Tetrahedron Letters 53 (2012) 6577–6583

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

$AgNO_3$ mediated C–N bond forming reaction: synthesis of 3-substituted benzothiazines as potential COX inhibitors

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ARTICLE INFO

Article history:
Received 8 August 2012
Revised 20 September 2012
Accepted 22 September 2012
Available online 28 September 2012

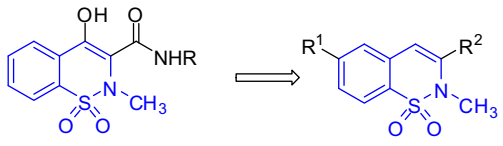
Keywords:
Benzothiazine
Benzenesulfonamides
$AgNO_3$
COX
Docking

ABSTRACT

$AgNO_3$ facilitated the intramolecular ring closure of *o*-(1-alkynyl)benzenesulfonamides via a regioselective C–N bond forming reaction leading to the formation of 3-substituted benzothiazine derivatives. A number of compounds were prepared in good yields by using this inexpensive and safe methodology. All the compounds synthesized were evaluated for their cyclooxygenase (COX) inhibiting properties in vitro. A number of compounds that do not contain an enolic hydroxyl group showed selectivities toward COX-2 over COX-1 inhibition. This was further supported by the predictive binding mode of two compounds with COX-1 and -2 proteins through molecular docking studies.

Benzothiazine, an important heterocyclic compound consists of a benzene ring attached to the six-membered heterocycle thiazine. Compounds containing benzothiazine framework have been studied widely because of their numerous pharamacological importance. For example, various benzothiazine based compounds have been reported as potent anti-inflammatory agents.[1] Some of these compounds, particularly oxicams[2a,b] have already been marketed. Well known anti-inflammatory drugs such as meloxcicam (**A**, Fig. 1) and piroxicam (**B**, Fig. 1) belong to this class of compounds. Both meloxicam and piroxicam inhibit cyclooxygenase (COX), the enzyme responsible for converting arachidonic acid into prostaglandin H_2 (the first step in the synthesis of prostaglandins) that are mediators of inflammation. While piroxicam showed non-selective inhibition of COX isozymes, meloxicam did show low selectivity towards COX-2 over COX-1 especially at low therapeutic dosage.[2c] Notably, selective inhibition of COX-2 has been reported to be beneficial to avoid gastrointestinal side effects of non-selective NSAIDs (non-steroidal anti-inflammatory drugs). While meloxicam showed fewer gastrointestinal side effects than diclofenac, piroxicam and naproxen, its long term use causes gastrointestinal toxicity and bleeding that was thought to be due to the presence of acidic enolic OH in addition to its COX-1 inhibition. Thus, derivatization[3] of this group provided compounds that were stable under gastric conditions and caused lower gastrointestinal irritation.[3b–e] This prompted us to evaluate the COX inhibiting properties of a library of small molecules (**C**, Fig. 1) based on benzothiazine devoid of enolic OH to identify new COX-2 inhibitors. The structure of the target compound **C** therefore was reached by omitting the enolic OH of **A** or **B** followed by introduction of R^1 and R^2 to generate diversity around the core structure.

Because of their various pharmacological significance, synthesis of benzothiazines has attracted the particular attention of organic and medicinal chemists. This is exemplified by the continued effort devoted towards the development of new and better synthetic methods for the construction of the 2*H*-benzo[*e*][1,2]thiazine ring.[4–8] Transition-metal catalyzed reactions are now considered as a powerful tool for the construction of various carbocyclic and heterocyclic structures. Accordingly, a Pd-mediated one-step



R = 5-methylthiazole-2-yl (**A**)
= 2-pyridyl (**B**)

C

Figure 1. Meloxicam (**A**), piroxicam (**B**) and design of benzothiazine based new COX inhibitors.

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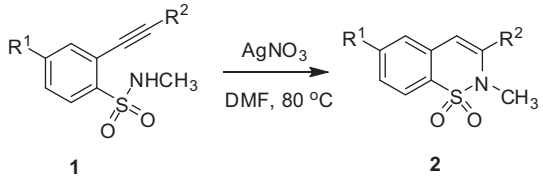
0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.09.102

synthesis of benzothiazines involving the coupling of bromosulfoximine with terminal alkynes under Sonogashira conditions has been reported.[9] One of the major drawbacks of this methodology is the formation of isomeric 1,2-benzoisothiazoles as side products. Thus, a more convenient synthesis of benzothiazines was developed following a coupling-iodocyclization strategy.[10] While this methodology was free from the generation of isomeric side products, it required an additional step to remove the C-4 iodo group. To overcome this problem a direct synthesis of benzothiazine derivatives was developed that involved intramolecular cyclization of *o*-(1-alkynyl)benzenesulfonamides in the presence of $AgSbF_6$ and Et_3N.[11] While this reaction was found to be highly regioselective and afforded good to excellent yields of desired products the methodology, however, involved the use of relatively expensive and corrosive $AgSbF_6$ catalyst. As part of our continuing effort on the identification of biologically active small organic molecules we required a library of benzothiazine derivatives for various in vitro pharmacological screens. We, therefore, were in need of an inexpensive and safer method for accessing this class of compounds. Herein we report our results on $AgNO_3$ mediated synthesis of 3-substituted benzothiazines **2** (or **C**, Fig. 1) from *o*-(1-alkynyl)benzenesulfonamides (**1**) via a regioselective C–N bond forming reaction (Scheme 1). To the best of our knowledge the use of $AgNO_3$ for a similar C–N bond forming reaction has not been studied extensively. We also report COX inhibiting properties of compounds **2** in vitro.[12]

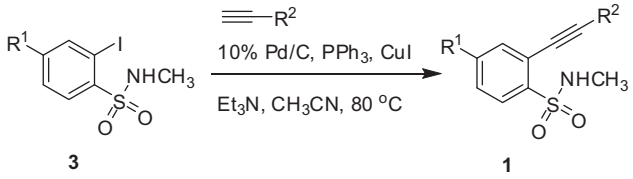
The synthesis of our key starting material *o*-(1-alkynyl)benzenesulfonamides (**1**) was carried out via the Pd/C mediated coupling of *o*-iodobenzenesulfonamide (**3**) with terminal alkynes in good yields (Scheme 2).[10,11] The required sulfonamide (**3**) was prepared either via treating 2-iodobenzenesulfonyl chloride[13] with $MeNH_2$ in dioxane/THF[14] or iodination of *N*-methyl benzene sulfonamide derivative[15] using *n*-BuLi in THF according to the literature.[10]

To establish the optimized reaction conditions we examined the $AgNO_3$ mediated intramolecular cyclization of *N*-methyl-2-*p*-toluylethynyl benzenesulfonamide (**1a**) under various conditions (Table 1). Initially, the reaction was carried out in DMF at 25 °C when no formation of product was observed (Table 1, entry 1). While increasing the temperature to 60 °C improved the product yield, the best result was achieved when the reaction was performed at 80 °C (Table 1, entry 3). Increasing the reaction time (Table 1, entry 4) or temperature (Table 1, entry 5) did not improve the product yield. The use of other solvents, for example, CH_3CN (Table 1, entry 6) and DCE (Table 1, entry 7) was examined and all other solvents were found to be less effective. Notably, the reaction did not proceed in the absence of catalyst (Table 1, entry 8) indicating the key role played by $AgNO_3$ in the present C–N bond forming reaction.

Using the optimized reaction conditions we examined the generality and scope of the $AgNO_3$ mediated synthesis of benzothiazines. Accordingly, a number of alkynes were employed in the present reaction[16] and the results are summarized in Table 2. It is evident from Table 2 that the reaction proceeded well in all these cases affording good yields of the desired product (Table 2, entries

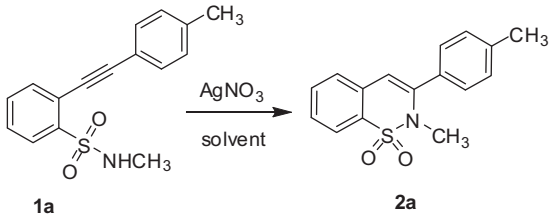


Scheme 1. $AgNO_3$ mediated synthesis of 3-substituted benzothiazines.



Scheme 2. Pd/C-mediated synthesis of *o*-(1-alkynyl)benzenesulfonamides (**1**).

Table 1
$AgNO_3$-mediated cyclization of *N*-methyl-2-*p*-toluylethynyl benzenesulfonamide (**1a**)[a]



Entry	Solvent	Time (h)	Temp (°C)	Yield[b] (%)
1	DMF	2	25	0
2	DMF	2	60	55
3	DMF	2	80	80
4	DMF	6	80	73
5	DMF	2	120	70
6	CH_3CN	2	80	70
7	DCE	2	80	20
8	DMF	2	80	0[c]

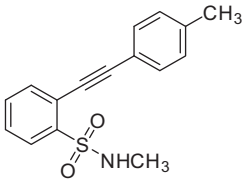
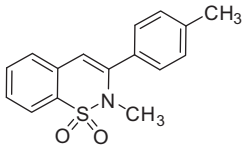
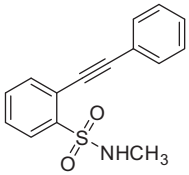
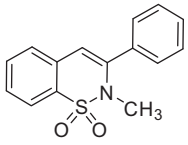
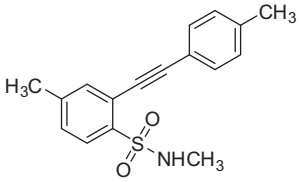
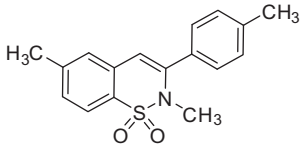
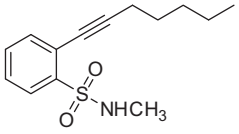
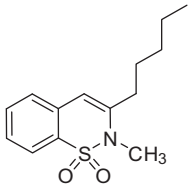
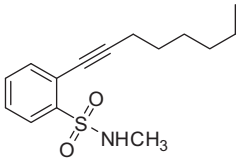
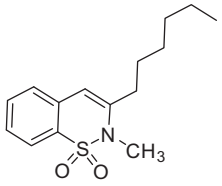
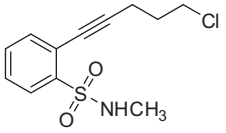
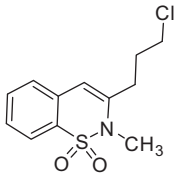
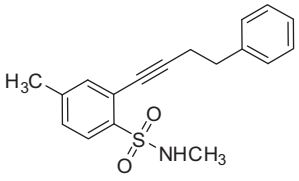
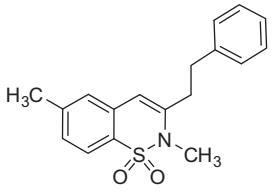
[a] All the reactions were carried out with **1a** with 15 mol % catalyst.
[b] Isolated yields.
[c] The reaction was performed without catalyst. (DCE = 1,2-dichloroethane).

1–9). Both aryl and alkyl substituents present in the alkyne **1** were well tolerated.

Mechanistically, the reaction proceeds (Scheme 3) via activation of the triple bond of **1** by coordination to the Ag-salt to form the σ-complex **E-1**. DMF being a Lewis base form a S–N–H···O=C hydrogen bond which enhances the nucleophilicity of the sulfonamide nitrogen. Regioselective nucleophilic attack of the sulfonamide group to the Ag-coordinated triple bond through its nitrogen in a '6-endo dig' fashion provides the Ag-vinyl species **E-2**. On subsequent protonation of the complex **E-2** regenerates the catalyst affording the desired product **2**. While the reason for observed selectivity towards the six-membered ring formation was not clearly understood the longer S-N bond length perhaps favored endo ring closure due to the less geometric constraint.

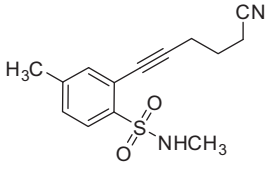
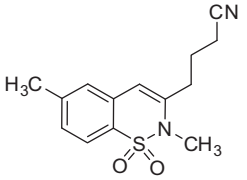
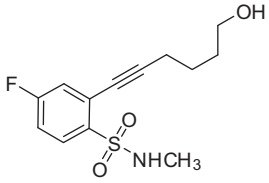
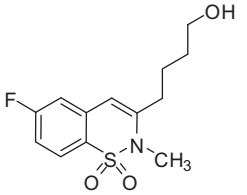
All the synthesized products were evaluated for their COX inhibition potential and selectivity by using biochemical COX (COX-1 & COX-2) enzyme based assay. The COX-1 enzyme was isolated from Ram seminal vesicles whereas the recombinant human COX-2 was expressed in insect cell expression system. These enzymes were purified by employing conventional chromatographic techniques. Enzymatic activities of COX-1 and COX-2 were measured according to the method reported earlier,[17] with slight modifications using a chromogenic assay based on the oxidation of *N*,*N*,*N*′,*N*′-tetramethyl-*p*-phenylene diamine (TMPD) during the reduction of PGG_2 to PGH_2.[18,19] The known non-selective inhibitor indomethacin and COX-2 inhibitor celecoxib were used as reference compounds in this assay. The IC_{50} values determined for all the compounds along with their selectivity (COX-2/COX-1 ratio) are listed in Table 3. Among all the compounds tested **2a–c** and **2g** showed COX-2 selectivity. While all the compounds showed COX

Table 2
Synthesis of 3-substituted benzothiazines (**2**) via $AgNO_3$ mediated cyclization of *o*-(1-alkynyl)benzenesulfonamides (**1**)[a]

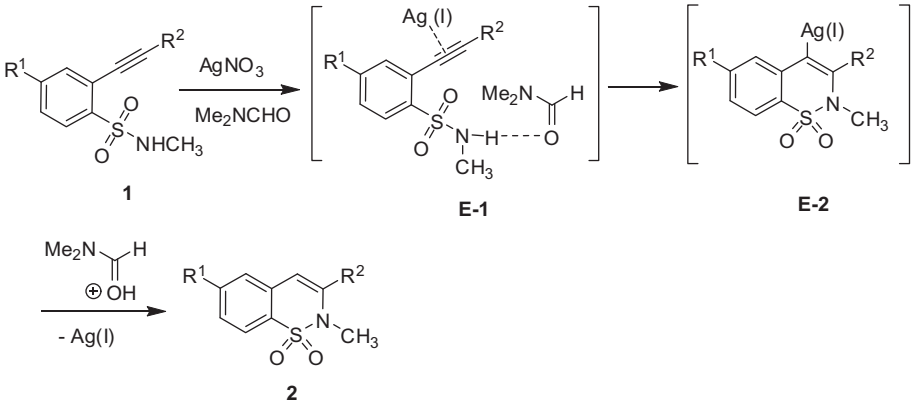
Entry	Alkynes (**1**)	Benzothiazines (**2**)	Time (h)	Yield[b,c] (%)
1	 **1a**	 **2a**	2	80
2	 **1b**	 **2b**	1.5	77
3	 **1c**	 **2c**	2	79
4	 **1d**	 **2d**	2.5	79
5	 **1e**	 **2e**	2	80
6	 **1f**	 **2f**	2	75
7	 **1g**	 **2g**	2	77

(*continued on next page*)

Table 2 (*continued*)

Entry	Alkynes (**1**)	Benzothiazines (**2**)	Time (h)	Yield[b,c] (%)
8	 **1h**	 **2h**	2.5	78
9	 **1i**	 **2i**	2.5	80

[a] All the reactions were carried out at 80 °C with 15 mol % of $AgNO_3$ in DMF.
[b] Isolated yields.
[c] All the compounds synthesized are known and well characterized by NMR, MS and IR.



Scheme 3. Probable mechanism for the $AgNO_3$ mediated formation of benzothiazine ring.

inhibiting properties in vitro only four of them were found to be COX-2 selective. Compounds **2a–c** and **2g** (Table 3, entries 1–3 and 7) showed selectivity towards COX-2 inhibition among which **2g** was found to have the best activity as well as selectivity. It is better than indomethacin though inferior to celecoxib in terms of selectivity. Notably, meloxicam showed an IC_{50} value of 4.7 μM for COX-2 inhibition (with COX-2/COX-1 ratio of 0.12) whereas that of piroxicam was found to be 4.4 μM.[20] Compound **2g**, which lacks of an enolic hydroxyl group, is therefore of high interest.

Table 3
In vitro COX inhibition by 3-substituted benzothiazine derivatives (**2**)

Entry	Compound	IC_{50} (μM)[a]		COX-2/COX-1 Selectivity ratio
		COX-1	COX-2	
1	**2a**	11.52	4.91	0.43
2	**2b**	13.95	5.29	0.38
3	**2c**	14.63	6.83	0.47
4	**2d**	12.27	18.71	1.53
5	**2e**	15.60	20.25	1.30
6	**2f**	15.13	20.09	1.33
7	**2g**	20.76	3.25	0.15
8	**2h**	17.26	23.27	1.35
9	**2i**	22.98	21.02	0.91
10	Indomethacin	0.0067	0.048	7.16
11	Celecoxib	15.0	0.042	0.0028

[a] The result is the mean value of two determinations, and the deviation from the mean is <10% of the mean value.

In silico docking studies were performed to understand the interaction of compounds **2a** and **2g** as well as meloxicam with both the COX isoforms. The PDB ID 1EQG (COX1) and 1CX2 (COX2) were used for the docking study and all these molecules were docked into COX-1 and COX-2 (see Tables 1 and 2 in Supplementary data). Both **2a** and **2g** showed good dock score, that is, −8.45 and −8.37, respectively, when docked into the COX-2 by making good π–π stacking and sitting well within the hydrophobic pocket. These are comparable to the standard drug meloxicam (see Table 1 in Supplementary data). When docked into the COX-1, both **2a** and **2g** showed comparatively lower score than that of COX-2, for example, −7.86 and −7.55, respectively, indicating the selectivity of these molecules towards COX-2 over COX-1 (see Supplementary data, Table 1 versus 2). Notably, a similar trend was observed in case of meloxicam.

The interaction of **2a** with COX-1 was mainly contributed by a π–π stacking between the phenyl ring of **2a** and tyrosine 385 residue (Fig. 2) whereas that of **2g** was contributed by a π–π stacking between its phenyl ring and the tyrosine 355 residue of COX-1 (Fig. 3). Meloxicam showed a π–π stacking between its (i) phenyl ring and tyrosine 385 as well tryptophan 387 and (ii) thiazole ring and tyrosine 355 residue of COX-1 (see Supplementary data).

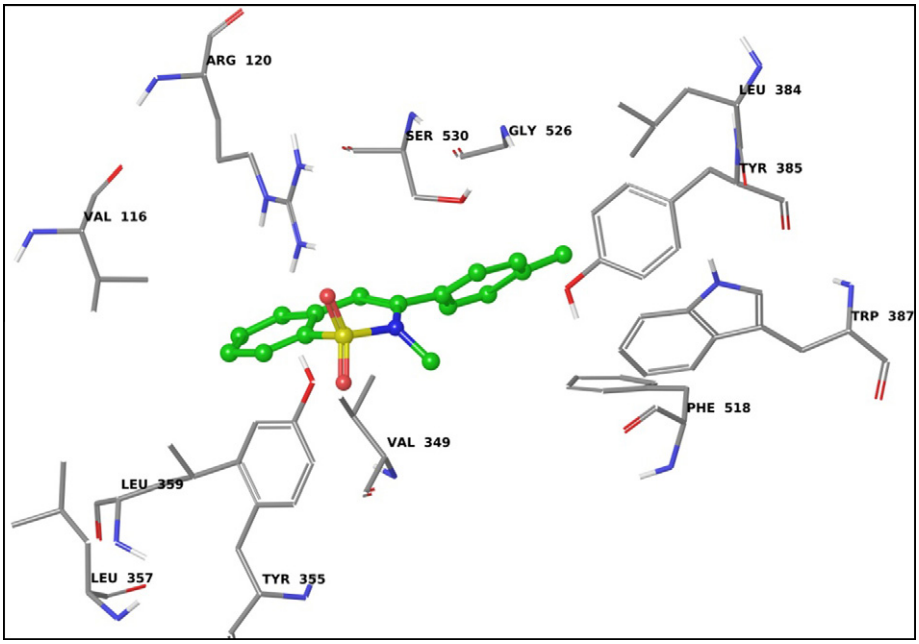


Figure 2. Docking of **2a** at the active site of COX-1.

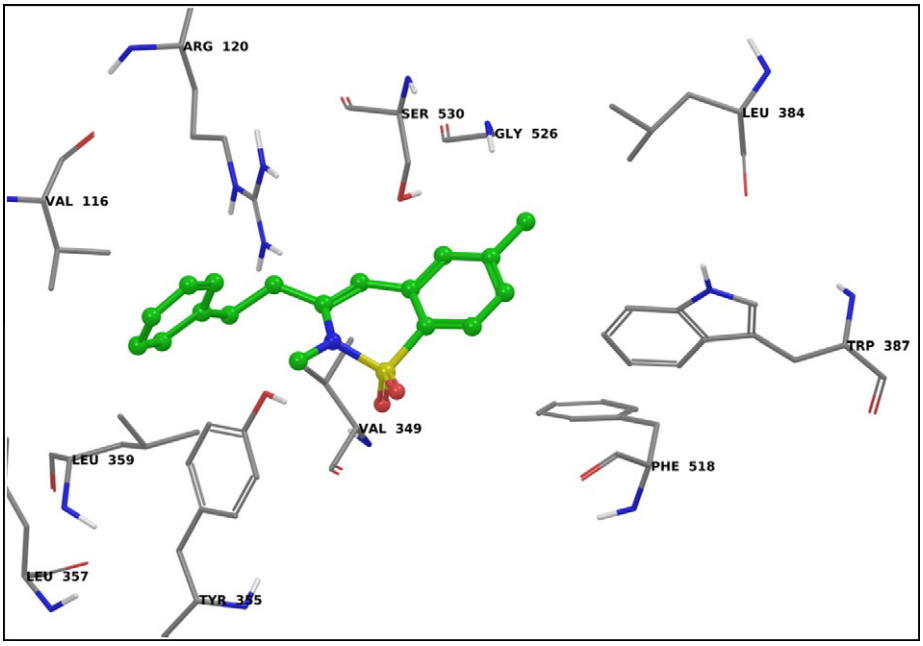


Figure 3. Docking of **2g** at the active site of COX-1.

While interacting with COX-2 both **2a** (Fig. 4) and **2g** (Fig. 5) showed good π–π stacking with tyrosine 355, tyrosine 385 and tryptophan 387 (not shown in 2D interaction diagram, due to default software parameters). Additionally, their hydrophobic parts occupied the hydrophobic region of the receptor site. Meloxicam showed a (i) π–π stacking between its phenyl ring and tyrosine 385 as well tryptophan 387, (ii) π-cation interaction between its thiazole ring and arginine 120 and (iii) H-bonding between its sulphoxide oxygen and the side chain of serine 530 (see Supplementary data).

In conclusion, 3-substituted benzothiazine derivatives devoid of enolic hydroxyl group were designed based on oxicam family of anti-inflammatory agents and explored as potential COX inhibitors. An inexpensive and safer method has been developed for their synthesis which involved $AgNO_3$ mediated intramolecular ring closure of *o*-(1-alkynyl)benzenesulfonamides via a regioselective C–N bond forming reaction. A number of compounds were prepared by using this methodology in good yields. All the compounds synthesized were evaluated for their cyclooxygenase (COX) inhibiting properties in vitro some of which showed selectivities toward COX-2 over COX-1 inhibition. This was further supported by the predictive binding mode of two compounds with COX-1 and -2 proteins through molecular docking studies. Overall, the benzothiazine framework presented here could be an attractive template for the identification of novel cyclooxygenase inhibitors. Due to the atom economic nature, functional group tolerance and efficiency, the

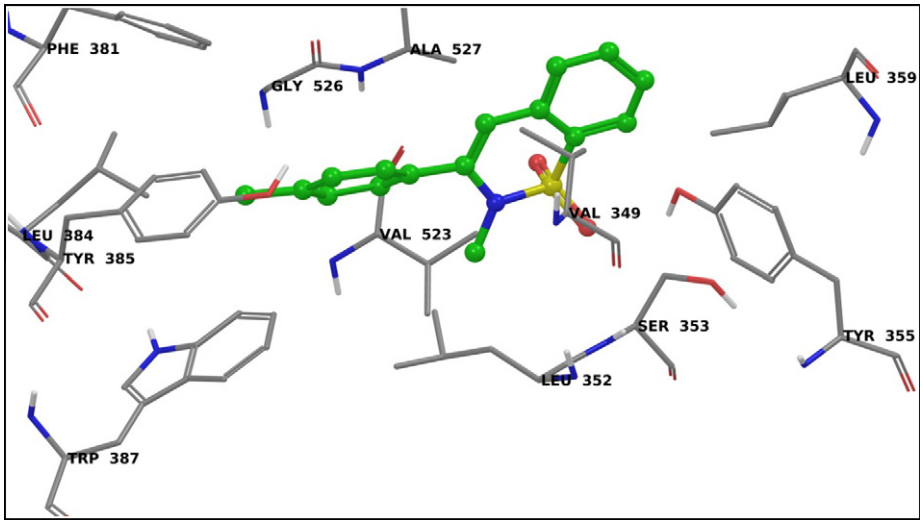


Figure 4. Docking of **2a** at the active site of COX-2.

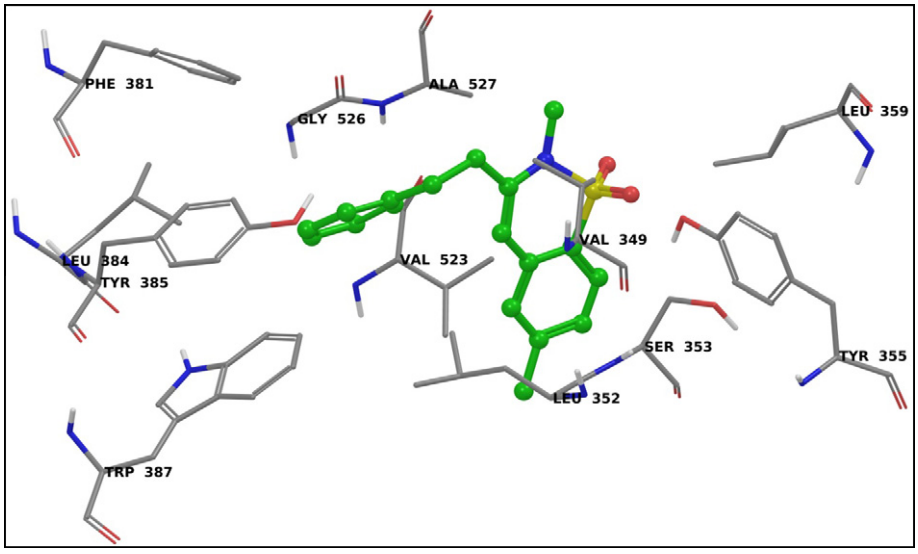


Figure 5. Docking of **2g** at the active site of COX-2.

present methodology could find application in the construction of diverse benzothiazine based small molecules of potential pharmacological interest.

Acknowledgment

The authors thank the management of Institute of Life Sciences for encouragement and support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.09.102.

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16. *Typical procedure for the preparation of 2a:* To a mixture of **1a** (0.27 g, 0.94 mmol), and triethylamine (0.28 g, 0.39 mL, 2.8 mmol) in ethanol (5.4 mL) was added $AgNO_3$ (0.031 g, 0.18 mmol, 0.2 equiv) and the mixture was stirred at 80 °C for 5 min. After completion of the reaction (indicated by TLC), the mixture was filtered through celite and washed with EtOAc. The filtrate was collected and concentrated under vacuum. The residue was purified by column chromatography (SiO_2) to afford the desired product as a white solid; mp 119–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (dd, J = 7.7 and 0.6 Hz, 1H), 7.63–7.26 (m, 7H), 6.69 (s, 1H), 3.01 (s, 3H), 2.41 (s, 3H); IR (cm^{-1}, $CHCl_3$) 1346, 1184; m/z (ES Mass) 286 (M+1, 100%); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.7, 140.1, 132.9, 132.1, 131.7, 131.3, 129.6 (2C), 128.0 (2C), 127.6, 127.5, 122.4, 111.5, 35.7, 21.3.
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19. *Enzyme assay:* Microsomal fraction of ram seminal vesicles were used as a source of COX-1 enzyme and microsomes from *sf*-9 cells infected with baculovirus containing human COX-2 c-DNA were used as a source of COX-2 enzyme. Enzyme activity was measured using a chromogenic assay based on oxidation of *N*,*N*,*N*′,*N*′-tetramethyl-*p*-phenylenediamine (TMPD) during the reduction of PGG_2 to PGH_2 as per the procedure described by Copeland et al[17] with the following modifications. The assay mixture (1000 μL) contained 100 mM Tris pH 8.0, 3 mM EDTA, 15 μM hematin, 150 units enzyme and 8% DMSO. The mixture was pre-incubated at 25 °C for 15 min before initiation of enzymatic reaction in the presence of compound/vehicle. The reaction was initiated by the addition of 100 μM arachidonic acid and 120 μM TMPD. The enzyme activity was measured by estimation of the initial velocity of TMPD oxidation over the first 25 s of the reaction followed from increase in absorbance at 603 nM. The IC_{50} values were calculated using non-linear regression analysis.
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