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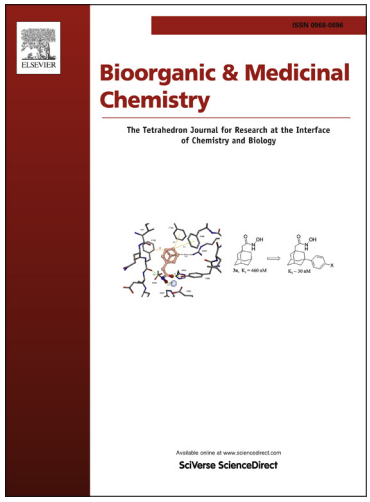


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PII: S0968-0896(13)00413-6
DOI: http://dx.doi.org/10.1016/j.bmc.2013.04.074
Reference: BMC 10814

To appear in: *Bioorganic & Medicinal Chemistry*

Received Date: 14 February 2013
Revised Date: 17 April 2013
Accepted Date: 25 April 2013

Please cite this article as: Kaur, J., Bhardwaj, A., Sharma, S.K., Wuest, F., 1,4-Diaryl-substituted triazoles as cyclooxygenase-2 inhibitors: Synthesis, biological evaluation and molecular modeling studies, *Bioorganic & Medicinal Chemistry* (2013), doi: http://dx.doi.org/10.1016/j.bmc.2013.04.074

# GRAPHICAL ABSTRACT

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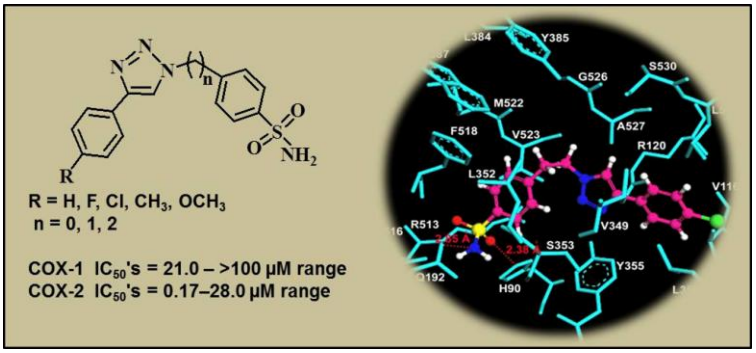




*Keywords:* Cyclooxygenase; COX-2 Inhibition; 1,4-diaryl-substituted triazoles; Click chemistry; Molecular modeling.

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# 1,4-Diaryl-substituted triazoles as cyclooxygenase-2 inhibitors: Synthesis, biological evaluation and molecular modeling studies

Jatinder Kaur, Atul Bhardwaj, Sai Kiran Sharma and Frank Wuest*

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**Abstract** − A novel group of 1,4-diaryl-substituted triazoles was designed and synthesized by introducing the cyclooxygenase-2 (COX-2) pharmacophore $SO_2NH_2$ attached to one aryl ring and various substituents (H, F, Cl, $CH_3$ or $OCH_3$) attached to the other aryl ring. The effects of size and flexibility of the compounds upon COX-1/COX-2 inhibitory potency and selectivity was studied by increasing the size of an alkyl linker chain [$(-CH_2)_n$, where n = 0, 1, 2]. In vitro COX-1/COX-2 inhibition studies showed that all compounds (**14**–**18**, **21**-**25** and **28**–**32**) are more potent inhibitors of COX-2 isozyme ($IC_{50}$ = 0.17–28.0 µM range) compared to COX-1 isozyme ($IC_{50}$ = 21.0 – >100 µM range). Within the group of 1, 4 diaryl-substituted triazoles, 4-{2-[4-(4-chloro-phenyl)-[1,2,3]triazol-1-yl]-ethyl}-benzenesulfonamide (compound **30**) displayed highest COX-2 inhibitory potency and selectivity (COX-1: $IC_{50}$ = >100 µM, COX-2: $IC_{50}$ = 0.17 µM, SI > 588). Molecular docking studies using the catalytic site of COX-1 and COX-2, respectively, provided complementary theoretical support for the obtained experimental biological structure–activity relationship data. Results of molecular docking studies revealed that COX-2 pharmacophore $SO_2NH_2$ in compound **30** is positioned in the secondary pocket of COX-2 active site; with the nitrogen atom of the $SO_2NH_2$ group being hydrogen bonded to Q192 (N----O=C = 2.85 Å), and one of the oxygen atoms of $SO_2NH_2$ group forming a hydrogen bond to H90 (S=O----N = 2.38 Å).

## 1. Introduction

Over the last 100 years, nonsteroidal anti-inflammatory drugs (NSAIDs) were among the most prominent and frequently used drugs in medicine for the treatment of pain, fever, inflammation and arthritis-associated disorders. The main therapeutic mechanism of NSAIDs action involves inhibition of cyclooxygenase-mediated biosynthesis of prostaglandins (PGs). Cyclooxygenase (prostaglandin endoperoxide synthase or COX) enzyme exists in at least two closely related isoforms[1-4] *viz*. COX-1 and COX-2. COX-1 is consecutively expressed in most tissues. COX-1 is involved in homeostasis of cytoprotective PGs in the gastrointestinal tract, homeostasis of proaggregatory thromboxane $A_2$ ($TXA_2$) in blood platelets[5] and in overall vascular homeostasis.[6] In contrast, inducible COX-2 isoform is absent in most organs and tissues, except for brain, kidney, pancreas, uterus, ovary, and macrophages. However, upon inflammatory or carcinogenic stimulation, COX-2 expression levels are elevated, and COX-2 is responsible for the production of inflammatory PGs.[7-9] Moreover, high levels of COX-2 were also found in various human cancers like gastric, breast, lung, colon, oesophageal, prostate, and hepatocellular carcinomas.[10-12]

Classical NSAIDs (aspirin, ibuprofen, meclofenamic acid and indomethacin) block the activity of both COX isoforms non-selectively to exhibit their anti-inflammatory effects, which leads to unwanted side effects by the inhibition of COX-1.[13,14] Inhibition of consecutively expressed COX-1 isoform and/or downfall in the production of physiological PGs by classical NSAIDs is considered as the basis of life-threatening side effects such as gastrointestinal irritation, ulcer, hepatic and renal toxicity.[15-17] In this context, selective inhibition of COX-2 was proposed to be a safer therapeutical approach to reduce deleterious side effects of classical NSAIDs. As a result, a variety of selective COX-2 inhibitors (COXIBs) such as celecoxib (**1**), rofecoxib (**2**), valdecoxib (**3**), etoricoxib (**4**) and lumiracoxib (**5**) have been developed (Figure 1).[18-21] Selective COX-2 inhibitors have widely been used for the treatment of inflammation and a variety of diseases such as rheumatoid arthritis, osteoarthritis, Alzheimer's disease (AD) and Parkinson's disease.[22-24] Besides these therapeutic applications, NSAIDs have also been found to play an important role in the prevention of several types of human cancer such as colon, lung, breast and prostate cancers.[12, 25]

Over the last two decades, numerous studies have been carried out to improve the COX-2 selectivity and safety profile.[14, 26-29] However, various selective COX-2 inhibitors came under scrutiny due to an increased risk of adverse cardiovascular side effects. This development led to the withdrawal of rofecoxib and valdecoxib from the market and stimulated the development of novel classes of selective

and safe COX-2 inhibitors with reduced cardiovascular side effects .[30-33] In this line, several nitric oxide releasing NSAIDs and dual COX/LOX inhibitors have been developed recently. [34-36]

Among the different classes of COXIBs, several vicinal diaryl heterocycles bearing a *p*-methylsulfonyl- or *p*-aminosulfonyl-aryl substituent rings represent the most important class of selective COX-2 inhibitors. Structure–activity relationship (SAR) data indicate that the nature and position of substituents on two vicinal aryl rings is an important determinant.[37, 38] It has been observed that compounds containing $RSO_2$ (R = $NH_2$, $CH_3$,) groups effectively interact with amino acid residues of the COX-2 secondary pocket resulting in a generally high COX-2 selectivity and potency profile.

Recently, our group has reported the synthesis of various 1,4 and 1,5-diaryl substituted 1,2,3-triazoles (**6-11**, Figure 1) as COX-2 inhibitors.[39] From this study it was concluded that compounds containing a vicinal diaryl substitution pattern display higher COX-2 inhibition potency compared to their corresponding 1,4-diaryl-substituted counterparts. Both series of compounds showed moderate COX-2 selectivity profiles. As an extension to this work, we now describe the synthesis of a novel class of 1,4 diaryl-substituted triazoles as potential selective COX-2 inhibitors. Novel compounds were designed based on Cu(I)-mediated click chemistry between azides containing the $SO_2NH_2$ COX-2 pharmacophore attached to an aryl ring and various aryl acetylenes containing different substitutents (H, F, Cl, $CH_3$ or $OCH_3$) attached to the *para* position of the aryl ring. Furthermore, the size of the molecule was increased through the introduction of an alkyl linker to enhance flexibility of the compound to facilitate COX-2 binding. The COX-1/COX-2 inhibitory activities of these compounds were determined in a COX binding assay, and plausible binding interactions within the COX-1/COX-2 active sites were explored using molecular docking studies.

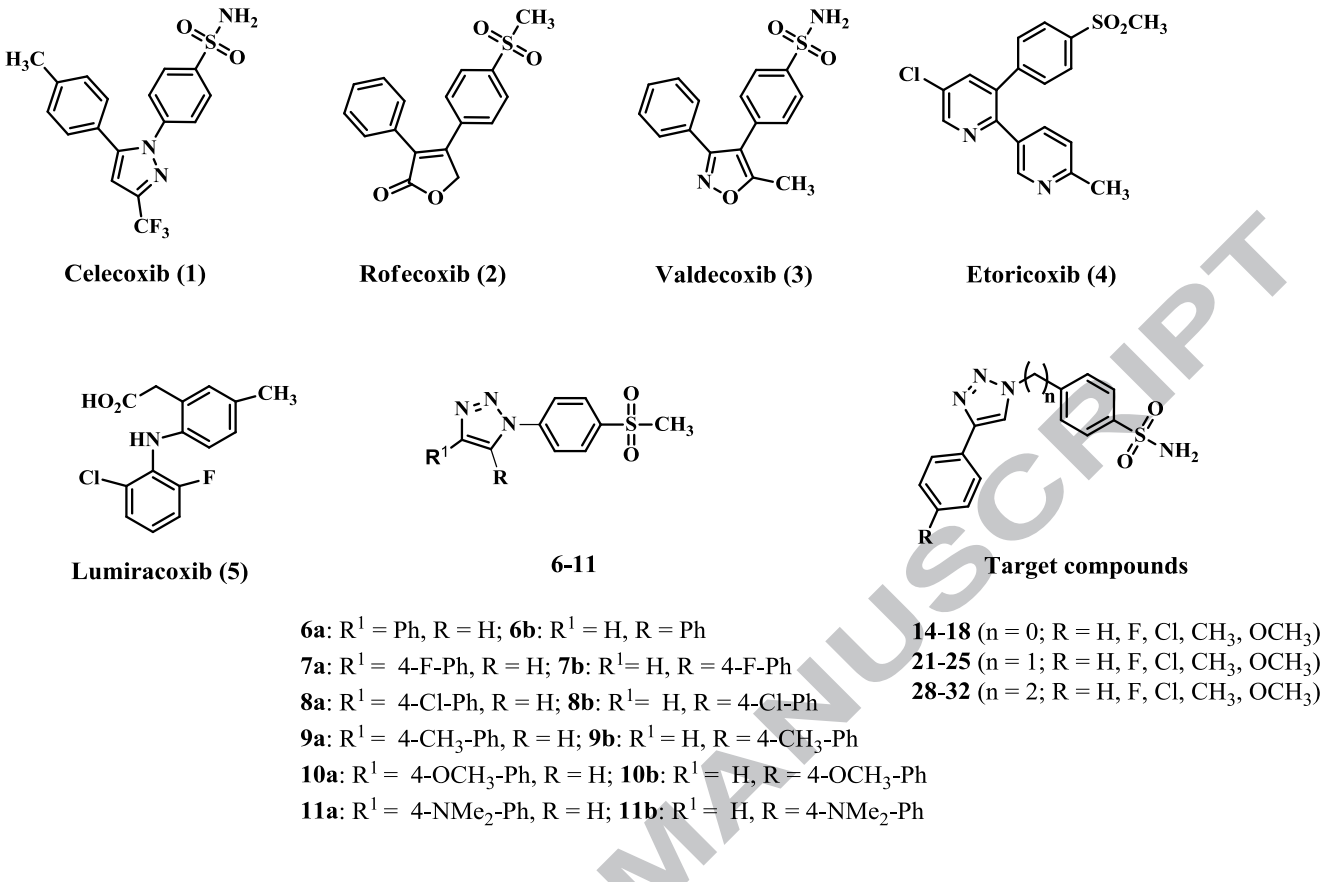
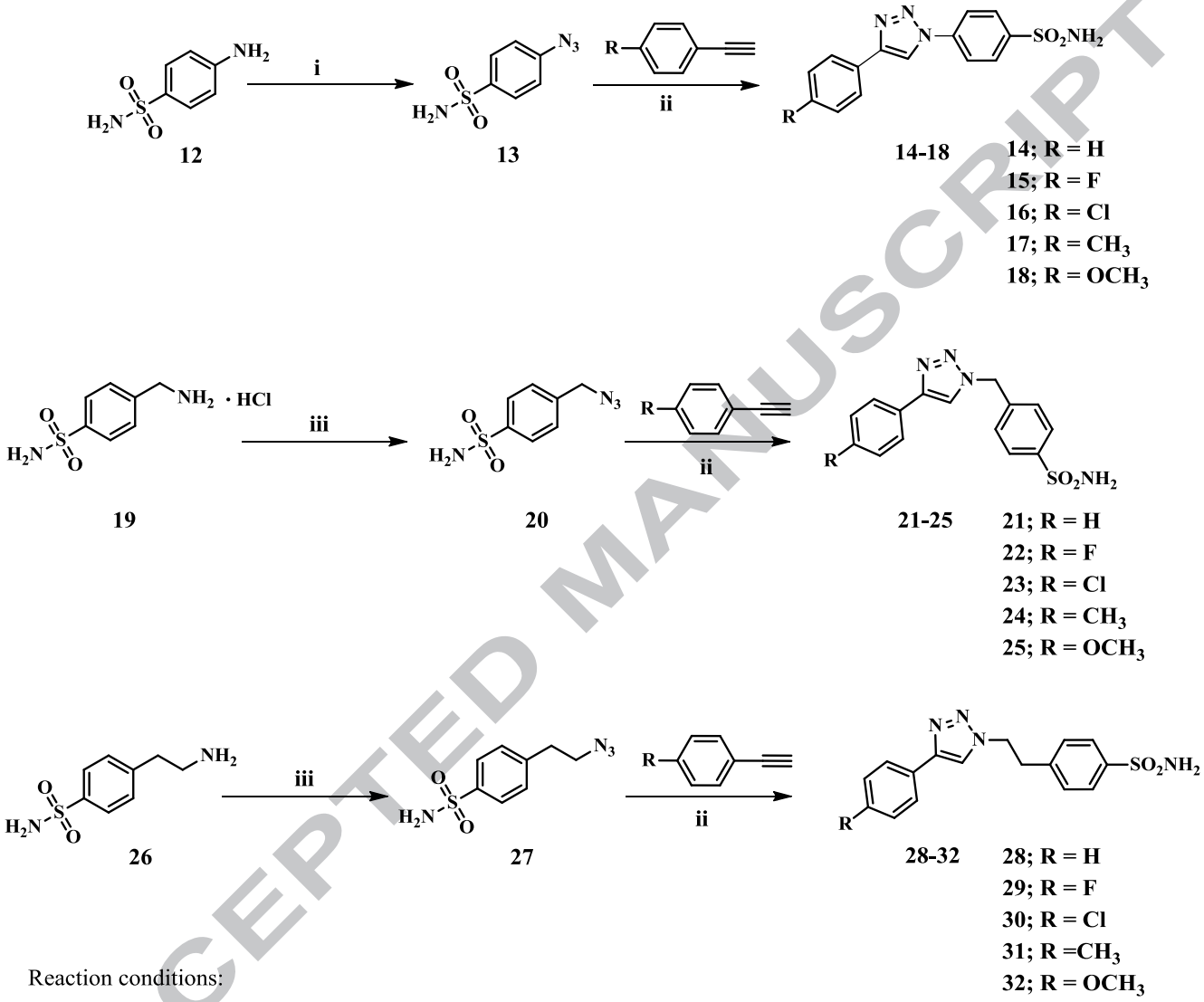



**Figure 1.** Chemical structures of some COX-2 inhibitors and target compounds.

## 2. Chemistry

The methodologies used for the synthesis of target compounds **14–18**, **21–25** and **28–32** are illustrated in Scheme 1. Based on our intention to investigate the effect of chain length, size and flexibility of the molecule on COX-1/COX-2 inhibitory potency and selectivity profile, we prepared three categories of compounds exhibiting different chain lengths (n = 0, 1, 2). The syntheses of precursor compounds 4-azido-benzenesulfonamide (**13**), 4-(azidomethyl)-benzenesulfonamide (**20**) and 4-(2-azidoethyl)-benzenesulfonamide (**27**) were carried out according to reported procedures.[40, 41] Employing popular click chemistry approach, Cu(I)-mediated [3+2] cycloaddition reaction of three aromatic azides (compounds **13**, **20** and **27**) with various *para*-substituted aryl acetylenes (4-H, 4-F, 4-Cl, 4-$CH_3$, 4-$OCH_3$) provided 1,4 diaryl substituted triazoles **14**–1**8**, **21-25** and **28**–**32** (Scheme 1). For this purpose, equimolar amounts of aryl acetylenes and azide **13**/**20**/**27** were used for click chemistry reaction in the presence of EtOH:$H_2O$ (1:1), CuI and triethylamine at 60 °C for 14-16 hrs to afford desired triazoles (**14**–1**8**, **21-25** and **28**–**32**) in moderate to good chemical yields (54-89%) after purification.

Synthesis of compounds **14**, **15**, **17** and **18** as potential inhibitors of carbonic anhydrases VA and VB was reported recently.[42]




**Scheme 1**. Synthesis of 1,4 diaryl-substituted triazoles (**14-18, 21-25** and **28-32**).

## 3. Results and Discussion

The COX-1/2 inhibitory potency and selectivity profile of compounds **14-18**, **21-25**, and **28-32** was determined in triplicate using a fluorescent COX-1/COX-2 inhibitor screening assay kit. The results of all synthesized compounds (category I: **14-18**; n = 0, R = H, F, Cl, $CH_3$, $OCH_3$), (category II: **21-25**; (n = 1, R = H, F, Cl, $CH_3$, $OCH_3$), (category III: **28-32**; (n = 2, R = H, F, Cl**,** $CH_3$, $OCH_3$), are summarized in Table 1.

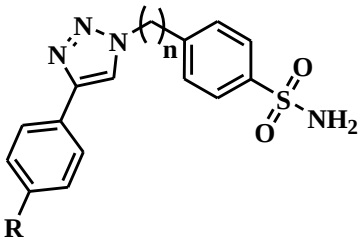
In vitro COX-1/COX-2 inhibition studies (Table 1) revealed that compounds (**14**–**18**, **21-25** and **28**–**32**) are more potent inhibitors of COX-2 ($IC_{50}$ = 0.17–28.0 μM range) than inhibitors of COX-1 ($IC_{50}$ = 21.0–>100 μM range). Among the first series of compounds (**14-18**) possessing a *p*-benzenesulfonamide (Ph-$SO_2NH_2$) substituent attached directly to *N*-1 of the triazole ring, compound **14** (n = 0, R = H) was identified as the most potent and selective COX-2 inhibitor (COX-1 $IC_{50}$ = >100 μM, COX-2 $IC_{50}$ = 1.3 μM, SI >77). Although compound **16** (n = 0, R = Cl), exhibited satisfactory COX-2 inhibitory potency (COX-2 $IC_{50}$ = 1.3 μM) its COX-2 selectivity was smaller (SI = 16.1).

In the second series of compounds (**21-25**) containing benzenesulfonamide (Ph-$SO_2NH_2$) substituent attached to *N*-1 of the triazole ring through a$CH_2$ linker (n =1), compound **24** (R = $CH_3$) was the most potent and selective inhibitor of COX-2 (COX-1 $IC_{50}$ >100 μM, COX-2 $IC_{50}$ = 1.2 μM, SI >83. Compound **22** (R = F) also displayed comparable COX-2 inhibitory potency (COX-2 $IC_{50}$ = 1.5 μM) but COX-2 selectivity index of compound **22** was smaller than that of compound **24** (SI = 13.3 *vs*. SI >83). Among the third series of compounds (**28-32**) which contained a $CH_2CH_2$ linker (n = 2), compound **30** (R = Cl) was identified as the most potent COX-2 inhibitor (COX-1 $IC_{50}$ >100 μM, COX-2 $IC_{50}$ = 0.17 μM) with an appreciable high COX-2 selectivity index (SI >588). Within this group of compounds (**28-32**), compounds **28** (R = H, COX-1 $IC_{50}$ >100 μM, COX-2 $IC_{50}$ = 1.1 μM, SI >91) and **29** (R = F, COX-1 $IC_{50}$ >100 μM, COX-2 $IC_{50}$ = 1.0 μM, SI >100) also displayed low micromolar inhibitory potency towards COX-2 while showing favorable COX-2 selectivity profile (SI >90).

Direct comparison of inhibitory potency and selectivity profiles of all three categories of compounds **14-18** (n = 0), **21-25** (n = 1) and **28-32** (n = 2) revealed that compounds of categories I (**14-18**) and II (**21-25**) possess comparably low COX-2 inhibitory potency and selectivity, except for compound **24**. However, significant improvement of COX-2 inhibitory potency and selectivity was achieved with compounds of category III (**28-32**) containing a more flexible molecular geometry through the introcuction of a ethyl linker chain with the exception of compound **32**.

Since the discovery of selective COX-2 inhibitors, the presence of two vicinal (adjacent) aryl substituents at a central heterocyclic/carbocyclic ring structure has been discussed as an important structural feature to provide favorable COX-2 inhibitory potency and selectivity. This rigid molecular geometry seems to fit into the COX-2 active site. Substituents present at adjacent positions have easy access to secondary subpocket residues and the compound can interact with amino acid residues effectively. Interestingly, the results of this study suggest that an increase in the flexibility of the molecule also results in an appreciable COX-2 inhibitory potency and selectivity profile.

**Table 1.** In vitro COX-1 and COX-2 enzyme inhibition data




| Compound | n | R | $IC_{50}$ (μM)[a] | | COX-2 SI[b] |
|---|---|---|---|---|---|
| | | | COX-1 | COX-2 | |
| **14** | 0 | H | >100 | 1.3 | >77 |
| **15** | 0 | F | >100 | 13.5 | >7.4 |
| **16** | 0 | Cl | 21 | 1.3 | 16.1 |
| **17** | 0 | $CH_3$ | 65 | 14 | 4.6 |
| **18** | 0 | $OCH_3$ | >100 | 11 | >9.1 |
| **21** | 1 | H | 39 | 6.5 | 6 |
| **22** | 1 | F | 20 | 1.5 | 13.3 |
| **23** | 1 | Cl | >100 | 28 | >3.6 |
| **24** | 1 | $CH_3$ | >100 | 1.2 | >83 |
| **25** | 1 | $OCH_3$ | >100 | 13 | >7.7 |
| **28** | 2 | H | >100 | 1.1 | >91 |
| **29** | 2 | F | >100 | 1.0 | >100 |
| **30** | 2 | Cl | >100 | 0.17 | >588 |
| **31** | 2 | $CH_3$ | >100 | 3.4 | >29 |
| **32** | 2 | $OCH_3$ | >100 | 27 | 3.7 |
| **Celecoxib** | | | >1 | 0.02 | >50 |

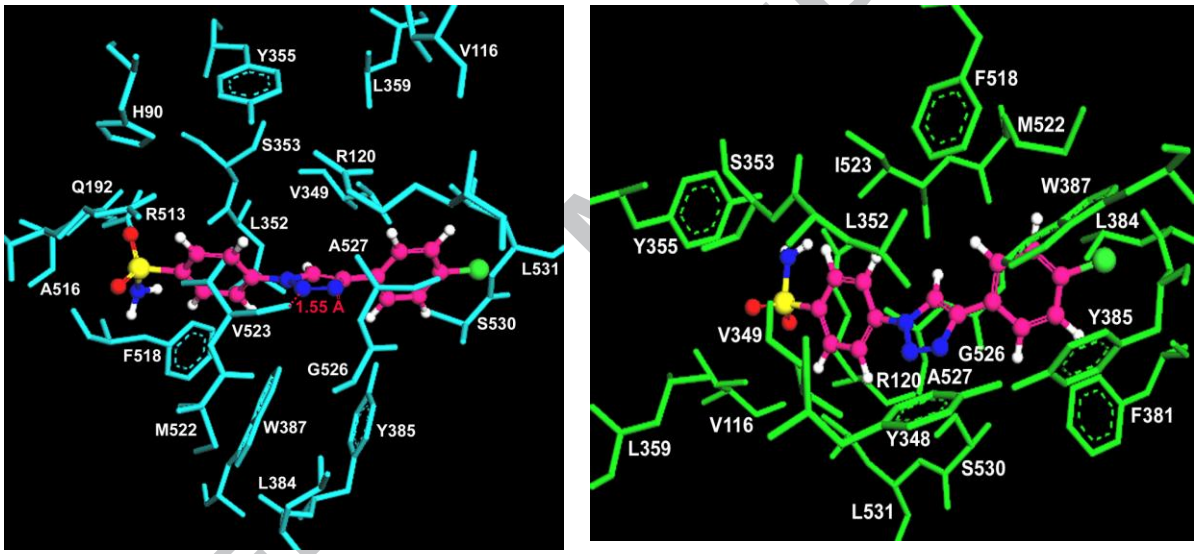
[a] The in vitro test compound concentration required to produce 50% inhibition of ovine COX-1 or human recombinant COX-2. The result ($IC_{50}$, μM) is the mean of three determinations acquired using the COX Fluorescent Inhibitor Screening Assay Kit (Item No. 700100, Cayman Chemical Company, Ann Arbor, MI, USA) and the deviation from the mean is <10% of the mean value.

[b] *In vitro* COX-2 selectivity index ($IC_{50}$ COX-1/$IC_{50}$ COX-2).

## 4. Molecular modeling (docking) studies

Molecular modeling (docking) studies were carried out for compounds (**16, 23, 30**) to gain more insights into the probable nature of their respective binding interactions within the active site of COX-1 and COX-2 isozymes. Docking experiments were performed using X-ray crystal structure data for COX-1 and COX-2 obtained from the protein data bank.[43, 44]

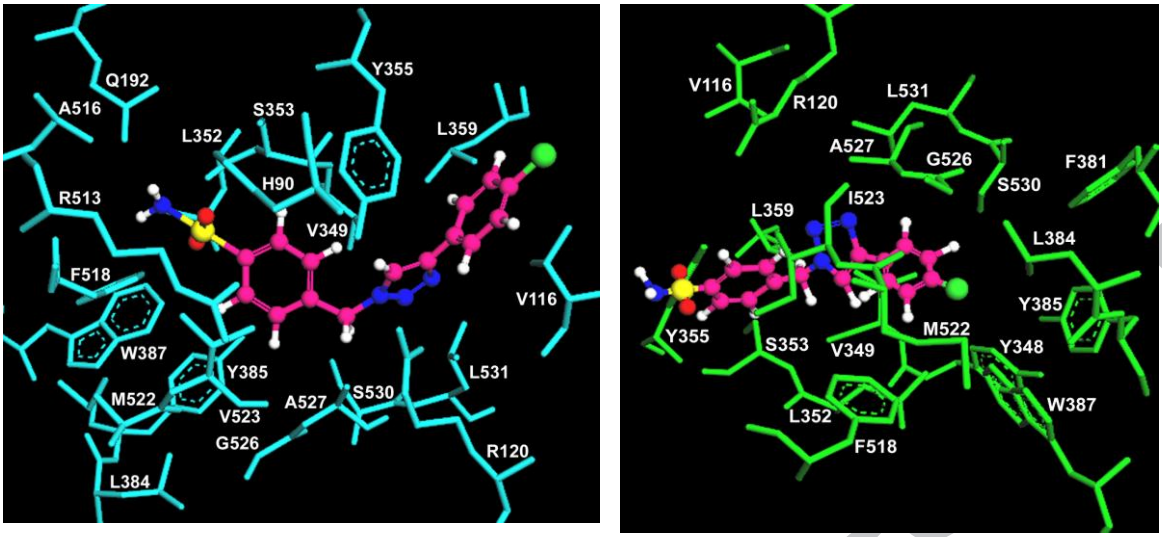
Compound **16**, when docked into the COX-2 binding site (Figure 2a), comfortably enters into the COX-2 active site and places its *para*-Cl-phenyl substituent near S530, L531residues, while one of the nitrogen atom of the triazole ring indicates hydrogen bonding interactions with V523 residue of COX-2 active site (N---O = 1.55 Å). The $SO_2NH_2$ group as prominent and effective COX-2 pharmacophore) is pointed near the COX-2 isozyme secondary pocket amino acid residues (A516, F518, R513 Q192 and H90).




**(a)** **(b)**

**Figure 2.** a) Molecular modeling (docking) of compound **16** (carbon atoms in pink) in the binding site of COX-2 (PDB ID: 6COX; $E_{intermolecular}$ = -10.21 kcal $mol^{-1}$) and b) COX-1 (PDB ID: 1EQG; $E_{intermolecular}$ = -8.12 kcal $mol^{-1}$). Hydrogen atoms of amino acid residues have been removed for clarity**.**

In a comparable manner, compound **23** displays a favorable orientation in the COX-2 active site and the $SO_2NH_2$ group is oriented at the entrance of the secondary pocket. This places the $SO_2NH_2$ group near the R513, L352 residues (Figure 3a). The 4-chlorophenyl substituent was moved near to the L359 amino acid of the COX-2 binding site.

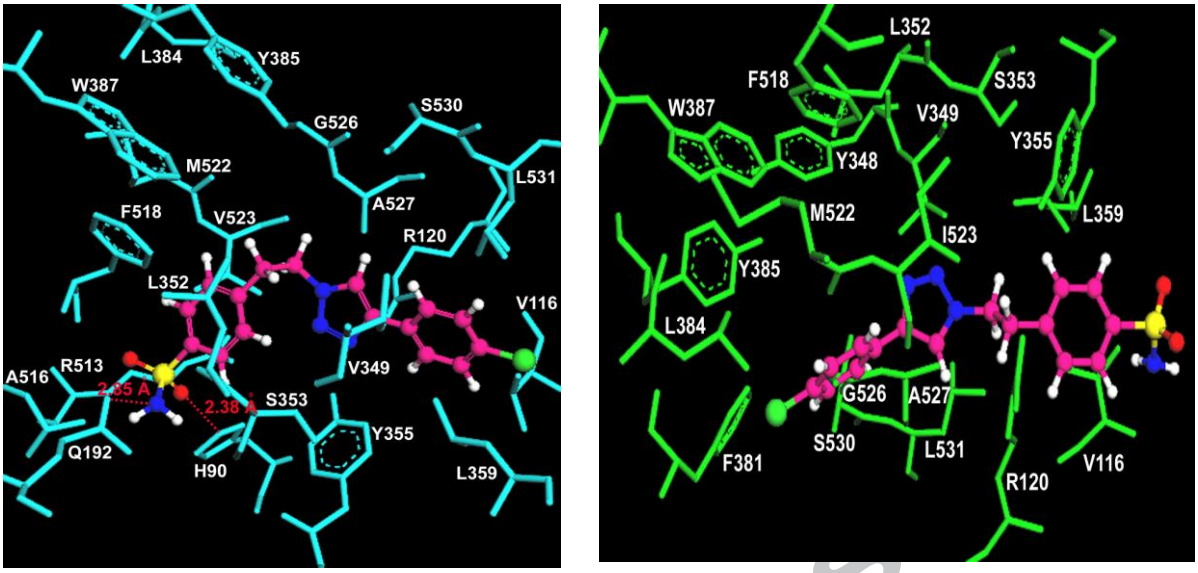



**(a)** **(b)**

**Figure 3.** a) Molecular modeling (docking) of compound **23** (carbon atoms in pink) in the binding site of COX-2 (PDB ID: 6COX; $E_{intermolecular}$ = -8.55 kcal $mol^{-1}$) and b) COX-1 (PDB ID: 1EQG; $E_{intermolecular}$ = -6.12 kcal $mol^{-1}$). Hydrogen atoms of amino acid residues have been removed for clarity**.**

A similar molecular docking simulation for compound **30** within the COX-2 active site (Figure 4a), showed noticeable interactions between compound **30** and active binding site residues ($E_{intermolecular}$ = -12.48 Kcal $mol^{-1}$). The $SO_2NH_2$ group in compound **30** deeply enters into the secondary pocket region of the COX-2 active site, where it is oriented towards Q192, R513, H90, and S353 residues. The nitrogen atom of the $SO_2NH_2$ group indicates hydrogen bonding interactions with the oxygen of carbonyl group of Q192 (N----O=C = 2.85 Å), and one of the oxygen atom of $SO_2NH_2$ group is hydrogen bonded to the nitrogen atom of H90 residue (S=O----N = 2.38 Å) (Figure 4a).

However, in contrast to binding interactions of compound **16** (Figure 2a) and **23** (Figure 3a), the docking results of compound **30** (Figure 4a) indicate that upon increasing the size of the linker chain (n = 2), there is an increase in the flexibility of the molecule which facilitates the deeper insertion of the $SO_2NH_2$ group into the secondary binding pocket and more significant intermolecular binding interactions. This favorable orientation and electrostatic binding interactions of compound **30** with COX-2 active site residues are consistent with experimentally observed high COX-2 inhibitory potency (COX-2 $IC_{50}$ = 0.17 µM). A comparison of the binding mode of compounds **16**, **23** and **30** in the COX-2 active site using a molecular docking structure containing all three compounds (**16**, **23** and **30**) docked in the same COX-2 active site is given in the supplementary section (Figure S1).




**(a)** **(b)**

**Figure 4.** Molecular modeling (docking) of compound **30** (carbon atoms in pink) in the binding site of COX-2 (PDB ID: 6COX; $E_{intermolecular}$ = -12.48 kcal $mol^{-1}$) and b) COX-1 (PDB ID: 1EQG; $E_{intermolecular}$ = -5.90 kcal $mol^{-1}$). Hydrogen atoms of amino acid residues have been removed for clarity**.**

Alternatively, docking results for compound **16**, **23** and **30** in COX-1 active site show that compound **16** comfortably enters into the COX-1 active site (Figure 2b) and its *p*-Cl-phenyl substituent has moved into the hydrophobic subpocket of COX-1isozyme constituted by W387, Y385 and F381 residues. However, during docking studies of compound **23** (Figure 3b) and **30** (Figure 4b) into COX-1, compounds were not able to enter into the COX-1 active site completely (Figure 3b and 4b). This inability is likely due to the increase in their size or/and due to the steric conflict with side chains of amino acid residues of the active site. This body of data evidently supports the experimentally observed weak COX-1inhibitory activity of compound **23** and **30**.

## 5. Conclusions

In conclusion, a new class of 1,4-diaryl-substituted triazoles was synthesized using high yielding Cu(I)-mediated click chemistry. In vitro COX-1/COX-2 inhibition studies showed that some compounds of this novel class of 1,4-diaryl-substituted triazoles are able to inhibit COX-2 with high otency and selectivity. Especially compounds (**28**-**30**) were identified as highly potent ($IC_{50}$ range 0.17–1.1 μM) and selective novel COX-2 inhibitors (SI >91–>588). Among all investigated compounds, a "lead compound" 4-{2-[4-(4-Chloro-phenyl)-[1,2,3]triazol-1-yl]-ethyl}-benzenesulfon-amide was identified that exhibited appreciable COX-2 inhibitory potency and selectivity (COX-1 $IC_{50}$ >100 μM, COX-2 $IC_{50}$ = 0.17 μM; SI > 588). Molecular docking analyses for compounds **16**, **23** and **30** on the COX-1/COX-2 isozymes complement the experimental results. From both the experimental structure–activity data and the molecular docking results it can be concluded that an increase of the length of the linker chain is accompanied with an enhancement in molecular interactions between functional groups of the compounds and amino acid residues of the secondary pocket of the COX-2 active site.

## 6. Experimental

### 6.1. General

Melting points were measured in capillaries using a Thomas-Hoover capillary apparatus and are uncorrected. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Bruker Avance III 600 MHz NMR spectrometer using DMSO-$d_6$ as solvent. Chemical shifts are given in parts per million (ppm) with tetramethylsilane (TMS) as an internal reference. Mass spectra (MS) were recorded on a Water's Micromass ZQ 4000 mass spectrometer using the ESI ionization mode. The purity of the compounds was established using elemental analyses which were performed for C, H, N by the Microanalytical Service Laboratory, Department of Chemistry, University of Alberta. Compounds showed a single spot on Macherey-Nagel Polygram Sil G/UV254 silica gel plates (0.2 mm) using a low, medium, and highly polar solvent system, and no residue remained after combustion, indicating a purity >98%. All other commercial reagents and solvents were used without further purification. Compound **13**, **20,** and **27** were prepared according to already reported procedure .[40, 41]

### 6.2. Chemical Synthesis

#### 6.2.1. 4-(Azidomethyl)-benzenesulfonamide (**20**)[41]

$^{1}H$ NMR (600 MHz, DMSO-$d_6$): $\delta$ 4.57 (s, 2H, $CH_2$), 7.40 (s, 2H, $NH_2$), 7.57 (d, $J$ = 8.4 Hz, 2H, Ar-H), 7.86 (d, $J$ = 8.4 Hz, 2H, Ar-H).

#### 6.2.2. 4-(2-Azidoethyl)-benzenesulfonamide (**27**) [41]

$^{1}H$ NMR (600 MHz, DMSO-$d_6$): $^{1}H$ NMR (600 MHz, DMSO-$d_6$): $\delta$ 2.94 (t, $J$ = 6.9 Hz, 2H, $N_3CH_2CH_2$), 3.63 (t, $J$ = 6.9 Hz, 2H, $N_3CH_2CH_2$), 7.31 (s, 2H, $NH_2$, 7.48 (d, $J$ = 8.4 Hz, 2H, Ar-H), 7.77 (d, $J$ = 8.4 Hz, 2H, Ar-H).

#### 6.2.3. General procedure for the Cu (I)-catalyzed synthesis of triazoles (**14**–**18**, **21**-**25** and **28**–**32**)[39]

A mixture of respective aryl acetylene (0.575 mmol), CuI (0.0575 mmol) and triethylamine (0.0575 mmol) in 15 ml of EtOH/$H_2O$ (1:1) was stirred at room temperature for 15 min. Then, 4-Azido-benzenesulfonamide/ 4-(Azidomethyl)-benzenesulfonamide/ 4-(2-Azidoethyl)-benzenesulfonamide (0.575 mmol) in 5 ml of EtOH/$H_2O$ (1:1) was added and the resulting mixture was stirred at 60°C for 14-16 h. The precipitate obtained were filtered and washed with water and then with diethyl ether. These precipitates were further recrystallized from ethanol.

**6.2.3.1. 4-(4-Phenyl-[1,2,3]triazol-1-yl)-benzenesulfonamide** (**14**). Yield: 70%; mp 210-212°C; $^{1}$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 7.40 (m, 1H, Ar-H), 7.51 (m, 2H, Ar-H), 7.55 (s, 2H, $NH_2$), 7.95 (m, 2H, Ar-H), 8.06 (d, $J$ = 8.4 Hz, 2H, Ar-H), 8.18 (d, $J$ = 8.4, 2H, Ar-H), 9.43 (s, 1H, CH); $^{13}$C NMR (150 MHz, DMSO-$d_6$): $\delta$ 119.73, 120.08, 125.27, 127.45, 128.33, 128.96, 129.85, 138.50, 143.72, 147.48; ESI-MS: 301 $[M+H]^+$; Anal Calcd for $C_{14}H_{12}N_4O_2S$: C, 55.99; H, 4.03; N, 18.65; S, 10.68; Found: C, 55.25; H, 3.92; N, 17.83; S, 10.36.

**6.2.3.2. 4-[4-(4-Fluoro-phenyl)-[1,2,3]triazol-1-yl]-benzenesulfonamide** (**15**). Yield: 81%; mp 118-119°C; $^{1}$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 7.37 (m, 2H, Ar-H), 7.55 (s, 2H, $NH_2$), 7.99 (m, 2H, Ar-H), 8.06 (d, $J$ = 8.3 Hz, 2H, Ar-H), 8.17 (d, $J$ = 8.3 Hz, 2H, Ar-H), 9.42 (s, 1H, CH); $^{13}$C NMR (150 MHz, DMSO-$d_6$): $\delta$ 116.54 (d, $J_{C\text{-}F}$ = 21.0 Hz), 120.26, 120.68, 127.02 (d, $J_{C\text{-}F}$ = 3.0 Hz), 127.94 (d, $J_{C\text{-}F}$ = 9.0 Hz), 128.06, 139.05, 144.36, 147.20, 162.57 (d, $J_{C\text{-}F}$ = 243.0 Hz); ESI-MS: 319 $[M+H]^+$; Anal Calcd for $C_{14}H_{11}FN_4O_2S$: C, 52.82; H, 3.48; N, 17.60; S, 10.07; Found: C, 52.15; H, 3.11; N, 17.22; S, 9.78.

**6.2.3.3. 4-[4-(4-Chloro-phenyl)-[1,2,3]triazol-1-yl]-benzenesulfonamide** (**16**). Yield: 82%; mp 215-217°C; $^{1}$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 7.55 (s, 2H, $NH_2$), 7.59 (d, $J$ = 8.4 Hz, 2H, Ar-H), 7.97 (d, $J$ = 8.4 Hz, 2H, Ar-H), 8.06 (d, $J$ = 8.4 Hz, 2H, Ar-H), 8.16 (d, $J$ = 8.4, 2H, Ar-H), 9.47 (s, 1H, CH); $^{13}$C NMR (150 MHz, DMSO-$d_6$): $\delta$ 120.14, 126.95, 127.47, 128.77, 129.06, 132.78, 138.42, 143.40, 143.81, 146.38; ESI-MS: 335 $[M+H]^+$; Anal Calcd for $C_{14}H_{11}ClN_4O_2S$: C, 50.23; H, 3.31; N, 16.74; S, 9.58; Found: C, 49.89; H, 3.13; N, 16.03; S, 9.26.

**6.2.3.4. 4-(4-p-Tolyl-[1,2,3]triazol-1-yl)-benzenesulfonamide** (**17**). Yield: 89%; mp 211-212°C; $^{1}$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 2.36 (s, 3H, $CH_3$), 7.32 (d, $J$ = 8.0 Hz, 2H, Ar-H), 7.54 (s, 2H, $NH_2$), 7.84 (d, $J$ = 8.0 Hz, 2H, Ar-H), 8.05 (d, $J$ = 8.4 Hz, 2H, Ar-H), 8.17 (d, $J$ = 8.4, 2H, Ar-H), 9.37 (s, 1H, CH); $^{13}$C NMR (150 MHz, DMSO-$d_6$): $\delta$ 20.80, 119.28, 120.04, 125.22, 127.07, 127.45, 129.52, 137.75, 138.53, 143.67, 147.57; ESI-MS: 315 $[M+H]^+$; Anal Calcd for $C_{15}H_{14}N_4O_2S$: C, 57.31; H, 4.49; N, 17.82; S, 10.20; Found: C, 56.97; H, 4.21; N, 17.55; S, 9.79.

**6.2.3.5. 4-[4-(4-Methoxy-phenyl)-[1,2,3]triazol-1-yl]-benzenesulfonamide** (**18**). Yield: 83%; mp 199-201°C; $^{1}$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 3.81 (s, 3H, $OCH_3$), 7.08 (d, $J$ = 8.8 Hz, 2H, Ar-H), 7.54 (s, 2H, $NH_2$), 7.88 (d, $J$ = 8.8 Hz, 2H, Ar-H), 8.05 (d, $J$ = 8.4 Hz, 2H, Ar-H), 8.16 (d, $J$ = 8.4, 2H, Ar-H), 9.31 (s, 1H, CH); $^{13}$C NMR (150 MHz, DMSO-$d_6$): $\delta$ 55.13, 114.39, 118.67, 119.97, 122.37,

126.68, 127.45, 138.56, 143.61, 147.45, 159.31; ESI-MS: 331 $[M+H]^+$; Anal Calcd for $C_{15}H_{14}N_4O_3S$: C, 54.53; H, 4.27; N, 16.96; S, 9.71; Found: C, 54.07; H, 4.11; N, 16.47; S, 9.35.

**6.2.3.6. 4-(4-Phenyl-[1,2,3]triazol-1-ylmethyl)-benzenesulfonamide** (**21**).Yield: 72%; mp 210-213°C; $^1$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 5.76 (s, 2H, $CH_2$), 7.30-7.36 (m, 1H, Ar-H), 7.38 (s, 2H, $NH_2$), 7.44-7.47 (m, 2H, Ar-H), 7.51 (d, $J$ = 8.4 Hz, 2H, Ar-H), 7.83-7.87 (m, 4H, Ar-H), 8.68 (s, 1H, CH); $^{13}$C NMR (150 MHz, DMSO-$d_6$): $\delta$ 52.83, 122.28, 125.66, 126.63, 128.43, 128.79, 129.39, 131.05, 140.23, 144.31, 147.21; ESI-MS: 315 $[M+H]^+$; Anal Calcd for $C_{15}H_{14}N_4O_2S$: C, 57.31; H, 4.49; N, 17.82; S, 10.20; Found: C, 57.25; H, 4.52; N, 17.63; S, 10.16.

**6.2.3.7. 4-[4-(4-Fluoro-phenyl)-[1,2,3]triazol-1-ylmethyl]-benzenesulfonamide** (**22**). Yield: 80%; mp 197-200°C; $^1$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 5.76 (s, 2H, $CH_2$), 7.28-7.31 (m, 2H, Ar-H), 7.38 (s, 2H, $NH_2$), 7.51 (d, $J$ = 8.4 Hz, 2H, Ar-H), 7.84 (d, $J$ = 8.4 Hz, 2H, Ar-H), 7.89-7.91 (m, 2H, Ar-H), 8.67 (s, 1H, CH); $^{13}$C NMR (150 MHz, DMSO-$d_6$): $\delta$ 52.89, 116.17 (d, $J_{C\text{-}F}$ = 22.5 Hz), 122.19, 126.64, 127.62 (d, $J_{C\text{-}F}$ = 3.0 Hz), 127.70 (d, $J_{C\text{-}F}$ = 7.5 Hz), 128.81, 140.17, 144.33, 146.36, 162.28 (d, $J_{C\text{-}F}$ = 243.0 Hz); ESI-MS: 333 $[M+H]^+$; Anal Calcd for $C_{15}H_{13}FN_4O_2S$: C, 54.21; H, 3.94; N, 16.86; S, 9.65; Found: C, 54.17; H, 3.92; N, 16.79; S, 9.52.

**6.2.3.8. 4-[4-(4-Chloro-phenyl)-[1,2,3]triazol-1-ylmethyl]-benzenesulfonamide** (**23**). Yield: 54.2%; mp 212-215°C; $^1$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 5.76 (s, 2H, $CH_2$), 7.39 (s, 2H, $NH_2$), 7.50-7.53 (m, 4H, Ar-H), 7.84 (d, $J$ = 8.4 Hz, 2H, Ar-H), 7.88 (d, $J$ = 8.4 Hz, 2H, Ar-H), 8.73 (s, 1H, CH); $^{13}$C NMR (150 MHz, DMSO-$d_6$): $\delta$ 52.93, 122.63, 126.68, 127.73, 128.84, 129.45, 129.96, 132.84, 140.10, 144.35, 146.13; ESI-MS: 349 $[M+H]^+$; Anal Calcd for $C_{15}H_{13}ClN_4O_2S$: C, 51.65; H, 3.76; N, 16.06; S, 9.19; Found: C, 51.58; H, 3.66; N, 16.11; S, 9.12.

**6.2.3.9. 4-(4-p-Tolyl-[1,2,3]triazol-1-ylmethyl)-benzenesulfonamide** (**24**). Yield: 75.3%; mp 215-217°C; $^1$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 2.33 (s, 3H, $CH_3$), 5.74 (s, 2H, $CH_2$), 7.26 (d, $J$ = 7.8 Hz, 2H, Ar-H), 7.38 (s, 2H, $NH_2$), 7.51 (d, $J$ = 8.4 Hz, 2H, Ar-H), 7.74 (d, $J$ = 7.8 Hz, 2H, Ar-H), 7.84 (d, $J$ = 8.4 Hz, 2H, Ar-H), 8.62 (s, 1H, CH); $^{13}$C NMR (150 MHz, DMSO-$d_6$): $\delta$ 21.31, 52.84, 121.83, 125.60, 126.62, 128.29, 128.80, 129.92, 137.73, 140.25, 144.30, 147.27; ESI-MS: 329 $[M+H]^+$; Anal Calcd for $C_{16}H_{16}N_4O_2S$: C, 58.52; H, 4.91; N, 17.06; S, 9.76; Found: C, 58.48; H, 4.95; N, 17.11; S, 9.69.

**6.2.3.10. 4-[4-(4-Methoxy-phenyl)-[1,2,3]triazol-1-ylmethyl]-benzenesulfonamide** (**25**). Yield: 78.7 %; mp 218-220°C; $^{1}$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 3.76 (s, 3H, $OCH_3$), 5.73 (s, 2H, $CH_2$), 7.01 (d, $J$ = 8.4 Hz, 2H, Ar-H), 7.38 (s, 2H, $NH_2$), 7.51 (d, $J$ = 8.4 Hz, 2H, Ar-H), 7.78 (d, $J$ = 8.4 Hz, 2H, Ar-H), 7.84 (d, $J$ = 8.4 Hz, 2H, Ar-H), 8.56 (s, 1H, CH); $^{13}$C NMR (150 MHz, DMSO-$d_6$): $\delta$ 52.81, 55.71, 114.77, 121.29, 123.63, 126.63, 127.01, 128.77, 140.29, 144.32, 147.46, 159.52; ESI-MS: 345 $[M+H]^+$; Anal Calcd for $C_{16}H_{16}N_4O_3S$: C, 55.80; H, 4.68; N, 16.27; S, 9.31; Found: C, 55.89; H, 4.60; N, 16.19; S, 9.31.

**6.2.3.11. 4-[2-(4-Phenyl-[1,2,3]triazol-1-yl)-ethyl]-benzenesulfonamide** (**28**). Yield: 80.4%; mp 220-222°C; $^{1}$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 3.32 (t, $J$ = 6.9 Hz, 2H, $NCH_2CH_2$), 4.71 (t, $J$ = 6.9 Hz, 2H, $NCH_2CH_2$), 7.30 (s, 2H, $NH_2$), 7.32-7.35 (m, 1H, Ar-H), 7.42-7.49 (m, 4H, Ar-H), 7.73 (d, $J$ = 8.4 Hz, 2H, Ar-H), 7.81 (d, $J$ = 8.4 Hz, 2H, Ar-H), 8.58 (s, 1H, CH); $^{13}$C NMR (150 MHz, DMSO-$d_6$): $\delta$ 35.61, 50.62 121.79, 125.55, 126.22, 129.17, 129.39, 129.55, 131.23, 142.28, 142.96, 146.68; ESI-MS: 329 $[M+H]^+$; Anal Calcd for $C_{16}H_{16}N_4O_2S$: C, 58.52; H, 4.91; N, 17.06; S, 9.76; Found: C, 58.58; H, 4.97; N, 17.12; S, 9.71.

**6.2.3.12. 4-{2-[4-(4-Fluoro-phenyl)-[1,2,3]triazol-1-yl]-ethyl}-benzenesulfonamide** (**29**). Yield: 78.2%; mp 175-179°C; $^{1}$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 3.32 (t, $J$ = 7.2 Hz, 2H, $NCH_2CH_2$), 4.71 (t, $J$ = 7.2 Hz, 2H, $NCH_2CH_2$),7.27-7.29 (m, 2H, Ar-H), 7.30 (s, 2H, $NH_2$), 7.42 (d, $J$ = 8.4 Hz, 2H, Ar-H), 7.73 (d, $J$ = 8.4 Hz, 2H, Ar-H), 7.83-7.87 (m, 2H, Ar-H), 8.57 (s, 1H, CH); $^{13}$C NMR (150 MHz, DMSO-$d_6$): $\delta$ 35.60, 50.65, 116.32 (d, $J_{C\text{-}F}$ = 22.5 Hz), 121.70, 126.23, 127.56 (d, $J_{C\text{-}F}$ = 7.5 Hz), 127.80 (d, $J_{C\text{-}F}$ = 3.0 Hz), 129.58, 142.25, 142.97, 145.83, 162.21 (d, $J_{C\text{-}F}$ = 243.0 Hz); ESI-MS: 347 $[M+H]^+$; Anal Calcd for $C_{16}H_{15}FN_4O_2S$: C, 55.48; H, 4.36; N, 16.17; S, 9.26; Found: C, 55.45; H, 4.36; N, 16.11; S, 9.34.

**6.2.3.13. 4-{2-[4-(4-Chloro-phenyl)-[1,2,3]triazol-1-yl]-ethyl}-benzenesulfonamide** (**30**). Yield: 76.2%; mp 200-205°C; $^{1}$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 3.32 (t, $J$ = 7.2 Hz, 2H, $NCH_2CH_2$), 4.72 (t, $J$ = 7.2 Hz, 2H, $NCH_2CH_2$), 7.30 (s, 2H, $NH_2$), 7.42 (d, $J$ = 8.4 Hz, 2H, Ar-H), 7.52 (d, $J$ = 9.0 Hz, 2H, Ar-H), 7.73 (d, $J$ = 8.4 Hz, 2H, Ar-H), 7.83 (d, $J$ = 9.0 Hz, 2H, Ar-H), 8.63 (s, 1H, CH); $^{13}$C NMR (150 MHz, DMSO-$d_6$): $\delta$ 35.58, 50.68, 122.15, 126.20, 127.25, 129.46, 129.68, 130.13, 132.72, 142.22, 142.98, 145.61; ESI-MS: 363 $[M+H]^+$; Anal Calcd for $C_{16}H_{15}ClN_4O_2S$: C, 52.96; H, 4.17; N, 15.44; S, 8.84; Found: C, 52.89; H, 4.23; N, 15.46; S, 8.88.

**6.2.3.14. 4-[2-(4-p-Tolyl-[1,2,3]triazol-1-yl)-ethyl]-benzenesulfonamide** (**31**). Yield: 82.3%; mp 210-214°C; $^{1}$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 2.38 (s, 3H, $CH_3$), $\delta$ 3.36 (t, $J$ = 7.2 Hz, 2H, $NCH_2CH_2$), 4.75 (t, $J$ = 7.2 Hz, 2H, $NCH_2CH_2$), 7.30 (d, $J$ = 7.8 Hz, 2H, Ar-H), 7.35 (s, 2H, $NH_2$), 7.47 (d, $J$ = 8.4 Hz, 2H, Ar-H), 7.75 (d, $J$ = 8.4 Hz, 2H, Ar-H), 7.78 (d, $J$ = 7.8 Hz, 2H, Ar-H), 8.56 (s, 1H, CH); $^{13}$C NMR (150 MHz, DMSO-$d_6$): $\delta$ 21.30, 35.61, 50.58, 121.37, 125.50, 126.22, 128.46, 129.68, 129.77, 137.60, 142.30, 142.96, 146.74; ESI-MS: 343 $[M+H]^+$; Anal Calcd for $C_{17}H_{18}N_4O_2S$: C, 59.63; H, 5.30; N, 16.36; S, 9.36; Found: C, 58.74; H, 5.32; N, 16.30; S, 9.33.

**6.2.3.15. 4-{2-[4-(4-Methoxy-phenyl)-[1,2,3]triazol-1-yl]-ethyl}-benzenesulfonamide** (**32**). Yield: 78.4%; mp 216-218°C; $^{1}$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 3.31 (t, $J$ = 7.2 Hz, 2H, $NCH_2CH_2$), 3.78 (s, 3H, $OCH_3$), 4.69 (t, $J$ = 7.2 Hz, 2H, $NCH_2CH_2$), 7.01 (d, $J$ = 8.4 Hz, 2H, Ar-H), 7.31 (s, 2H, $NH_2$), 7.42 (d, $J$ = 8.4 Hz, 2H, Ar-H), 7.73-7.75 (m, 4H, Ar-H), 8.46 (s, 1H, CH); $^{13}$C NMR (150 MHz, DMSO-$d_6$): $\delta$ 35.63, 50.55, 55.63, 114.79, 120.82, 123.83, 126.22, 126.90, 129.68, 142.32, 142.95, 146.62, 159.44; ESI-MS: 359 $[M+H]^+$; Anal Calcd for $C_{17}H_{18}N_4O_3S$: C, 56.97; H, 5.06; N, 15.63; S, 8.95; Found: C, 56.90; H, 5.06; N, 15.69; S, 8.96.

### 6.3. In vitro cyclooxygenase inhibition assays

The ability of test compounds **14-18**, **21-25** and **28-32** to inhibit COX-1 and COX-2 isozyme ($IC_{50}$ values, µM) was determined using COX Fluorescent Inhibitor Screening Assay Kit (Item No. 700100, Cayman Chemical Company, Ann Arbor, MI, USA).[45, 46]

### 6.4. Molecular modeling (docking) procedure

The molecular docking experiments were performed using crystal coordinates from the X-ray crystal structure of COX-1 (ovine, 1EQG, ibuprofen bound in the active site) and COX-2 (murine, 6COX, SC558 bound in the active site) were obtained from the protein data bank. Compounds were built using the builder toolkit of the software package ArgusLab 4.0.1 (Mark, A. ArgusLab, Version 4.0.1; Thompson Planaria Software LLC: Seattle, WA) and energy minimized using the semi-empirical quantum mechanical method PM3. The monomeric structure of the enzyme was chosen and the active site was defined around the ligand. The molecule to be docked in the active site of the enzyme was inserted in the work space carrying the structure of the enzyme. The docking program implements an efficient grid based docking algorithm which approximates an exhaustive search within the free volume of the binding site cavity. The conformational space was surveyed by the geometry optimization of the flexible ligand (rings are treated as rigid) in combination with the incremental

construction of the ligand torsions. Thus, docking occurred between the flexible ligand parts of the compound and enzyme. The ligand orientation was determined by a shape scoring function based on Ascore and the final positions were ranked by lowest interaction energy values. The $E_{interaction}$ is the sum of the energies involved in H-bond interactions, hydrophobic interactions and van der Waal's interactions. H-bond and hydrophobic interactions between the compound and enzyme were explored by distance measurements.

**Acknowledgements**

The authors would like to thank the Dianne and Irving Kipnes Foundation and the Canadian Institute for Health Research (CIHR) for supporting this work.

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