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Docking studies and the crystal structure of two tetrazole derivatives: 5-(4-chlorophenyl)-1-{4-(methylsulfonyl)phenyl}-1*H*-tetrazole and 4-{5-(4-methoxyphenyl)-1*H*-tetrazol-1-yl}benzenesulfonamide

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ABSTRACT

The structures of 5-(4-chlorophenyl)-1-{4-(methylsulfonyl)phenyl}-1*H*-tetrazole (**3**) and 4-{5-(4-methoxyphenyl)-1*H*-tetrazol-1-yl}benzenesulfonamide (**5**) have been determined by X-ray crystallography. Tetrazoles **3** and **5** crystallize in the monoclinic space groups *Ia* and $P2_1/c$, respectively. The cell dimensions of azole **3** are $a = 11.0413\ (5)$ Å, $b = 11.8428\ (5)$ Å, $c = 12.2483\ (5)$ Å^3, $\beta = 111.7129\ (4)^\circ$, $V = 1487.95\ (11)$ Å^3, and $Z = 4$. Its structure was refined to $R_1 = 0.0254$ (for 3429 observed reflections [$I \geq 2\sigma(I)$]) and $wR_2 = 0.0651$ (for all 3300 unique reflections). The cell dimensions of azole **5** are $a = 17.112\ (3)$ Å, $b = 6.5904\ (10)$ Å, $c = 12.935\ (2)$ Å^3, $\beta = 93.1981\ (19)^\circ$, $V = 1456.5\ (4)$ Å^3, and $Z = 4$. Its structure was refined to $R_1 = 0.0336$ (for 3010 observed reflections [$I \geq 2\sigma(I)$]) and $wR_2 = 0.0875$ (for all 2463 unique reflections). The tetrazole rings are essentially planar, while the aryl rings at the 1- and 5-positions of each compound show no conjugation to the tetrazole groups. Compound **5** exhibits a network of intermolecular hydrogen bonds generated by interactions between adjacent sulfonamide groups. The molecular docking studies were carried out to understand the orientation and the interaction of each molecule inside the active site of the cyclooxygenase-2 enzyme, followed by comparison with the bioassay studies as COX-2 inhibitors.

1. Introduction

Cyclooxygenases (COXs) are involved in the complex conversion of arachidonic acid to various prostanoids like prostaglandins, prostacyclin and thromboxanes [1–3]. COX is a membrane-bound heme, protein that exists in two distinct isoforms, a constitutive form (COX-1) and an inducible form (COX-2) [4,5]. Recently, a novel COX-1 splice variant termed as COX-3 has been reported [6]. The X-ray structures of both enzymes COX-1 and COX-2, which catalyze the same reactions using identical catalytic mechanisms, suggest that the proteins are very similar in their tertiary conformation [7,8]. The house keeping enzyme (COX-1) is found in platelets, kidneys, and the gastrointestinal tract and is believed to be responsible for the maintenance of physiological functions such as gastro protection and vascular homeostasis [9]. However, the COX-2 expression is significantly upregulated as part of various acute and chronic inflammatory conditions and is also found in neoplastic tissues [10,11].

In general, tetrazole compounds have been widely used in many applications such as medicine, pharmacology and explosives [12–14]. 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 isosteres of the *cis*-amide bond in peptides. It was shown that the tetrazole-containing compounds adopt almost the same conformation as the original peptide. Prominent examples involve α-methylene tetrazole-based peptidomimetics as HIV-protease inhibitors [15]. Other 1,5-disubstituted tetrazoles have

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been described in recent patent literature such as glucokinase activators [16], NAD(P)H oxidase inhibitors [17], anti-migraine agents [18], and hepatitis C virus serine protease NS3 inhibitors [19].

Recently, we have described various 1,5-diaryl substituted tetrazoles containing the 4-(methylsulfonyl)phenyl or 4-(aminosulfonyl)phenyl substituent attached to position 1 (N − 1) or position 5 (C − 5) of the tetrazole ring as a novel class of COX-2 inhibitors [20–22]. In this work, we are reporting the docking studies and the single crystal X-ray structures of the two previously prepared [21] 1,5-diaryl substituted tetrazoles: 5-(4-chlorophenyl)-1-{4-(methylsulfonyl)phenyl}-1*H*-tetrazole (**3**) and 4-{5-(4-methoxyphenyl)-1*H*-tetrazol-1-yl}benzenesulfonamide (**5**), as shown in Scheme 1.

2. Experimental

2.1. Instrumentation and materials

^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 600 MHz NMR spectrometer, with the solvent as internal reference in the case of ^{1}H, ^{13}C. The mass spectra were performed at the Mass Spectrometry Laboratory at the Department of Chemistry, University of Alberta. High resolution ESI mass spectra were recorded on a Kratos-Analytical MS-50 spectrometer at the University of Alberta. Melting points measured using BÜCHI B-545 ranged between (25–400 °C). All samples were measured with a starting temperature at 25 °C–280 °C with gradient of 3 °C/min. Flash chromatography was performed on silica gel 0.04–0.063 mm columns. Thin layer chromatography (TLC) was carried out on POLYGRAM SIL G/UV_{254} ready foils from MACHEREY-NAGEL company. Commercially available starting materials and solvents were purchased from TCI America, Fisher, and Caledon Laboratory Chemicals.

2.2. Syntheses

The synthesis of 5-(4-chlorophenyl)-1-{4-(methylsulfonyl) phenyl}-1*H*-tetrazole (**3**) and 4-{5-(4-methoxyphenyl)-1*H*-tetrazol-1-yl}benzenesulfonamide (**5**) was obtained by the treatment of the aryl-benzamides with tetrachlorosilane/sodium azide in acetonitrile at 90 °C, followed by the oxidation for tetrazole **2** of the methyl sulfide functionality as depicted in Scheme 1 [21].

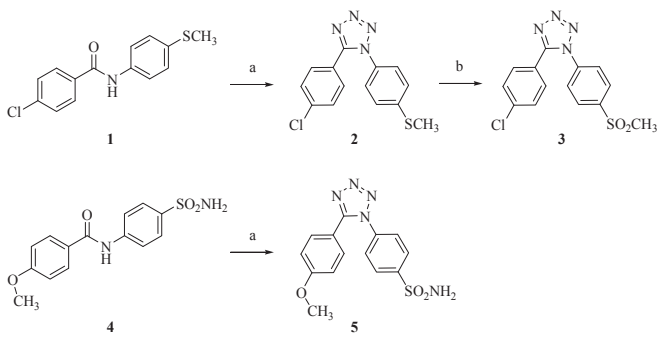
2.3. General procedure for the synthesis of 5-(4-chlorophenyl)-1-(4-(methylsulfonyl)phenyl)-1H-tetrazole (*3*) and 4-{5-(4-methoxyphenyl)-1H-tetrazol-1-yl}benzenesulfonamide (*5*)

Amide (1.0 equiv.) (**1**, **4**) and powdered sodium azide (4.0 equiv.) were added to a 48 mL HW pressure vessel. After flashing the reaction vessel with N_2, dry CH_3CN (4 mL) was added under N_2 atmosphere. Perchlorosilane (4.0 equiv.). The reaction vessel closed and immersed in a pre-heated oil bath at 90 °C. After stirring tetrazole **3** for 24 h and tetrazole **5** for 72 h the reaction was worked out as stated below.

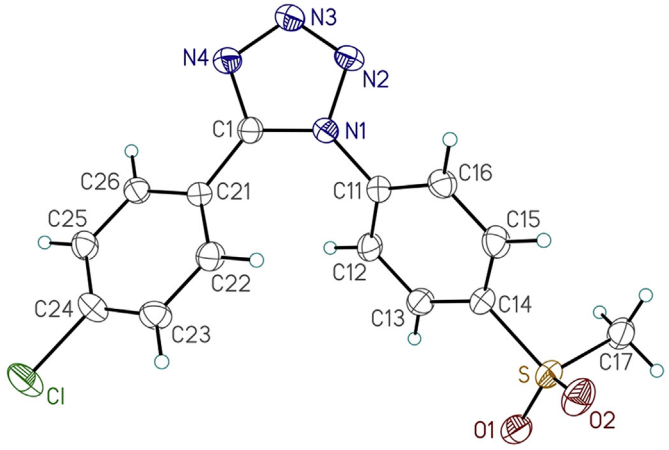
The reaction vessel was opened and immersed in the oil bath under a stream of nitrogen to reduce the amount of the CH_3CN to be just under 1 mL. After the reaction was cooled to r. t., a cold saturated solution of K_2CO_3 (40 mL) was carefully added and stirred for 30 min. The precipitate was filtered off and washed with water (3 × 20 mL) and diethyl ether (2 × 5 mL) to give quantitatively the pure tetrazoles 5-(4-chlorophenyl)-1-(4-(methylthio)phenyl)-1H-tetrazole (**2**) and 4-{5-(4-methoxyphenyl)-1*H*-tetrazol-1-yl}benzenesulfonamide (**5**). Tetrazole **2** was used directly for the next step.

Tetrazole **2** was dissolved in acetone, CH_2Cl_2, or MeOH (20 mL), followed by the addition of a solution of potassium peroxymonosulfate (20 mL, 2.5 equiv.). After 3 h water (60 mL) was added, and the precipitate was filtered off and washed with water (3 × 20 mL) and ether (3 × 5 mL) to give a quantitative and pure yield of 5-(4-Chlorophenyl)-1-(4-(methylsulfonyl)phenyl)-1*H*-tetrazole (**3**).

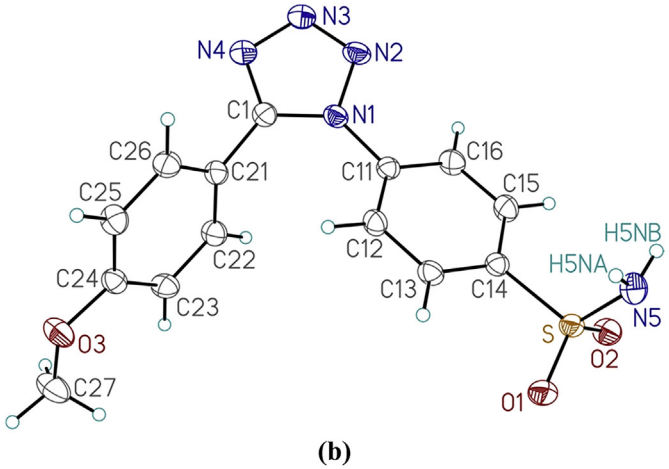
5-(4-Chlorophenyl)-1-(4-(methylsulfonyl)phenyl)-1*H*-tetrazole (**3**) White solid; crystallization from methanol gave a white solid;



Scheme 1. Reagents: (a) $SiCl_4/NaN_3$, CH_3CN, 90 °C, 1–3 days; (b) oxone®/acetone/MeOH/H_2O, 3 h, r. t.



(a)



(b)

Fig. 1. Molecular structures of tetrazole **3** (a) and tetrazole **5** (b). Atomic displacement ellipsoids are drawn at the 50% probability level, except for hydrogens, which are shown with arbitrarily-small isotropic displacement parameters.

Table 1
Crystal data and experimental details of X-ray diffraction for compounds **3** and **5**.

	3	5
formula	$C_{14}H_{11}ClN_4O_2S$	$C_{14}H_{13}N_5O_3S$
formula weight	334.78	331.35
crystal dimensions (mm)	0.31 × 0.30 × 0.20	0.72 × 0.17 × 0.07
crystal system, space group	monoclinic, *Ia* (an alternate setting of *Cc* [No. 9])	monoclinic, $P2_1/c$ (No. 14)
a (Å)	11.0413 (5)	17.112 (3)
b (Å)	11.8428 (5)	6.5904 (10)
c (Å)	12.2483 (5)	12.935 (2)
β (deg)	111.7129 (4)	93.1981 (19)
V (Å^3)	1487.95 (11)	1456.5 (4)
Z	4	4
D, calculated density (g cm^{-3})	1.494	1.511
μ (mm^{-1})	0.409	0.246
diffractometer	Bruker D8/APEX II CCD	
radiation (*λ* [Å])	graphite-monochromated Mo K*α* (0.71073)	
temperature (K)	173(1)	
scan type	*ω* scans (0.3°) (15 s exposures)	*ω* scans (0.3°) (20 s exposures)
data collection 2*θ* limit (deg)	55.04	53.00
total data collected	6575 ($-14 \le h \le 14$, $-15 \le k \le 15$, $-15 \le l \le 15$)	11,239 ($-21 \le h \le 21$, $-8 \le k \le 8$, $-16 \le l \le 16$)
independent reflections (R_{int})	3429 ($R_{int} = 0.0151$)	3010 ($R_{int} = 0.0330$)
observed reflections ($I \ge 2\sigma(I)$)	3300	2463
structure solution method	direct methods (*SHELXD*)	
refinement method	full-matrix least-squares on F^2 (*SHELXL-97*)	
absorption correction method	Gaussian integration (face-indexed)	
range of transmission factors	0.9241–0.8827	0.9839–0.8424
data/restraints/parameters	3429/0/200	3010/0/216
extinction coefficient (*x*)	0.0017(4)	
Flack absolute structure param.	0.02(4)	
goodness-of-fit (*S*)[a] (all data)	1.045	1.032
R_1, *wR*2 ($I \ge 2\ \sigma(I)$)[b]	0.0254, 0.0637	0.0336, 0.0445
R_1, *wR*2 (all data)[b]	0.0269, 0.0651	0.0817, 0.0875
largest difference peak and hole (e Å^{-3})	0.316, −0.263	0.287, −0.405

[a] $S = [\Sigma w(F_o^2 - F_c^2)^2/(n-p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (a_0P)^2 + a_1P]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$; for **3**, $a_0 = 0.0367$, $a_1 = 0.4652$; for **5**, $a_0 = 0.0398$, $a_1 = 0.6839$.
[b] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Table 2
Bond lengths (Å) for compounds **3** and **5**.

	3	5
Cl–C24	1.7355(17)	
S–O1	1.4396(14)	1.4350(12)
S–O2	1.4382(13)	1.4341(12)
S–N5		1.6054(15)
S–C14	1.7735(16)	1.7629(16)
S–C17	1.7584(18)	
O3–C24		1.3675(19)
O3–C27		1.427(2)
N1–N2	1.3667(18)	1.3634(18)
N1–C1	1.350(2)	1.354(2)
N1–C11	1.426(2)	1.433(2)
N2–N3	1.286(2)	1.288(2)
N3–N4	1.360(2)	1.364(2)
N4–C1	1.316(2)	1.318(2)
C1–C21	1.468(2)	1.474(2)
C11–C12	1.382(2)	1.386(2)
C11–C16	1.392(2)	1.389(2)
C12–C13	1.389(2)	1.380(2)
C13–C14	1.387(2)	1.387(2)
C14–C15	1.392(2)	1.393(2)
C15–C16	1.377(2)	1.376(2)
C21–C22	1.389(2)	1.386(2)
C21–C26	1.398(2)	1.394(2)
C22–C23	1.386(2)	1.389(2)
C23–C24	1.382(2)	1.388(2)
C24–C25	1.386(2)	1.390(2)
C25–C26	1.381(2)	1.381(2)

m.p. 183.6 °C. ^{1}H 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.

4-{5-(4-methoxyphenyl)-1*H*-tetrazol-1-yl}benzenesulfonamide (**5**) White solid; crystallization from methanol gave a white solid; 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-$\underline{Ph}_p$), 153.5 (C_5-tetrazole), 145.6 (NH_2SO_2-$\underline{Ph}_p$), 136.6 (NH_2SO_2-$\underline{Ph}_i$), 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.

2.4. Single crystal X-ray structure determination

Colorless single crystals of both compounds **3** and **5** were obtained by slow evaporation of chloroform solutions of the compounds at room temperature. Suitable single crystals were selected, coated with Paratone-N oil, and attached to glass fibers. Diffraction data for both compounds were collected on a Bruker D8 diffractometer equipped with an APEX II CCD detector. Diffraction measurements were made with the crystals cooled to 173(1) K and using graphite-monochromated Mo K*α* radiation (λ = 0.71073 Å). The structures were solved by iterative dual-space direct methods using *SHELXD* [23] and were refined by full-matrix least-squares procedures on F^2, using *SHELXL-97* [24]. The positions of the hydrogen atoms were generated based on the sp^2 or sp^3 hybridizations of their parent carbon atoms, and assigned isotropic displacement parameters 120% of the U_{eq}'s for their parent atoms. The molecular structure and the atomic numbering scheme of **3** and **5** are shown in Fig. 1.

Table 3
Bond angles (deg) for compounds **3** and **5**.

	3	5
O1–S–O2	118.15(8)	118.63(8)
O1–S–N5		107.55(8)
O1–S–C14	108.49(8)	107.13(7)
O1–S–C17	109.38(9)	
O2–S–N5		106.57(8)
O2–S–C14	107.67(8)	108.08(8)
O2–S–C17	108.10(9)	
N5–S–C14		108.58(8)
C14–S–C17	104.14(9)	
C24–O3–C27		117.33(14)
N2–N1–C1	107.82(13)	107.85(13)
N2–N1–C11	119.80(12)	119.00(13)
C1–N1–C11	132.38(13)	132.96(14)
N1–N2–N3	106.26(12)	106.48(13)
N2–N3–N4	111.25(13)	111.15(13)
N3–N4–C1	106.25(13)	106.15(14)
N1–C1–N4	108.43(13)	127.53(15)
N1–C1–C21	127.78(14)	124.09(15)
N4–C1–C21	123.70(14)	120.39(14)
N1–C11–C12	120.18(14)	118.08(14)
N1–C11–C16	118.02(14)	121.44(15)
C12–C11–C16	121.80(15)	119.00(15)
C11–C12–C13	119.27(15)	119.95(15)
C12–C13–C14	118.96(15)	119.92(12)
S–C14–C13	120.25(13)	119.33(13)
S–C14–C15	118.20(12)	120.67(15)
C13–C14–C15	121.54(15)	119.57(15)
C14–C15–C16	119.45(15)	119.35(15)
C11–C16–C15	118.97(15)	127.53(15)
C1–C21–C22	121.93(15)	121.06(15)
C1–C21–C26	117.66(14)	119.45(15)
C22–C21–C26	120.17(15)	119.42(15)
C21–C22–C23	120.01(15)	120.66(16)
C22–C23–C24	119.09(16)	119.34(16)
C23–C24–C25	121.71(16)	120.41(15)
C24–C25–C26	119.13(15)	119.79(16)
C21–C26–C25	119.90(15)	120.36(16)
Cl–C24–C23	119.70(13)	
Cl–C24–C25	118.59(13)	
O3–C24–C23		124.37(15)
O3–C24–C25		115.22(15)

Table 4
Dihedral angles (deg) between ring planes for compounds **3** and **5**.

	3	5
Angle between planes A and B	46.48(6)	24.23(8)
Angle between planes A and C	38.63(4)	62.26(5)
Angle between planes B and C	58.73(5)	69.51(4)

Plane A: N1, N2, N3, N4, C1 (tetrazole).
Plane B: C11, C12, C13, C14, C15, C16 (4-(methylsulfonyl)phenyl (**3**) or 4-(amino-sulfonyl)phenyl (**5**)).
Plane C: C21, C22, C23, C24, C25, C26 (4-chlorophenyl (**3**) or 4-methoxyphenyl (**5**)).

2.5. Molecular docking studies

The cyclooxygenase-2 (COX-2) crystal structure was obtained from the RCSB Protein Data Bank (PDB identifier 1PXX). Chain A of 1PXX was only used for the present study. The ligand flexible docking study of compound **3** and **5** was achieved using AutoDock Vina [25]. The used simulation box was adequately large to involve the entire region of interaction between the ligand and the enzyme. Default parameters were used except for the exhaustiveness parameter in which it was set to 500. The most energetically favorable conformation obtained was examined, and its binding energy with COX-2 active site was evaluated.

3. Results and discussion

3.1. Crystal structure analysis

Table 1 lists crystallographic and experimental details for the diffraction experiments, while the molecular structure and the atomic numbering scheme of **3** and **5** are shown in Fig. 1.

Bond lengths and angles for these compounds are listed in Tables 2 and 3, respectively. A side-by-side comparison of these lengths and angles shows the effects of the 4-chloro (**3**) vs. 4-methoxy (**5**) and 4-methylsulfonyl (**3**) vs. 4-sulfonamide (**5**) substitutions upon the geometries of the phenyl and tetrazole groups to be essentially negligible. For both compounds, the intramolecular dihedral angles between the ring planes (Table 4) indicate no conjugation between attached rings of the molecules.

Compound **3** exhibits an intermolecular π-stacking arrangement of the tetrazole group and the 4-chlorophenyl group of the adjacent molecule related by the $(^{-1}/2 + x, 1 - y, z)$ symmetry operation. The dihedral angle between these ring planes is 6.43(10)°. The distances of the symmetry-related 4-chlorophenyl group atoms out of the tetrazole ring plane are as follows: Cl: 3.623(2) Å; C21: 3.192(4) Å; C22: 3.319(4) Å; C23: 3.462(3) Å; C24, 3.471(3) Å; C25: 3.349(3) Å; C26: 3.208(4) Å. The closest heteroatom–hydrogen interaction between neighboring molecules includes O2⋯ H25(at $x, y, 1 + z$) = 2.45 Å, N4⋯H17C(at $^{-1}/2 + x, 1 - y, z - 1$) = 2.45 Å, and Cl⋯H17B(at $^{1}/2 + x, ^{-1}/2 + y, ^{-1}/2 + z$) = 2.69 Å.

For compound **5** the most notable intermolecular interactions are those between the sulfonamide groups of adjacent symmetry-related molecules. The SO_2NH_2 groups related by the inversion center ($^{1}/2, ^{-1}/2, 0$) form a cyclic interaction, specifically through hydrogen bonds between O2 and the inversion-related H5NB, and vice versa as shown in Fig. 2. The O1 atom is hydrogen-bonded to H5NA at $(-x, ^{-1}/2 + y, ^{1}/2 - z)$, while H5NA interacts with O1 at $(-x, ^{1}/2 + y, ^{1}/2 - z)$. Thus an additional chain propagating in a direction parallel to the crystal *b*-axis is formed. An intermolecular π-stacking interaction is observed between the tetrazole ring and the methoxyphenyl group related by $(x, ^{1}/2 - y, ^{-1}/2 + z)$, where the dihedral angle between the tetrazole and phenyl ring planes is 2.02(12)°. The symmetry-related atoms closest to the tetrazole rings, and their distances to the tetrazole ring plane, are as follows: O3: 3.5106(18) Å; C23, 3.466(2) Å; C24: −3.4999(19) Å; C25: 3.532(2) Å. The closest heteroatom–hydrogen interaction between neighboring molecules includes H25⋯N4(at $x, ^{3}/2 - y, ^{1}/2 + z$) = 2.55 Å, H16⋯O1(at $x, ^{-1}/2 - y, -^{1}/2 + z$) = 2.61 Å, H22⋯O3(at $x, ^{1}/2 - y, -^{1}/2 + z$) = 2.65 Å, and H25⋯N3(at $x, ^{3}/2 - y, ^{1}/2 + z$) = 2.66 Å.

3.2. Molecular docking studies

Molecular docking study on the interaction of both molecules with the binding site of COX-2 was conducted to have a clear picture of the types of interactions involved in the recognition process. The docking of the **3** and **5** into the COX-2 binding site resulted in a calculated binding free energy $\Delta G = -8.9$ and -9.1 kcal/mol, respectively. Similar amino acid residues, His90, Arg120, Gln192, Tyr348, Val349, Leu352, Ser353, Tyr355, Tyr385, Trp387, Ala516, Phe518, Val523, Gly526, Ala527, and Ser530, are interacting with both ligands within a 4 Å distance. This indicates more or less a similar location within the binding site of COX-2 (Fig. 3).

Zooming in on the docked structure reveals that compound **3** forms four hydrogen bonds with the nearby amino acid residues (Fig. 4 (left)). The presence of Tyr355 and Arg120 in the binding moiety results in the formation of a hydrogen bonding interaction between the hydroxyl group of Tyr355 and the guanidine group of Arg120 with the N2 (distance = 3.08 Å, moderate interaction) and

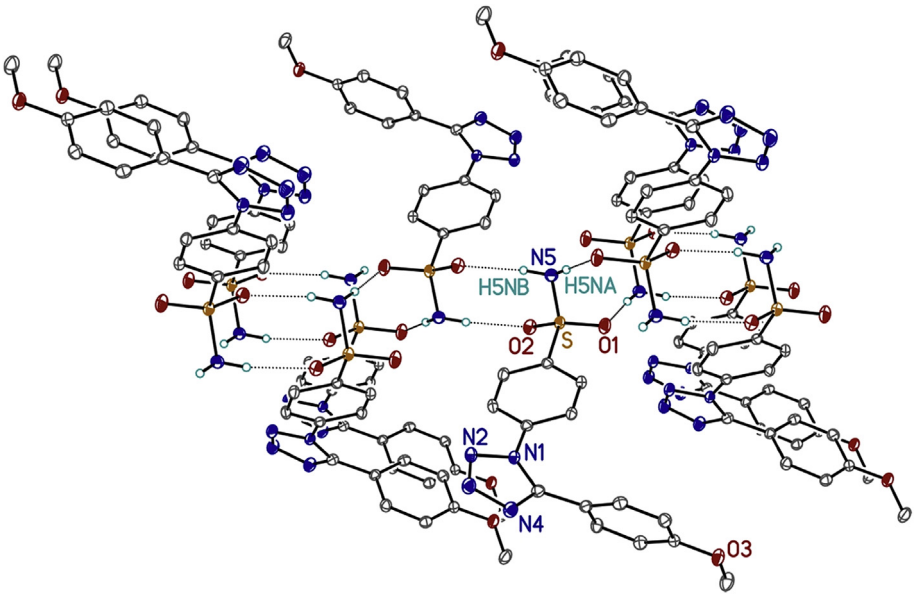


Fig. 2. Illustration of hydrogen-bonded interactions (indicated by dotted lines) between the sulfonamide groups of adjacent molecules in the crystal lattice for the structure of **5**.

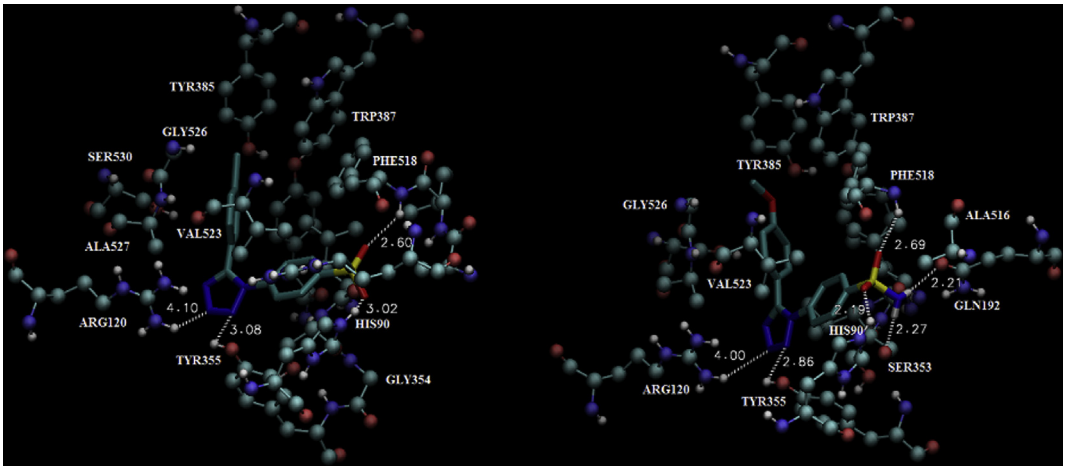


Fig. 3. Docked structure of the tetrazole **3** (left) and tetrazole **5** (right) surrounded by selected amino acid residues involved in the recognition process in the COX-2 enzyme.

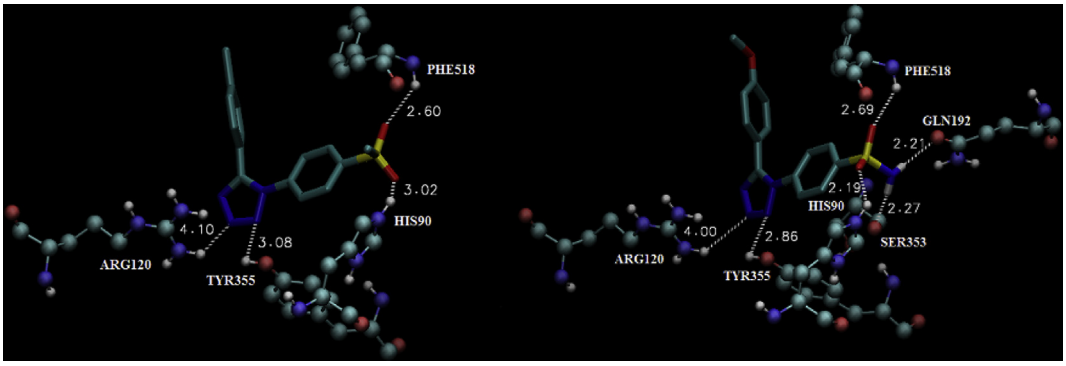


Fig. 4. Hydrogen bonding inside the catalytic site between compound **3** and the amino acid residues His90, Arg120, Tyr355, and Phe518 (left). Hydrogen bonding inside the catalytic site between compound **5** and the amino acid residues His90, Arg120, Gln192, Ser353, Tyr355, and Phe518 (right).

N5 (distance = 4.10 Å, weak interaction) of the central tetrazole moiety, respectively. Furthermore, Phe518 and His90 form hydrogen bonds with the two oxygen atoms of the methylsulfonyl group ($MeSO_2$) with distances of 2.60 (NH···O═S═O) and 3.02 Å (O═S═O···NH), respectively. The two oxygen atoms of the sulfonamide pharmacophore unit (H_2NSO_2) of compound **5** form four

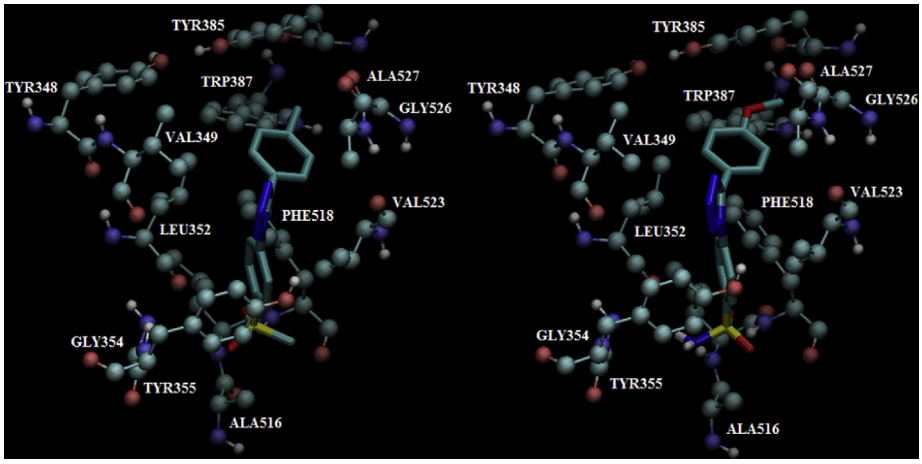


Fig. 5. The hydrophobic environment of the amino acid residues in the catalytic site of COX-2 surrounding the compounds **3** (left) and **5** (right).

hydrogen bonds. Two of them result from the interaction with the NH group of both Phe518 and His90 with distances of 2.69 (NH···O═S═O) and 2.19 Å (O═S═O···NH), respectively (Fig. 4 (right)). Obviously, there is a shorter hydrogen bond interaction of the NH group (His90)···O═S(SO2) in compound **5** than in compound **3**. Two additional strong hydrogen bonds are observed between the hydroxyl group of Ser353 and Gln192 with the hydrogens of NH2 group in the sulfonamide unit. Similar to adduct **3**, the N2 and N5 of the central tetrazole moiety establish hydrogen bonds with the hydroxyl group of Tyr355 (2.86 Å) and with the guanidine group of Arg120 (4.00 Å).

The phenyl groups of both compounds are surrounded by a hydrophobic colony of Tyr385, Tyr348, Trp387, Ala527, Val349, Gly526, Leu352, Phe518, Val523, Gly354, Tyr355, and Ala516 (Fig. 5).

Docking results exhibit better interactions of **5** with the COX-2 binding site; however, the reported IC_{50} values from the *in vitro* bioassay studies indicate that **3** has higher inhibition potency than **5** [21]. The computed Log *P* values of **3** and **5** are 2.64 and 1.86, respectively [21]. This significant difference of the lipophilicity might explain the discrepancy between the docked results and the bioassay screening values. A previous report indicates that the nature of the substituent on the *para* position of the benzene rings plays a significant role in the inhibition potency of the compound. For example, replacing the MeO (Log $P = 1.86$, $IC_{50}(\mu M) > 100$) substituent with Cl on the phenyl (Log $P = 2.46$, $IC_{50}(\mu M) = 62$) ring of tetrazole **5** showed a better inhibition potency toward the COX-2 enzyme. A similar case was reported with **3** regarding replacement of the Cl group (Log $P = 2.64$, $IC_{50}(\mu M) = 32$) with the MeO substituent (Log $P = 2.04$, $IC_{50}(\mu M) > 100$) [21]. Moreover, the present docking study was performed in a continuum solvation model. Therefore the effect of explicit water molecules in the strength of the interaction as well as the geometry of the molecular complex was not addressed, which might have a decisive factor on such systems. As a future study, molecular dynamics simulations using an explicit solvation model should be carried out to investigate the role of water in the binding process. Moreover, other substituents located at the benzene ring ranging in their polarity should also be studied.

4. Conclusions

The molecular structures of 5-(4-chlorophenyl)-1-{4-(methylsulfonyl)phenyl}-1*H*-tetrazole (**3**) and 4-{5-(4-methoxyphenyl)-1*H*-tetrazol-1-yl}benzenesulfonamide (**5**) have been determined by X-ray diffraction methods. An intermolecular π-stacking arrangement was found in compound **3** between the tetrazole group and the 4-chlorophenyl group of the adjacent molecule related by the $(^{-1}/2 + x, 1 - y, z)$ symmetry operation. Hydrogen-bonded interactions between sulfonamide groups dominate the intermolecular framework within the solid-state structure of **5**. Compound **5** revealed a similar intermolecular π-stacking arrangement of the tetrazole group and the 4-methoxyphenyl group of the adjacent molecule related by the $(x, {}^{1}/2 - y, {}^{-1}/2 + z)$ symmetry operation. The intramolecular dihedral angles between the ring planes show no conjugation between the substituted phenyl rings and the tetrazole groups for either compound. A number of weak nonbonded heteroatom–hydrogen interactions are observed in both compounds. Our molecular docking studies explained the main interactions of compounds **3** and **5**, as weak COX-2 inhibitors, with the COX-2 enzyme. The docking studies showed stronger hydrogen bonding between compound **5** and the active site of the COX-2 enzyme than compound **3**. Surprisingly, *in vitro* studies showed that no inhibition potency toward the COX-2 enzyme was found by compound **5** and slightly better inhibition potency could be observed by compound **3**. The discrepancy between the docked results and bioassay screening values may be attributed to the significant difference of the computed Log *P* values of **3** and **5**, 2.64 and 1.86, respectively.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.molstruc.2015.08.025.

Supplementary data

Crystallography data for compounds **3** and **5** have been deposited with the Cambridge Crystallographic Centre. CCDC No. 963302 and 1024261, respectively. The Data can be obtained free of charge from CDCC, 12 Union Road, Cambridge CB2 1EZ, UK, Fax +44 1223 336 033, email: deposit@cdcc.cam.ac.uk or http://www.ccdc.cam.ac.uk/getstructures.

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