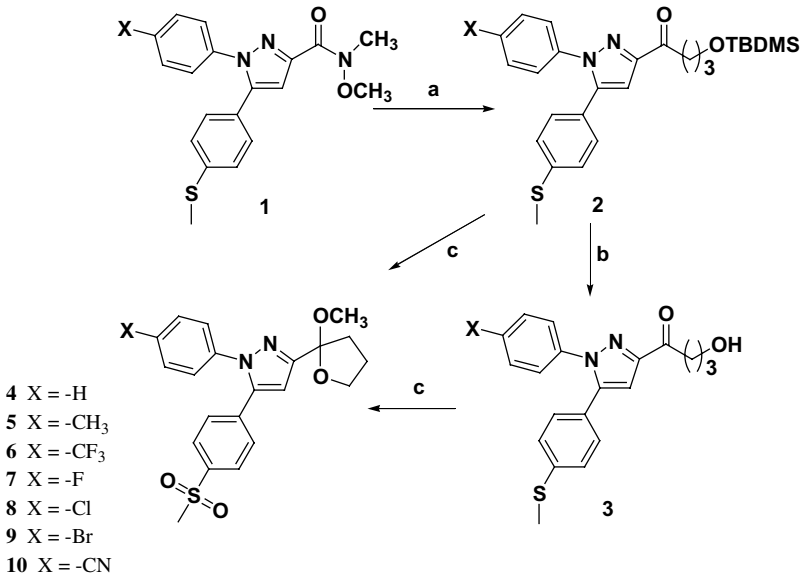
Valdecoxib



I

Keywords: Cyclooxygenase-2 (COX-2); Pyrazole; Tetrahydrofuran-2-yl.
* Corresponding author. Tel.: +1 781 266 4139; fax: +1 781 274 8080; e-mail: ramani@nitromed.com
† Following the senior author, contributors appear in alphabetical order.

0960-894X/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2004.09.073



Scheme 1. Reagents and conditions: (a) $TBDMSO(CH_2)_3MgBr$, THF; (b) TBAF, THF; (c) Oxone, $MeOH/H_2O$, rt.

2. Chemistry

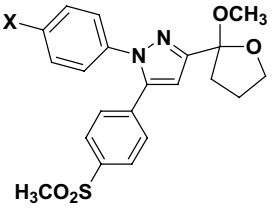
The pyrazole containing COX-2 inhibitor, celecoxib has a 1,5-diaryl substitution pattern as well as a trifluoromethyl group at C-3. Our recent studies suggested that COX-2 selectivity and potency may be enhanced by modifying the C-3 substituent of the central pyrazole ring to incorporate alkyl, alkenyl, ketone, and oxime groups.[10,11] During the course of this work, we observed formation of the cyclic ethers (**4**–**10**) and found that they functioned as COX-2 selective inhibitors.

The synthesis of compounds **4**–**10** was adapted from our earlier work (Scheme 1).[11] Weinreb amides **1** were prepared from the reaction of corresponding methyl esters[11,12] with N,O-dimethylhydroxylamine hydrochloride in the presence of trimethylaluminum.[11,13,14a] The reaction of **1** with the Grignard reagent prepared from (3-bromopropoxy) *tert*-butyldimethylsilane (1 equiv) and magnesium turnings (2.2 equiv) gave **2** in good yield. Deprotection of the TBDMS group with TBAF gave the hydroxyketones **3**. Oxidation of the sulfide (**3**) was accompanied by simultaneous cyclization to give the cyclic acetals **4**–**10**. It has been reported that a solution of Oxone® (1 equiv) is useful for the deprotection of a TBDMS group from alcohols.[15] In our studies, the use of excess Oxone® (3 equiv) promoted the one-pot deprotection, oxidation and cyclization to afford compounds **4**–**10** directly from **2** in good yield (Scheme 1).[16]

3. Biology

The inhibition of the COX-1 and COX-2 isoforms by 3-(2-methoxytetrahydrofuran-2-yl)pyrazole derivatives **4**–**10** in human whole blood (HWB) is presented in Table 1, together with comparative data for celecoxib and rofecoxib.[17–19] As an initial in vitro screen, compounds were assayed against COX-1 at 100 μM and COX-2 at 10 and 1 μM. For the most potent and selective COX-2 inhibitors, the IC_{50}'s were then determined (Table 2).

Table 1. In vitro human whole blood COX-1 and COX-2 inhibition by 1-(2-methoxytetrahydrofuran-2-yl)pyrazole derivatives



Compd	X	% inhibition HWB[a]		
		COX-1	COX-2	
		100 μM	10 μM	1 μM
4	–H	20	65	30
5	$–CH_3$	55	90	55
6	$–CF_3$	50	70	25
7	–F	25	75	40
8	–Cl	60	80	25
9	–Br	72	84	13
10	–CN	0	25	30
	Celecoxib	65[b]	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 (HWB). Average percent inhibition using blood from two donors. Assays were performed on duplicate blood samples, each of which was assayed in duplicate by enzyme-linked immunoassay (EIA), as described in Refs. 11, 17–19.

[b] COX-1 inhibition at 30 μM celecoxib.

In general, lipophilic or electron-rich substituents (**4**–**7**) were preferred at the C4 phenyl ring over electron deficient ones (**8**–**10**). Thus, the presence of a 4-chloro or 4-bromo substituent increased COX-1 inhibition and weakened COX-2 inhibition at the lower screening concentration (1 μM). In the presence of a cyano group (**10**),

Table 2. IC_{50} for 1-(2-methoxytetrahydrofuran-2-yl)pyrazole derivative **5**

Compound	IC_{50} (μM)	
	COX-1	COX-2
Celecoxib	14	1.2
Rofecoxib	40	0.3
5	>100[a]	1.2[a]

[a] Average of three blood donors.

COX-1 inhibitory activity was abrogated, and the potency for COX-2 was reduced with no difference at the two screening concentrations. The unsubstituted (**4**), trifluoromethyl- (**6**) and fluoro-substituted (**7**) compounds showed less COX-1 and COX-2 inhibition than celecoxib. The best substituent found on C-4 of the phenyl ring, a C-4 methyl is not particularly surprising or unexpected since it is also found in celecoxib at the 5-position of the central pyrazole ring. Thus, the most potent and selective COX-2 inhibitor was the 4-methyl substituted derivative (**5**), with activity (IC_{50}'s for COX-1: >100 μM and COX-2 = 1.2 μM in HWB) comparable to celecoxib and rofecoxib (Table 2).

In summary, we have prepared a series of novel 3-(2-methoxytetrahydrofuran-2-yl)pyrazole COX-2 inhibitors, from which compound **5** was identified as a highly selective and potent COX-2 inhibitor with IC_{50}'s for COX-1: >100 μM and COX-2 = 1.2 μM in HWB (Table 2). The reported identification of **5** invites further exploration of cyclic substituents at C3 of the pyrazole-containing COX-2 selective inhibitors, an area which so far has received very little attention.

Acknowledgements

The authors wish to thank Dr. Radha Iyengar for helpful comments and suggestions.

References and notes

1. 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*, 1347–1365.
2. Prasit, P.; Wang, Z.; Brideau, C.; Chan, C.-C.; Charleson, S.; Cromlish, W.; Ethier, D.; Evans, J. F.; Ford-Hutchinson, A. W.; Gauthier, J. Y.; Gordon, R.; Guay, J.; Gresser, M.; Kargman, S.; Kennedy, B.; Leblanc, Y.; Leger, S.; Mancini, J.; O'Neill, G. P.; Ouellet, M.; Percival, M. D.; Perrier, H.; Riendeau, D.; Rodger, I.; Tagari, P.; Therien, M.; Vikers, P.; Wong, E.; Xu, L.-J.; Young, R. N.; Zamboni, R.; Boyce, S.; Rupniak, N.; Forrest, M.; Visco, D.; Patrick, D. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1773–1778.
3. Talley, J. J.; Brown, D. L.; Carter, J. S.; Graneto, M. J.; Koboldt, C. M.; Masferrer, J. L.; Perkins, W. E.; Rogers, R. S.; Shaffer, A. F.; Zhang, Y. Y.; Zweifel, B. S.; Seibert, K. *J. Med. Chem.* **2000**, *43*, 775–777.
4. Jackson, L. M.; Hawkey, C. J. *Exp. Opin. Invest. Drugs* **1999**, *8*, 963–971.
5. Meyer-Kirchrath, J.; Schror, K. *Curr. Med. Chem.* **2000**, *7*, 1121–1129.
6. Wolfe, M. M.; Lichtenstein, D. R.; Singh, G. *N. Engl. J. Med.* **1999**, *340*, 1888–1899.
7. Catella-Lawson, F.; Crofford, L. J. *Am. J. Med.* **2001**, *110*, 28S–32S.
8. Mukherjee, D.; Nissen, S. E.; Topol, E. J. *JAMA* **2001**, *286*, 954–959.
9. de Gaetano, G.; Donati, M. B.; Cerletti, C. *Trends Pharm. Sci.* **2003**, *24*, 245–246.
10. Bandarage, R. R.; Augustyniak, M. E.; Bandarage, U. K.; Cochran, E. D.; Earl, R. A.; Garvey, D. S.; Janero, D. R.; Letts, L. G.; Marek, P.; Martino, A. M.; Murty, M. G.; Richardson, S. K.; Schroeder, J. D.; Shumway, M. J.; Tam, S. W.; Trocha, A. M.; Young, D. V. #314, 224th ACS National Meeting, Boston, MA, August 18–22, 2002.
11. Ranatunge, R. R.; Augustyniak, M. E.; Bandarage, U. K.; Earl, R. A.; Ellis, J. L.; Garvey, D. S.; Janero, D. R.; Letts, L. G.; Martino, A. M.; Murty, M. G.; Richardson, S. K.; Schroeder, J. D.; Shumway, M. J.; Tam, S. W.; Trocha, A. M.; Young, D. V. *J. Med. Chem.* **2004**, *47*, 2180–2193.
12. Kiyoshi, K.; Nobukiyo, S.; Ogino, T.; Nakamura, K.; Tojo, T.; Ochi, T.; Shimojo, F.; Senoh, H.; Matsuo, M. *Chem. Pharm. Bull.* **1997**, *45*, 1475–1481.
13. Shimizu, T.; Osako, K.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 2685–2688.
14. (a) Nemoto, H.; Nagamochi, M.; Ishibashi, H.; Fukumoto, K. *J. Org. Chem.* **1994**, *59*, 74–79; (b) Handrick, G. R.; Atkinson, E. R. *Tetrahedron Lett.* **1981**, *22*, 3815.
15. Sabitha, G.; Syamala, M.; Yadav, J. S. *Org. Lett.* **1999**, *1*, 1701–1703.
16. Spectral data for compounds **4**–**10**.
5-(4-Methanesulfonylphenyl)-3-(2-methoxytetrahydrofuran-2-yl)-1-phenyl-1H-pyrazole (**4**). White solid. Yield 71%. Mp 63–66 °C. ^{1}H NMR δ 7.86 (d, J = 8.4 Hz, 2H), 7.22–7.51 (m, 7H), 6.67 (s, 1H), 4.00–4.28 (m, 2H), 3.27 (s, 3H), 3.06 (s, 3H), 2.32–2.58 (m, 1H), 1.95–2.32 (m, 3H). ^{13}C NMR δ 153.5, 141.5, 140.0, 139.6, 135.8, 129.3, 129.2, 128.2, 127.6, 125.7, 107.5, 106.5, 68.2, 50.1, 44.5, 38.7, 24.4. MS m/z 367 (M−OCH_3), 457 (M+OAc). Anal. Calcd ($C_{21}H_{22}N_2O_4S$): C, 63.30; H, 5.56; N, 7.03. Found: C, 63.27; H, 5.42; N, 6.80.
5-(4-Methanesulfonylphenyl)-3-(2-methoxytetrahydrofuran-2-yl)-1-*p*-tolyl-1H-pyrazole (**5**). White foam. Yield 65%. Mp 65–68 °C. ^{1}H NMR δ 7.85 (d, J = 8.5 Hz, 2H), 7.41 (dd, J = 1.8 and 6.8 Hz, 2H), 7.12–7.19 (m, 4H), 6.45 (s, 1H), 4.02–4.21 (m, 2H), 3.27 (s, 3H), 3.06 (s, 3H), 2.40–2.50 (m, 1H), 2.37 (s, 3H), 2.12–2.28 (m, 2H), 1.97–2.12 (m, 1H). ^{13}C NMR δ 153.2, 141.4, 139.8, 138.2, 137.1, 135.9, 129.8, 129.3, 127.6, 125.6, 107.2, 106.5, 68.1, 50.0, 44.4, 38.7, 24.4, 21.3. MS m/z 381 (M−OCH_3). Anal. Calcd ($C_{22}H_{24}N_2O_4S$): C, 64.06; H, 5.86; N, 6.79. Found: C, 64.33; H, 6.03; N, 6.51.
5-(4-Methanesulfonylphenyl)-3-(2-methoxytetrahydrofuran-2-yl)-1-(4-trifluoromethyl-phenyl)-1H-pyrazole (**6**). White solid. Yield 78%. Mp 120–123 °C. ^{1}H NMR δ 7.94 (d, J = 8.3 Hz, 2H), 7.64 (d, J = 8.6 Hz, 2H), 7.40–7.51 (m, 4H), 6.71 (s, 1H), 4.03–4.28 (m, 2H), 3.29 (s, 3H), 3.11 (s, 3H), 2.40–2.55 (m, 1H), 1.95–2.30 (m, 3H). ^{13}C NMR δ 154.5, 142.3, 141.9, 140.6, 135.5, 130.0 (J_{C-F} = 33.2), 129.5, 128.0, 126.5, 125.5, 122.0, 108.7, 106.4, 68.4, 50.2, 44.5, 38.8, 24.5. MS m/z 467 (MH^+), 489 (MNa^+), 435 (M−OCH_3). Anal. Calcd ($C_{22}H_{21}F_3N_2O_4S$): C, 56.65; H, 4.54; N, 6.01; F, 12.22; S, 6.87. Found: C, 56.46; H, 4.50; N, 5.83; F, 11.98; S, 6.69.

1-(4-Fluoro-phenyl)-5-(4-methanesulfonylphenyl)-3-(2-methoxytetrahydrofuran-2-yl)-1H-pyrazole (**7**). White foam. Yield 69%. ^{1}H NMR δ 7.88 (dd, J = 1.8 and 6.7 Hz, 2H), 7.42 (dd, J = 1.8 and 8.6 Hz, 2H), 7.24–7.34 (m, 2H), 7.04–7.15 (m, 2H), 6.66 (s, 1H), 4.08–4.50 (m, 2H), 3.27 (s, 3H), 3.07 (s, 3H), 2.35–2.51 (m, 1H), 1.91–2.58 (m, 3H). ^{13}C NMR δ 163.6, 160.3, 153.6, 141.6, 140.1, 135.7, 129.2, 127.7, 116.3, 116.0, 107.5, 106.4, 68.2, 50.0, 44.4, 38.7, 24.3. MS m/z 385 ($M-OCH_3$). Anal. Calcd ($C_{21}H_{21}FN_2O_4S$): C, 60.56; H, 5.08; N, 6.73. Found: C, 60.61; H,5.12; N, 6.45.

1-(4-Chloro-phenyl)-5-(4-methanesulfonylphenyl)-3-(2-methoxytetrahydrofuran-2-yl)-1H-pyrazole (**8**). White foam. Yield 65%. Mp 65–68 °C. ^{1}H NMR δ 7.91 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 7.18–7.37 (m, 4H), 6.68 (s, 1H), 4.00–4.22 (m, 2H), 3.27 (s, 3H), 3.09 (s, 3H), 2.30–2.52 (m, 1H), 1.98–2.30 (m, 3H). ^{13}C NMR δ 153.9, 141.6, 140.3, 138.1, 135.6, 133.9, 129.43, 129.39, 127.8, 126.8, 107.9, 106.4, 68.3, 50.1, 44.5, 38.8, 24.4. MS m/z 401 ($M-OCH_3$), 491 (M+OAc). Anal. Calcd ($C_{21}H_{21}ClN_2O_4S$): C, 58.26; H, 4.89; N, 6.47, S, 7.41; Cl, 8.19. Found: C, 58.03; H, 4.90; N, 6.20; S, 7.11; Cl, 8.10.

1-(4-Bromo-phenyl)-5-(4-methanesulfonylphenyl)-3-(2-methoxytetrahydrofuran-2-yl)-1H-pyrazole (**9**). White solid. Yield 76%. Mp 68–70 °C. ^{1}H NMR δ 7.90 (d, J = 8.4 Hz, 2H), 7.31–7.53 (m, 4H), 7.18 (dd, J = 1.9 and 6.7 Hz, 2H), 6.66 (s, 1H), 4.00–4.25 (m, 2H), 3.27 (s, 3H), 3.08 (s, 3H), 2.32–2.50 (m, 1H), 2.10–2.30 (m, 2H), 1.92–2.10 (m, 1H). ^{13}C NMR δ 154.0, 141.6, 140.3, 138.6, 135.6, 132.4, 129.4, 127.8, 127.1, 121.9, 108.0, 106.4, 68.3, 50.1, 44.5, 38.8, 24.4. MS m/z 445/447 ($M-OCH_3$), 535/537 (M+OAc). Anal. Calcd ($C_{21}H_{21}BrN_2O_4S1/4$ mol H_2O): C, 52.34; H, 4.50; N, 5.81. Found: C, 52.48; H, 4.54; N, 5.42.

4-[5-(4-Methanesulfonylphenyl)-3-(2-methoxytetrahydrofuran-2-yl)-pyrazol-1-yl]-benzecarbonitrile (**10**). White solid. Yield 65%. Mp 148–150 °C. ^{1}H NMR δ 7.94 (d, J = 8.2 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 7.40–7.48 (m, 4H), 6.69 (s, 1H), 4.00–4.20 (m, 2H), 3.27 (s, 3H), 3.10 (s, 3H), 2.40–2.52 (m, 1H), 2.00–2.30 (m, 3H).^{13}C NMR δ 155.0, 142.9, 141.9, 140.9, 135.4, 133.3, 129.5, 128.1, 125.6, 118.1, 111.5, 109.2, 106.3, 68.4, 50.2, 44.5, 38.8, 24.4. MS m/z 392 ($M-OCH_3$). Anal. Calcd ($C_{22}H_{21}N_3O_4S$): C, 62.40; H, 5.00; N, 9.92. Found: C, 62.19; H, 4.83; N, 9.76.

17. Young, J. M.; Panah, S.; Satchawatcharaphong, C.; Cheung, P. S. *Inflamm. Res.* **1996**, *45*, 246–253.
18. Glaser, K.; Sung, M. L.; O'Neill, K.; Belfast, M.; Hartman, D.; Carlson, R.; Kreft, A.; Kubrak, D.; Hsiao, C. L.; Weichman, B. *Eur. J. Pharmacol.* **1995**, *281*, 107–109.
19. Ranatunge, R. R.; Garvey, D. S.; Janero, D. R.; Letts, L. G.; Martino, A. M.; Murty, M. G.; Richardson, S. K.; Young, D. V.; Zemtseva, I. S. *Bioorg. Med. Chem.* **2004**, *12*, 1357–1366.