Bioorganic & Medicinal Chemistry Letters 22 (2012) 2235–2238

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Novel 5-substituted 1*H*-tetrazoles as cyclooxygenase-2 (COX-2) inhibitors

Baker Jawabrah Al-Hourani [a,c], Sai Kiran Sharma [a,b], Mavanur Suresh [b], Frank Wuest [a,b,*]

[a] Department of Oncology, University of Alberta, Edmonton, Canada
[b] Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Canada
[c] Department of Chemistry, Faculty of Science, American University of Madaba, Madaba, Jordan

ARTICLE INFO

Article history:
Received 14 December 2011
Revised 22 January 2012
Accepted 24 January 2012
Available online 2 February 2012

Keywords:
Cyclooxygenase
COX-2 inhibitors
5-Substituted 1*H*-tetrazoles

ABSTRACT

A series of novel 5-substituted 1*H*-tetrazoles as cyclooxygenase-2 (COX-2) inhibitors was prepared via treatment of various diaryl amides with tetrachlorosilane/sodium azide. All compounds were tested in cyclooxygenase (COX) assays in vitro to determine COX-1 and COX-2 inhibitory potency and selectivity. Tetrazoles contained a methylsulfonyl or sulfonamide group as COX-2 pharmacophore displayed only low inhibitory potency towards COX-2. Most potent compounds showed IC_{50} values of 6 and 7 μM for COX-2. All compounds showed IC_{50} values greater 100 μM for COX-1 inhibition.

Cyclooxygenases (COXs) are involved in the complex conversion of arachidonic acid to various prostanoids like prostaglandins, prostacyclin and thromboxanes.[1–3] As signaling molecules, prostanoids trigger as autocrine and paracrine chemical messengers many physiological and pathophysiological events. COX is a membrane-bound heme protein which exists in two distinct isoforms, a constitutive form (COX-1) and an inducible form (COX-2). More recently, a novel COX-1 splice variant termed as COX-3 has been reported.[4]

The X-ray crystal structures of both enzymes suggest that the proteins are very similar in their tertiary conformation.[5,6] The amino acids which constitute the substrate binding pocket and catalytic site are nearly identical in both enzymes. The COX-1 enzyme is expressed in resting cells of most tissues, functions as a housekeeping enzyme, and is responsible for maintaining homeostasis (gastric and renal integrity) and normal production of prostaglandins. COX-2 is predominantly found in brain, kidney and endothelial cells while being virtually absent in most other tissues. However, COX-2 is induced by mitogenic and inflammatory stimuli resulting in an enhanced prostaglandin synthesis in neoplastic and inflamed tissue.

Since the discovery of the COX-2 enzyme in the early 1990s, many efforts have been made in the development of COX-2 selective inhibitors. A common structural feature of many selective COX-2 inhibitors is the presence of two vicinal aryl rings containing a sulfonamide or methylsulfonyl pharmacophore attached to a central 5-membered heterocyclic or carbocyclic motif. Recent reviews on the current status of COX-2 inhibitors further confirm the flexibility of the carbocyclic/heterocyclic core motif upon COX-2 binding.[7]

Recently, we have described various 1,5-diaryl substituted tetrazoles containing a 4-(methylsulfonyl)phenyl substituent attached to position 1 of the tetrazole ring as novel class of COX-2 inhibitors. All compounds studied displayed only weak COX-2 inhibitory potency in the micromolar range.[8] This finding is consistent with recently reported 1,5-diaryl substituted tetrazoles containing a 3,4-difluorophenyl motif displaying IC_{50} values of >30 μM for COX-2 inhibitory potency.[9]

However, a docking study involving our most potent tetrazole containing a 4-(methylsulfonyl)phenyl substitutent attached to position 1 suggests the flexibility of the COX-2 binding pocket to accommodate 1,5-diaryl-substituted tetrazoles with reversed substitution pattern of the vicinal aryl rings.[8] Therefore, in this work we describe the synthesis and in vitro COX-1 and COX-2 inhibitory activity evaluation of a series of 1,5-diaryl-substituted tetrazoles containing a benzene sulfonamide or 4-(methylsulfonyl)phenyl moiety attached to position 5 of the tetrazole ring. Vicinal aryl groups contain a broad variety of different functional groups to study their steric and electronic effects upon COX-1 and COX-2 binding.

Whereas 5-substituted 1*H* tetrazoles have found numerous applications in medicinal chemistry as carboxylic acid isostere, considerably less use of 1,5-disubstituted tetrazoles has been reported in the literature. Several reports describe the use of 1,5-disubstituted tetrazoles as isosters of the *cis*-amide bond in peptides. It was shown that the tetrazole-containing compounds adopt almost the same conformation as the original peptide, and prominent examples involve α-methylene tetrazole-based peptidomimics as HIV-protease inhibitors.[10] Other 1,5-disub-stituted tetrazoles have

* Corresponding author.
E-mail address: wuest@ualberta.ca (F. Wuest).

0960-894X/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2012.01.093

been described in recent patent literature such as glucokinase activators,[11] NAD(P)H oxidase inhibitors,[12] anti-migraine agents,[13] and hepatitis C virus serine protease NS3 inhibitors.[14]

Likewise, many different preparative methods for 1,5-disubstituted tetrazoles have been developed. Popular and frequently used methods consist of (1) reactions of imidoyl chlorides with various azide sources,[15,16] (2) reactions of oximes, nitriles and nitrilium triflates with azides,[17] and (3) reactions of amidrazones with dinitrogen tetroxide or nitrous acid. Other methods involve various alkylation reactions of 5-substituted tetrazoles.[18]

Synthesis of 1,5-diaryl-substituted tetrazoles usually involves conversion of various aryl-benzamides into corresponding imidoyl chlorides using $SOCl_2$ or PCl_5 followed by treatment with azide. For the synthesis of our new set of 1,5-disubstituted tetrazoles we envisaged a novel approach based upon the tetrachlorosilane/sodium azide system. Tetrachlorosilane reacts with sodium azide in acetonitrile to form an equilibrated mixture of chloroazidosilanes according to the molar ratio of added sodium azide.[19] Treatment of various aryl benzamides with tetrachlorosilane/sodium azide furnished the desired 1,5-diaryl-substituted tetrazoles in high yield. The synthesis of 1,5-diaryl-substituted tetrazoles is depicted in Figure 1.

The synthesis of 5-aryl-1*H*-tetrazol-1-yl-benzenesulfonamides **4a–h** and 1-(4-(methylsulfonyl)-phenyl)-5-aryl-1*H*-tetrazoles **5a–h** commenced with the conversion of commercially available *para*-substituted benzoic acids **1a–h** (R = H, Me, OMe, F, Cl, CF_3, NO_2, and NMe_2) into amides **2a–h** and **3a–h** through treatment of **1a–h** with 1,1′-carbonyldiimidazole (CDI) to form the corresponding imidazolide derivatives in situ. Imidazolide formation can easily be monitored by the evolution of CO_2, which is the driving force of the reaction. Subsequent reaction of imidazolide intermediates with 4-(aminosulfonyl)aniline and 4-(methylthio)benzenamine afforded desired amides **2a–h** and **3a–h** in moderate chemical yields of 35–50% in the case of compounds **2a–h** and high chemical yields of 90–97% for compounds **3a–h**. Amides **2a–h** and **3a–h** were dissolved in dry THF and treated with tetrachlorosilane/sodium azide in a sealed vial at 90 °C to afford tetrazoles **4a–h** and **5a–h** in quantitative yields. To the best of our knowledge this is the first example of a synthesis of 1,5-diaryl-substituted tetrazoles starting from aryl-benzamides and treatment with tetrachlorosilane/sodium azide. The described reaction is very simple and high yielding compared to previously reported methods involving treatment of aryl-benzamides with $SOCl_2$ and PCl_5 to form corresponding imidoyl chlorides as intermediates followed by reaction with an azide source. Subsequent oxidation of tetrazoles **5a–h** with oxone® gave tetrazoles **6a–h** also in quantitative yield. All tetrazoles were obtained as readily crystalline compounds, which were fully characterized using ^1H NMR, ^{13}C NMR and high resolution mass spectrometry.[20]

Tetrazoles **4a–h** and **6a–h** were evaluated in a fluorescence-based COX assay to determine the different steric and electronic effects upon COX-1 and COX-2 inhibitory potency and selectivity.[21] The determined COX-1 and COX-2 inhibitory data, and calculated lipophilicity values ($Log P_{o/w}$) are summarized in Table 1.

All tetrazoles possess a tricyclic scaffold containing a central heterocyclic ring system with two vicinal aryl substituents as typically found in many selective and potent COX-2 inhibitors. One series (**4a–h**) contains a sulfonamide (SO_2NH_2) group, the other series of tetrazoles (**6a–h**) contains a methylsulfonyl (SO_2Me) group. Both groups were shown in numerous examples to be important pharmacophores to confer COX-2 selectivity and potency. Potent and selective COX-2 inhibitor celecoxib was used as reference compound in the COX assay.

Both series of 1,5-disubstituted tetrazoles displayed comparable inhibitory potencies in the micromolar range as observed with our previously reported tetrazoles possessing a reversed attachment of the aryl rings to the tetrazole ring. In our enzyme inhibitory assay, celecoxib showed high COX-2 inhibitory potency and selectivity with IC_{50} values of 0.06 μM for COX-2 and 10.0 μM for COX-1, which is in agreement with previously reported data in the literature. All prepared tetrazoles did not inhibit binding to COX-1 in the concentration range (10^{-9} to 10^{-4} M) studied.

Compounds containing a SO_2Me group displayed slightly higher COX-2 inhibitory potency compared to their respective counterparts possessing a sulfonamide group. This is somewhat in contrast to previous reports where COX-2 inhibitors containing a SO_2NH_2 pharmocophore showed more COX-2 inhibitory potency as their SO_2Me pharmacophore-containing counterparts.

However, inhibitory potency of all tested compounds is much lower compared to reference compound celecoxib, displaying IC_{50} values ranging from 6.0 μM to greater 100 μM. Compounds containing a OMe and a CF_3 group did not show inhibitory potency within the used concentration range (10^{-9} to 10^{-4} M) of the COX inhibition assay. The determined IC_{50} values for COX-2 inhibition were greater than 100 μM for compounds **4c**, **4f**, **6c**, and **6f**. Methyl and nitro group-containing compounds **4b** and **4g** from the sulfonamide series also displayed no inhibitory potency for COX-2 as indicated by the determined IC_{50} value of greater 100 μM. Highest COX-2 inhibitory potency was found for compounds **4h** and **6h** possessing a NMe_2 group in both series. The determined IC_{50} values were 7 μM

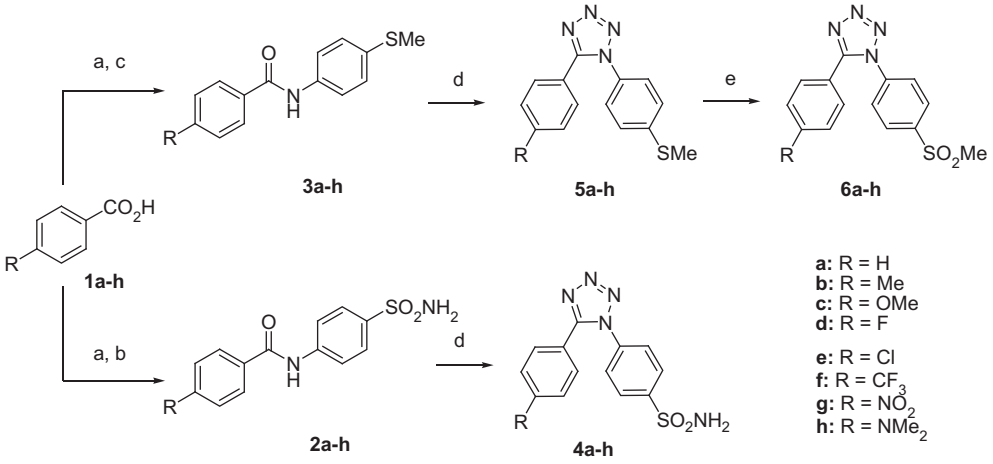

Figure 1. Reagents: (a) CDI, THF; (b) 4-(aminosulfonyl)aniline; (c) 4-(methylthio)benzenamine; (d) $SiCl_4/NaN_3$, CH_3CN, 90 °C, 1 d; (e) oxone®/acetone/MeOH/H_2O, 3 h, r.t.

Table 1
COX enzyme inhibitory data of tetrazoles **4a–h** and **6a–h**

Compound	R	IC_{50}[a] (μM)		$Log P_{o/w}$[b]
		COX-1	**COX-2**	
Celecoxib		10.0	0.06	3.0
4a	H	>100	15	1.70
4b	Me	>100	>100	2.16
4c	OMe	>100	>100	1.86
4d	F	>100	56	1.92
4e	Cl	>100	62	2.46
4f	CF_3	>100	>100	2.67
4g	NO_2	>100	>100	1.66
4h	NMe_2	>100	7	2.12
6a[19]	H	>100	30	1.87
6b	Me	>100	87	2.33
6c	OMe	>100	>100	2.04
6d	F	>100	15	2.09
6e	Cl	>100	32	2.64
6f	CF_3	>100	>100	2.84
6g	NO_2	>100	69	1.83
6h	NMe_2	>100	6	2.29

[a] Values are means of two determinations.
[b] $Log P_{o/w}$ values have been calculated based on Molinspiration program predictions (http://www.molinspiration.com/cgi-bin/properties).

(**4h**) and 6 μM (**6h**), respectively. All compounds have lower lipophilicities ($log P$) values compared to reference compound celecoxib.

The obtained results on COX-2 inhibitory potency and selectivity in this series of tetrazoles and our previously reported 1,5-diaryl-substituted tetrazoles suggest that the central tetrazole motif is not a suitable structural scaffold for the design of COX-2 inhibitors. The introduction of a polar tetrazole moiety into the COX-2 binding pocket seems to be detrimental as demonstrated by the very weak inhibitory potency. Most highly potent selective COX-2 inhibitors possess a lipophilic substituents at the central heterocyclic core structure like a CF_3, CH_3 or Br group as demonstrated for celecoxib (CF_3 group), valdecoxib (CH_3 group), and DuP-697 (Br group), respectively.

In summary, we have prepared and evaluated a series of 1,5-diaryl-substituted tetrazoles with reversed substitution pattern of the vicinal aryl rings as described in our previous work. All compounds displayed much lower COX-2 inhibitory potency compared to celecoxib and other previously reported COX-2 inhibitors displaying a lipophilic substituent at the central heterocycle of the molecular scaffold. We have described a novel and convenient synthesis route for the preparation of 1,5-diaryl substituted tetrazoles using the tetrachlorosilane/sodium azide system. This approach afforded tetrazoles **4a–h** and **6a–h** very high yields starting from the corresponding diarylamides.

Acknowledgments

F.W. thanks the Dianne and Irving Kipnes Foundation and the Canadian Institute for Health Research (CIHR) for supporting this work.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2012.01.093.

References and notes

1. Kurumbail, R. G.; Kiefer, J. R.; Marnett, L. J. *Curr. Opin. Struct. Biol.* **2001**, *11*, 752.
2. Marnett, L. J. *Curr. Opin. Chem. Biol.* **2000**, *4*, 545.
3. Fitzpatrick, F. A. *Curr. Pharm. Des.* **2004**, *10*, 577.
4. Wang, M. T.; Honn, K. V.; Nie, D. *Cancer Metastasis Rev.* **2007**, *26*, 525.
5. Xu, X. C. *Anticancer Drugs* **2002**, *13*, 127.
6. Jiménez, P.; García, A.; Santander, S.; Piazuelo, E. *Curr. Pharm. Des.* **2007**, *13*, 2261.
7. (a) Ramalho, T. C.; Rocha, M. V.; da Cunha, E. F.; Freitas, M. P. *Expert Opin. Ther. Patents* **2009**, *19*, 1193; (b) Jawabrah Al-Hourani, B.; Sharma, S. K.; Suresh, M.; Wuest, F. *Expert Opin. Ther. Pat.* **2011**, *21*, 1339.
8. Jawabrah Al-Hourani, B.; Sharma, S. K.; Mane, J. Y.; Tuszynski, J.; Baracos, V.; Kniess, T.; Suresh, M.; Pietzsch, J.; Wuest, F. *Bioorg. Med. Chem. Lett.* **1823**, *2011*, 21.
9. Gauthier, J. Y.; Leblanc, Y.; Black, W. C.; Chan, C.-C.; Cromlish, W. A.; Gordon, R.; Kennedey, B. P.; Lau, C. K.; Léger, S.; Wang, Z.; Ethier, D.; Guay, J.; Mancini, J.; Riendeau, D.; Tagari, P.; Vickers, P.; Wong, E.; Xu, L.; Prasit, P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 87.
10. May, B. C.; Abell, A. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 172.
11. Nonoshita, K.; Ogino, Y.; Ishikawa, M.; Sakai, F.; Nakashima, H.; Nagae, Y.; Tsukahara, D.; Arakawa, K.; Nishimura, T.; Eiki, J. PCT Int. Appl. WO 2004-JP19843, 2005; Chem. Abstr. **2005**, *143*, 153371.
12. Seki, M.; Tarao, Y.; Yamada, K.; Nakao, A.; Usui, Y.; Komatsu, Y. PCT Int. Appl. WO 2005-JP2974, 2005; Chem. Abstr. 2005, 143, 266938.
13. Luo, G.; Chen, L.; Degnan, A. P.; Dubowchik, G. M.; Macor, J. E.; Tora, G. O.; Chaturvedula, P. V. PCT Int. Appl. WO 2004-US40721, 2005;Chem. Abstr. **2005**, *143*, 78091.
14. Miao, Z.; Sun, Y.; Nakajima, S.; Tang, D.; Wu, F.; Xu, G.; Or, Y. S.; Wang, Z. U.S. Pat. Appl. Publ. US 2005153877, 2005; Chem. Abstr. **2005**, *143*, 153709.
15. Artamonova, T. V.; Zhivich, A. B.; Dubinskii, M. Y.; Koldobskii, G. I. *Synthesis* **1996**, 1428.
16. Kennedy, L. J. *Tetrahedron Lett.* **2010**, *2010*, 51.
17. (a) Butler, R. N.; O'Donoghue, D. A. *J. Chem. Res. Synop.* **1983**, 18; (b) Ueyama, N.; Yanagisawa, T.; Kawai, T.; Sonegawa, M.; Baba, H.; Mochizuki, S.; Kosakai, K.; Tomiyama, T. *Chem. Pharm. Bull.* **1841**, *1994*, 42; (c) Amer, M. I. K.; Booth, B. L. *Chem. Res. Synop.* **1993**, 4.
18. Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028.
19. *1-(4-(Aminosulfonyl)phenyl)-5-phenyl-1H-tetrazole (**4a**).* Mp: 233.6 °C. ^{1}H NMR (DMSO-d_6) δ 8.01 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.58–7.49 (m, 5H), 7.59 (s, 2H, SO_2NH_2); ^{13}C NMR (DMSO-d_6) δ 153.7 (C_5-tetrazole), 145.7 (NH_2SO_2-Ph_p), 136.3 (NH_2SO_2-Ph_i), 131.3, 128.96, 128.93, 127.2, 126.5, 123.1; HRMS (m/z) [M+H]$^+$ calcd for $C_{13}H_{12}N_5O_2S$, 302.0706; found 302.0704.
*1-(4-(Aminosulfonyl)phenyl)-5-p-tolyl-1H-tetrazole (**4b**).* Mp: 218 °C. ^{1}H NMR (DMSO-d_6) δ 8.01 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 7.8 Hz, 2H), 7.59 (s, 2H, SO_2NH_2), 7.42 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 7.8 Hz, 2H), 2.35 (s, 3H, Me); ^{13}C NMR (DMSO-d_6) δ 153.7 (C_5-tetrazole), 145.6 (NH_2SO_2-Ph_p), 141.4 (Me-Ph_p), 136.4 (NH_2SO_2-Ph_i), 129.5, 128.8, 127.2, 126.4, 120.2, 20.9; HRMS (m/z) [M+H]$^+$ calcd for $C_{14}H_{14}N_5O_2S$, 316.0863; found 316.0862.
*1-(4-(Aminosulfonyl)phenyl)-5-(4-methoxyphenyl)-1H-tetrazole (**4c**).* Mp: 235 °C. ^{1}H NMR (DMSO-d_6) δ 8.01 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.4 Hz, 2H), 7.61 (s, 2H, SO_2NH_2) 7.48 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 3.79 (s, 3H, OMe); ^{13}C NMR (DMSO-d_6) δ 161.4 (MeO-Ph_p), 153.5 (C_5-tetrazole), 145.6 (NH_2SO_2-Ph_p), 136.6 (NH_2SO_2-Ph_i), 130.5, 127.2, 126.5, 114.9, 114.5, 55.4; HRMS (m/z) [M+H]$^+$ calcd for $C_{14}H_{14}N_5O_3S$, 332.0812; found 332.0813.
*1-(4-(Aminosulfonyl)phenyl)-5-(4-fluorophenyl)-1H-tetrazole (**4d**).* Mp: 239.9 °C. ^{1}H NMR (DMSO-d_6) δ 8.01 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.4 Hz, 2H), 7.62 (dd, $J_{H,H}$ = 8.4 Hz, $^4J_{F,H}$ = 5.1 Hz, 2H), 7.60 (s, 2H, SO_2NH_2), 7.38 (dd, $J_{H,H}$ = 8.4 Hz, $^3J_{F,H}$ = 8.4 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 163.6 (d, $^1J_{F,C}$ = 248.3 Hz), 153.0 (C_5-tetrazole), 145.5 (NH_2SO_2-Ph_p), 136.2 (NH_2SO_2-Ph_i), 131.7 (d, $^3J_{F,C}$ = 9.3 Hz), 127.2, 126.4, 119.7 (d, $^4J_{F,C}$ = 3.6 Hz), 116.2 (d, $^2J_{F,C}$ = 21.8 Hz); ^{19}F NMR (DMSO-d_6) [reference- trifluorotoluene in C_6D_6] δ –109.05 (m, F); HRMS (m/z) [M+H]$^+$ calcd for $C_{13}H_{11}FN_5O_2S$, 320.0612; found 320.0611.
*1-(4-(Aminosulfonyl)phenyl)-5-(4-chlorophenyl)-1H-tetrazole (**4e**).* Mp: 271.2 °C. ^{1}H NMR (DMSO-d_6) δ 8.01 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.59 (s, 2H, SO_2NH_2), 7.56 (d, J = 8.4 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 152.9 (C_5-tetrazole), 145.6 (NH_2SO_2-Ph_p), 136.3 (NH_2SO_2-Ph_i), 136.1 (Cl-Ph_p), 130.8, 129.1, 127.2, 126.4, 122.1; HRMS (m/z) [M+H]$^+$ calcd for $C_{13}H_{11}ClN_5O_2S$, 336.0316; found 336.0316.
*1-(4-(Aminosulfonyl)phenyl)-5-(4-trifluoromethylphenyl)-1H-tetrazole (**4f**).* Mp: 210.5 °C. ^{1}H NMR (DMSO-d_6) δ 8.01 (d, J = 8.4 Hz, 2H), 7.91 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H), 7.59 (s, 2H, SO_2NH_2); ^{13}C NMR (DMSO-d_6) δ 152.8 (C_5-tetrazole), 145.7 (NH_2SO_2-Ph_p), 136.0 (NH_2SO_2-Ph_i), 131.2 (q, $^2J_{F,C}$ = 32.3 Hz) (CF_3-Ph_p), 130.1, 127.4, 127.3, 126.4, 125.9 (q, $^3J_{F,C}$ = 3.8 Hz), 123.6 (q, $^1J_{F,C}$ = 271.2 Hz); ^{19}F NMR (DMSO-d_6) [reference-trifluorotoluene in C_6D_6] δ –62.33 (s, CF_3); HRMS (m/z) [M+H]$^+$ calcd for $C_{14}H_{11}F_3N_5O_2S$, 370.0580; found 370.0585.
*1-(4-(Aminosulfonyl)phenyl)-5-(4-nitrophenyl)-1H-tetrazole (**4g**).* Mp: 236.9 °C. ^{1}H NMR (DMSO-d_6) δ 8.35 (d, J = 7.8 Hz, 2H), 8.00 (d, J = 7.8 Hz, 2H), 7.83 (d, J = 7.8 Hz, 2H), 7.79 (d, J = 7.8 Hz, 2H), 7.59 (s, 2H, SO_2NH_2); ^{13}C NMR (DMSO-d_6) δ 152.5 (C_5-tetrazole), 148.9 (NO_2-Ph_p), 145.7 (NH_2SO_2-Ph_p), 135.9 (NH_2SO_2-Ph_i), 130.7, 129.4, 127.2, 126.4, 123.9; HRMS (m/z) [M+H]$^+$ calcd for $C_{13}H_{11}N_6O_4S$, 347.0557; found 347.0558.
*1-(4-(Aminosulfonyl)phenyl)-5-(4-dimethylaminophenyl)-1H-tetrazole (**4h**).* Mp 253.0 °C. ^{1}H NMR (DMSO-d_6) δ 8.02 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H), 7.61 (s, 2H, SO_2NH_2), 7.33 (d, J = 8.4 Hz, 2H), 6.73 (d, J = 8.4 Hz, 2H), 2.95 (s, 6H, NMe_2); ^{13}C NMR (DMSO-d_6) δ 153.9 (C_5-tetrazole), 151.7 (NMe_2-Ph_p), 145.5 (NH_2SO_2-Ph_p), 137.0 (NH_2SO_2-Ph_i), 129.6, 127.2, 126.6, 111.5, 108.7, 39.4 (2xC,NMe_2) ; HRMS (m/z) [M+H]$^+$ calcd for $C_{15}H_{17}N_6O_2S$, 345.1128; found 345.1126.
*1-(4-(Methylsulfonyl)phenyl)-5-phenyl-1H-tetrazole **6a**.* Mp 195.9 °C. ^{1}H NMR (DMSO-d_6) δ 8.14 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H), 7.59–7.50 (m, 5H),

3.33 (s, 3H, SO_2Me). ^{13}C NMR (DMSO-d_6) δ 153.7, 142.3, 137.8, 131.4, 128.99, 129.98, 128.6, 126.7, 123.1, 43.1; HRMS (m/z) $[M+Na]^+$ calcd for $C_{14}H_{12}N_4NaO_2S$, 323.0573; found 323.0573.

(4-(Methylsulfonyl)phenyl)-5-p-tolyl-1H-tetrazole **6b**. Mp 190.9 °C. ^1H NMR (DMSO-d_6) δ 8.13 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 7.8 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 3.33 (s, 3H, SO_2Me), 2.35 (s, 3H, Me). ^{13}C NMR (DMSO-d_6) δ 153.8, 142.3, 141.4, 137.9, 129.6, 128.8, 128.6, 126.7, 120.1, 43.1, 20.9; HRMS (m/z) $[M+Na]^+$ calcd for $C_{15}H_{14}N_4NaO_2S$, 337.0730; found 337.0729.

5-(4-Methoxyphenyl)-1-(4-(methylsulfonyl)phenyl)-1H-tetrazole **6c**. Mp 177.1 °C. ^1H NMR (DMSO-d_6) δ 8.14 (d, J = 8.4 Hz, 2H), 7.84 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 3.80 (s, 3H, OMe), 3.33 (s, 3H, SO_2Me). ^{13}C NMR (DMSO-d_6) δ 161.4, 153.5, 142.2, 138.0, 130.6, 128.7, 126.8, 114.9, 114.5, 55.3, 43.1; HRMS (m/z) $[M+Na]^+$ calcd for $C_{15}H_{14}N_4NaO_3S$, 353.0679; found 353.0683.

5-(4-Fluorophenyl)-1-(4-(methylsulfonyl)phenyl)-1H-tetrazole **6d**. Mp: 173.1 °C. ^1H NMR (DMSO-d_6) δ 8.14 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H), 7.62 (dd, $J_{H,H}$ = 8.4 Hz, $^4J_{F,H}$ = 5.4 Hz, 2H), 7.37 (dd, $J_{H,H}$ = 8.4 Hz, $^3J_{F,H}$ = 8.4 Hz, 2H), 3.33 (s, 3H, SO_2Me). ^{13}C NMR (DMSO-d_6) δ 163.6 (d, $^1J_{F,C}$ = 248.4 Hz), 153.1, 142.3, 137.7, 131.6 (d, $^3J_{F,C}$ = 9.2 Hz), 128.7, 126.7, 119.3 (d, $^4J_{F,C}$ = 2.4 Hz), 116.3 (d, $^2J_{F,C}$ = 22.2 Hz), 43.1. ^{19}F NMR (DMSO-d_6) [reference- trifluorotoluene in C_6D_6] δ −109.00 (m, F); HRMS (m/z) $[M+Na]^+$ calcd for $C_{14}H_{11}FN_4NaO_2S$, 341.0479; found 341.0480.

5-(4-Chlorophenyl)-1-(4-(methylsulfonyl)phenyl)-1H-tetrazole **6e**. Mp 183.6 °C. ^1H NMR (DMSO-d_6) δ 8.15 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 9.0 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 9.0 Hz, 2H), 3.33 (s, 3H, SO_2Me). ^{13}C NMR (DMSO-d_6) δ 152.9, 142.3, 137.6, 136.3, 130.8, 129.1, 128.7, 126.7, 122.0, 43.1; HRMS (m/z) $[M+Na]^+$ calcd for $C_{14}H_{11}ClN_4NaO_2S$, 357.0183; found 357.0184.

5-(4-(Trifluoromethyl)phenyl)-1-(4-(methylsulfonyl)phenyl)-1*H*-tetrazole (**6f**). Mp: 140.0 °C. ^1H NMR (DMSO-d_6) δ 8.16 (d, J = 7.8 Hz, 2H), 7.91(d, J = 7.8 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H), 3.33 (s, 3H, SO_2Me); ^{13}C NMR (DMSO-d_6) δ 152.8 (C_5-tetrazole), 142.4 ($MeSO_2$-Ph_p), 137.5 ($MeSO_2$-Ph_i), 131.2 (q, $^2J_{F,C}$ = 32.2 Hz) (CF_3-Ph_p), 130.1, 128.7, 127.3, 126.6, 125.9 (q, $^3J_{F,C}$ = 3.4 Hz), 123.8 (q, $^1J_{F,C}$ = 271.4 Hz), 43.1; ^{19}F NMR (DMSO-d_6) [reference-trifluorotoluene in C_6D_6] δ −61.63 (s, CF_3); HRMS (*m/z*) $[M+Na]^+$ calcd for $C_{15}H_{11}F_3N_4NaO_2S$, 391.0447; found 391.0450.

1-(4-(Methylsulfonyl)phenyl)-5-(4-nitrophenyl)-1*H*-tetrazole (**6g**). Mp: 189.8 °C. ^1H NMR (DMSO-d_6) δ 8.35 (d, J = 8.4 Hz, 2H), 8.15 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2H), 7.84 (d, J = 8.4 Hz, 2H), 3.33 (s, 3H, SO_2Me); ^{13}C NMR (DMSO-d_6) δ 152.5 (C_5-tetrazole), 148.9 (NO_2-Ph_p), 142.5 ($MeSO_2$-Ph_p), 137.4 ($MeSO_2$-Ph_i), 130.7, 129.3, 128.8, 126.7, 124.0, 43.1; HRMS (*m/z*) $[M+Na]^+$ calcd for $C_{14}H_{11}N_5NaO_4S$, 368.0424; found 368.0426.

1-(4-(Methylsulfonyl)phenyl)-5-(4-dimethylaminophenyl)-1H-tetrazole (**6h**). Mp: 185.1 °C. ^1H NMR (DMSO-d_6) δ 8.16 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 6.73 (d, J = 8.4 Hz, 2H), 3.34 (s, 3H, SO_2Me), 2.96 (s, 6H, NMe_2); ^{13}C NMR (DMSO-d_6) δ 153.9 (C_5-tetrazole), 151.7 (NMe_2-Ph_p), 142.1 ($MeSO_2$-Ph_p), 138.5 ($MeSO_2$-Ph_i), 129.6, 128.7, 126.8, 111.5, 108.6, 43.1, 39.4 (2xC,NMe_2); HRMS (*m/z*) $[M+Na]^+$ calcd for $C_{16}H_{17}N_5NaO_2S$, 366.0995; found 366.0998.

20. In vitro cyclooxygenase (COX) inhibition assay: The ability of compounds **3a**–**e** and Celecoxib to inhibit ovine COX-1 and recombinant human COX-2 was determined using a COX fluorescence inhibitor assay (catalog number 700100, Cayman Chemical, Ann Arbor, MI, USA) according to the manufacturer's assay protocol. Compounds **3a**–**e** were assayed in concentrations ranging from 10^{-9} M to 10^{-4} M. PRISM5 software was used for the calculation of IC_{50} values.
21. Khanna, I. K.; Weier, R. M.; Yu, Yi.; Xu, X. D.; Koszyk, F. J.; Collins, P. W.; Koboldt, C. M.; Veenhuizen, A. W.; Perkins, W. E.; Casler, J. J.; Masferrer, J. L.; Zhang, Y. Y.; Gregory, S. A.; Seibert, K.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1634.