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Facile Synthesis, Characterization and *in Silico* Docking Studies of Novel Thiazolidine-2,4-Dione-Based Mannich Base Bearing Furan/Thiophene Moiety as Promising Anti-Inflammatory Agents

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Abstract

Mannich bases are compounds bearing a β-amino carbonyl moiety. They are formed in the Mannich reaction that consists of an amino alkylation of an acidic proton placed next to a carbonyl functional group by formaldehyde and a primary or secondary amine. Mannich base products are known for their curative properties such as anti-inflammatory, antibacterial, anticancer, antifungal, anthelmintic, anticonvulsant, analgesic, anti-HIV, antipsychotic, antiviral, and antimalarial activities. Further, thiazolidinedione derivatives have shown to be efficacious in inflammatory diseases as wide-ranging as psoriasis, ulcerative colitis and non-alcoholic steatohepatitis. In light of the above observations, new series of thiazolidine-2,4-dione based Mannich base derivatives were synthesized via a simple and catalyst-free procedure involving the condensation of thiazolidine-2,4-dione, formaldehyde and secondary amines in DMF solvent. The structures of the newly synthesized compounds were confirmed by their IR, ^{1}H-NMR, and Mass spectra. The synthesized compounds were tested for their *in silico* anti-inflammatory activity by Docking studies against COX-2 enzyme (PDB: 1CX2). Compounds 4a and 4b showed good *in silico* anti-inflammatory properties comparable to that of standard drug Diclofenac and may be considered as promising candidates for the development of new anti-inflammatory agents.

Keywords: Anti-inflammatory agents; Docking studies; Furan; Thiazolidine-2,4-dione; Thiophene.

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment and management of inflammation and pain associated with conditions such as osteoarthritis, rheumatoid arthritis, post-operative pain, orthopedic injuries, ankylosing spondylitis, gout, dysmenorrhea, dental pain and headache (Atzeni et al., 2018; Ong et al., 2007). Non-steroidal anti-inflammatory drugs are divided into two categories: non-selective inhibiting both cyclooxygenase enzymes COX-1 and COX-2, and selective inhibiting COX-2 enzyme (Brune and Patrignani, 2015). Although COX-1 and COX-2 are isoenzymes involved in the same physiological pathway converting arachidonic acid (AA) to prostaglandins (PDs) (Bakhle, 1999; Meek et al., 2010), COX-1 isoenzyme is a constitutive enzyme mainly found in the gastrointestinal lining with a "house-keeping" role in regulating many normal physiological processes in which prostaglandins serve a protective role (Fokunang et al., 2018), though COX-2 enzyme is facultative, and expressed at the sites of inflammation by pro-inflammatory molecules such as interleukin-1 (IL-1), tumor necrosis factor- (TNF-), lipopolysaccharide (LPS), and tissue plasminogen activator (TPA) (Fokunang et al., 2018; B Bari and D Firake, 2016) and produces the desirable effects of NSAIDs (Zarghi and Arfaei, 2011). For the reasons stated above, long term uses of non-selective NSAIDs is not advisable due to their severe gastrointestinal toxicities (Rodríguez and González-Pérez, 2005; Vostinaru, 2017), resulting from their stronger inhibition of COX-1 enzyme (Vostinaru, 2017). Examples of NSAIDs that were removed from the market due to their toxicities include Vioxx (rofecoxib) pulled from the worldwide market due to its increased risk for heart attacks and strokes (Sibbald, 2004); Bromfenac, Ibufenac, and Benoxaprofen that were reported to be hepatotoxic (Goldkind, 2006). Therefore, the present work intends to search for novel safe and selective COX-2 inhibitors for the management of pain and inflammation.

Thiazolidine-2,4-dione (TZD) derivatives were reported to exhibit diverse pharmacological properties such as anti-tubercular (Chilamakuru et al., 2013), antidiabetic, antimicrobial and anti-cancer (Durai Ananda Kumar et al., 2015). Recently, it was reported that TZD derivatives are

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potent anti-inflammatory agents (Srivastava et al., 2019). In the study conducted by Zhu et al. (2011), TZDs inhibited the release of a variety of inflammatory mediators from human Airway Smooth Muscle cells, suggesting their uses in the treatment of asthma. Ceriello (2007) reviewed the anti-inflammatory activity of TZDs and found that these compounds act by modulating the anti-inflammatory markers such as IL-6, IL-18, CRP, MMP-2, MMP-9. Mohanty et al. (2004) evidenced the anti-inflammatory effect of rosiglitazone as a drug of the thiazolidinedione class that exerts an anti-inflammatory effect at the cellular and molecular level, and in plasma. In addition to these useful properties of thiazolidinedione products; furan and thiophene derivatives form a class of compounds with a broad spectrum of biological properties such as antibacterial (Holla et al., 1987), anti-allergic, antidepressant, antidiabetic, analgesic and anti-inflammatory activities (Mishra et al., 2011).

Nowadays, *in silico* molecular docking studies of small molecules to protein binding sites has become an increasingly popular approach for the development of new drugs (Berry et al., 2015). This is because *in silico* molecular docking study requires very less time to differentiate from many compounds the most probable potent ones with desired biological activities when compared with traditional laboratory experiments (Naim et al., 2018; Afriza et al., 2018). In view of the above prominent properties of thiazolidinedione, furan and thiophene derivatives and rapid with higher precision of *in silico* docking studies, novel series of compounds incorporating both thiazolidine-2,4-dione and furan/thiophene moieties in one Mannich base molecule that might display synergetic and enhanced biological activities were synthesized, characterized and evaluated for their *in silico* COX-2 inhibitory activity.

2. Material and methods

2.1. Material

The innovative DTC-967A apparatus was used to determine the melting points of the new compounds and are uncorrected. The IR-spectra (in KBr pellets) were recorded on Shimadzu FT-IR Prestige-21 spectrophotometer and are expressed in cm^{-1}. The mass spectra were recorded on Shimadzu LC-MS-8030 mass spectrophotometer operating at 70 eV. A Bruker AVANCE II 400 MHz instrument was used to record ^{1}H-NMR spectra in $CDCl_3$ as solvent and TMS as an internal standard.

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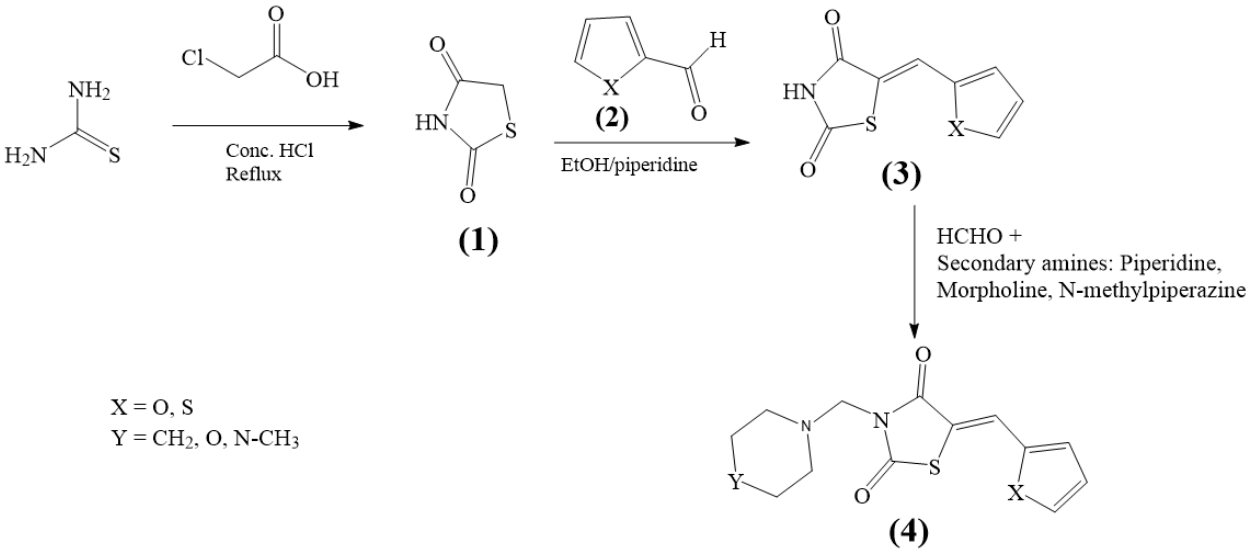
2.2. Chemistry method

Thiazolidine-2,4-dione (1) was synthesized by the cyclocondensation of thiourea with monochloroacetic acid in acidified water solvent (Kar et al., 2014). Knoevenagel condensation of thiazolidine-2,4-dione (1) with furan/thiophene-5-carbaldehyde (2) in ethanol solvent containing a catalytic amount of piperidine afforded the key intermediate: furfurylidene/thienylidene thiazolidine-2,4-dione (3) prepared according to Ha et al. (2012). Novel Mannich base products (4) were synthesized by reacting compounds (3) with formaldehyde and secondary amines: piperidine, morpholine or N-methylpiperazine (**Scheme 1**) in DMF solvent as given in the general procedure. The completion of the reaction, as well as the purity of the products (4), were checked by TLC using silica gel plates (Merck) with hexane:ethylacetate (6:4) as mobile phase.



Scheme 1: Synthesis of Mannich base derivatives of thiazolidinedione

Synthesis of 5-(furan-2/thiophen-2-ylmethylene)thiazolidine-2,4-dione-based Mannich bases (4a-e): General procedure

Furfurylidene/thienylidene thiazolidine-2,4-dione (3) (0.01 mol) and formaldehyde (40%, 1.5 mL) were added in 100 mL Erlenmeyer flask containing 10 mL DMF. Using a magnetic stirrer, the mixture was stirred at room temperature for 20 min. An appropriate secondary amine (0.01 mol): piperidine / morpholine / N-methyl piperazine was then added, and the resulting mixture

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was further stirred at room temperature for 6 hours to precipitate Mannich base products that were collected by filtration, washed with cold water, dried and recrystallized from ethanol.

2.3. Molecular Docking Studies

In silico docking study was performed according to Rizvi et al. (2013) to predict interactions of newly synthesized compounds (**4a-e**) with the target COX-2 enzyme's active site. The crystal structure of COX-2 (PDB code: 1CX2) was downloaded from RCSB Protein Data Bank (http://www.rcsb.org) as 1CX2.PDB (gz). It was then processed using Discovery Studio Biovia 2020 suite (Dassault Systèmes, San Diego, California, USA) in which protein inhibitor SC558, all water molecules, unwanted heteroatoms and similar chains B, C and D were deleted to generate the file saved as 1CX2.PDB. This file was further processed by adding polar hydrogen atoms and Kollman Charges to the individual protein atoms with Auto Dock Tool (ADT) software to get 1CX2.PDBT file required for Autogrid and AutoDock (Huey and Morris, 2008); Rizvi et al., 2013).

The Marvin Sketch software (Marvin suite 20.11.0) was used for drawing and energy minimization of each ligand structure (4a-e) to generate ligand.PDB. The ADT was then used to process these ligands in which nonpolar hydrogens were combined, Gasteiger changes and rotatable bonds were added and generated ligand.PDBQT format needed by Autogrid and Autodock (Rizvi et al., 2013; Morris, 2012). Autogrid parameters were set using ADT and a docking grid box was built with 40, 40, and 40 points in X, Y and Z dimensions with X=31.594, Y=24.653, and Z=12.650 as the position of the active site to generate a.GPF file. A docking parameter file a.DPF was prepared using the Lamarckian genetic algorithm 4.2 search method implemented in AutoDock 4.2 software integrated within Auto Dock Tools version 1.5.6 (ADT; Scripps Research Institute, La Jolla, San Diego, USA). The receptor was kept rigid, ligands were allowed to be flexible and all docking parameters were set to default. The molecular docking was performed on Microsoft windows 10, 64-bit laptop using Cygwin software. The docking results were analyzed by Discovery Studio Biovia 2020 suite software.

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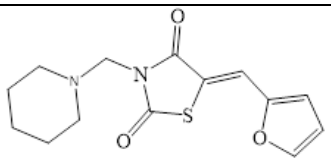
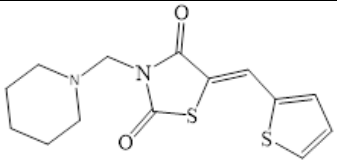
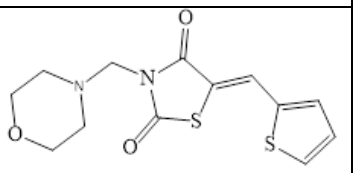
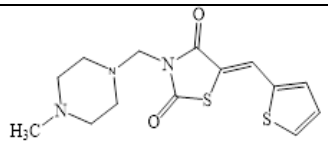
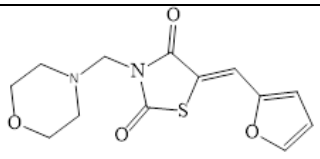
3. Results and discussion

3.1. Chemistry

The structures of newly synthesized compounds 5-(furan-2/thiophen-2 ylmethylene)thiazolidine-2,4-dione-based Mannich compounds (4a-e) were confirmed by their IR, 1H-NMR, and mass spectra. Other data that characterize the newly synthesized compounds are given in **Table 1**.

Table 1: Characterization data of synthesized thiazolidinedione based **Mannich bases (4a-e).**

Compd. No.	X	Y	M.P (°C) (Yield %)	Molecular formula	Mol. Wt	Chemical structure
4a	O	CH_2	189-191 (82)	$C_{14}H_{16}N_2O_3S$	292.35	
4b	S	CH_2	220-222 (74)	$C_{14}H_{16}N_2O_2S_2$	308.41	
4c	S	O	198-200 (76)	$C_{13}H_{14}N_2O_3S_2$	310.39	
4d	S	N-CH_3	206-208 (72)	$C_{14}H_{17}N_3O_3S$	307.37	
4e	O	O	176-178 (68)	$C_{13}H_{14}N_2O_4S$	294.33	

The table above gives the melting point: M.P (°C), molecular formula, molecular weight (Mt), and the chemical structure of the newly synthesized compounds **4a-4e**. The results from the

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above table show that the newly synthesized compounds were formed in a good yield ranging from 68% to 82% with molecular weight between 292 to 310.

The IR spectrum of 5-(furan-2-ylmethylene)-3-(piperidin-1-ylmethyl)thiazolidine-2,4-dione **(4a) (Figure 1)** showed prominent bands at 3089 cm^{-1} and 2964 cm^{-1} for C-H stretching frequencies. The bands at 1645 cm^{-1} and 1589 cm^{-1} are attributed for C=O stretching frequencies, while the C-O band appeared at 1273 cm^{-1} stretching frequency.

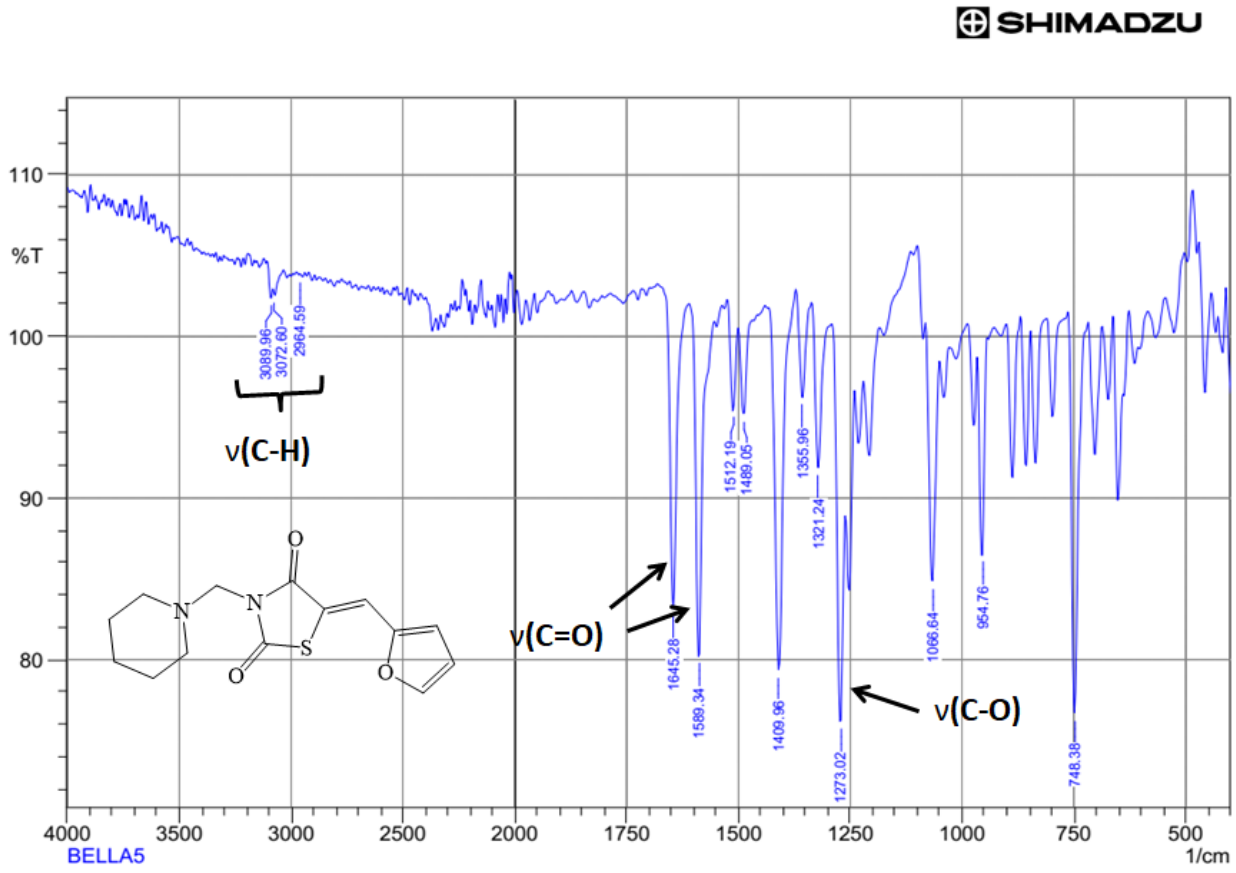

Figure 1: The IR spectrum of 5-(furan-2-ylmethylene)-3-(piperidin-1-ylmethyl)thiazolidine-2,4-dione **(4a)**

The formation of Mannich base products **(4a-e)** from compounds **(3)** was further confirmed by their ^{1}H NMR spectra. As a typical example, in the ^{1}H-NMR (400 MHz, $CDCl_3$) spectrum of 5-(furan-2-ylmethylene)-3-(piperidin-1-ylmethyl)thiazolidine-2,4-dione **(4a) (Figure 2)** the protons at the 4th position of piperidine moiety labelled as H_A appeared as a quintet at δ 1.33-1.39 ppm integrating for two protons. A quintet signal seen at δ 1.52-1.58 ppm is due to the resonance

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of four protons (H_B) located at the 3rd position of piperidine moiety. The four protons (H_C) from the 2nd position of the piperidine group resonated as a triplet at δ 2.59-2.62 ppm while methylene N-CH_2-N protons (H_D) came into resonance as a singlet at δ 4.69 ppm integrating for two protons. One proton (H_G) at the 4th position of furan ring come into resonance as a triplet at δ 6.57-6.58 ppm, whereas a doublet seen δ 6.77-6.78 ppm (J = 3.48 Hz) resulted from the resonance of a proton (H_F) located at the 3rd position of furan ring. The CH=C proton (H_E) resonated as a singlet at δ 7.62 ppm, and a proton (H_I) at 5th position of furan ring appeared as a doublet at δ 7.66-7.67 ppm (J = 1.64 Hz).

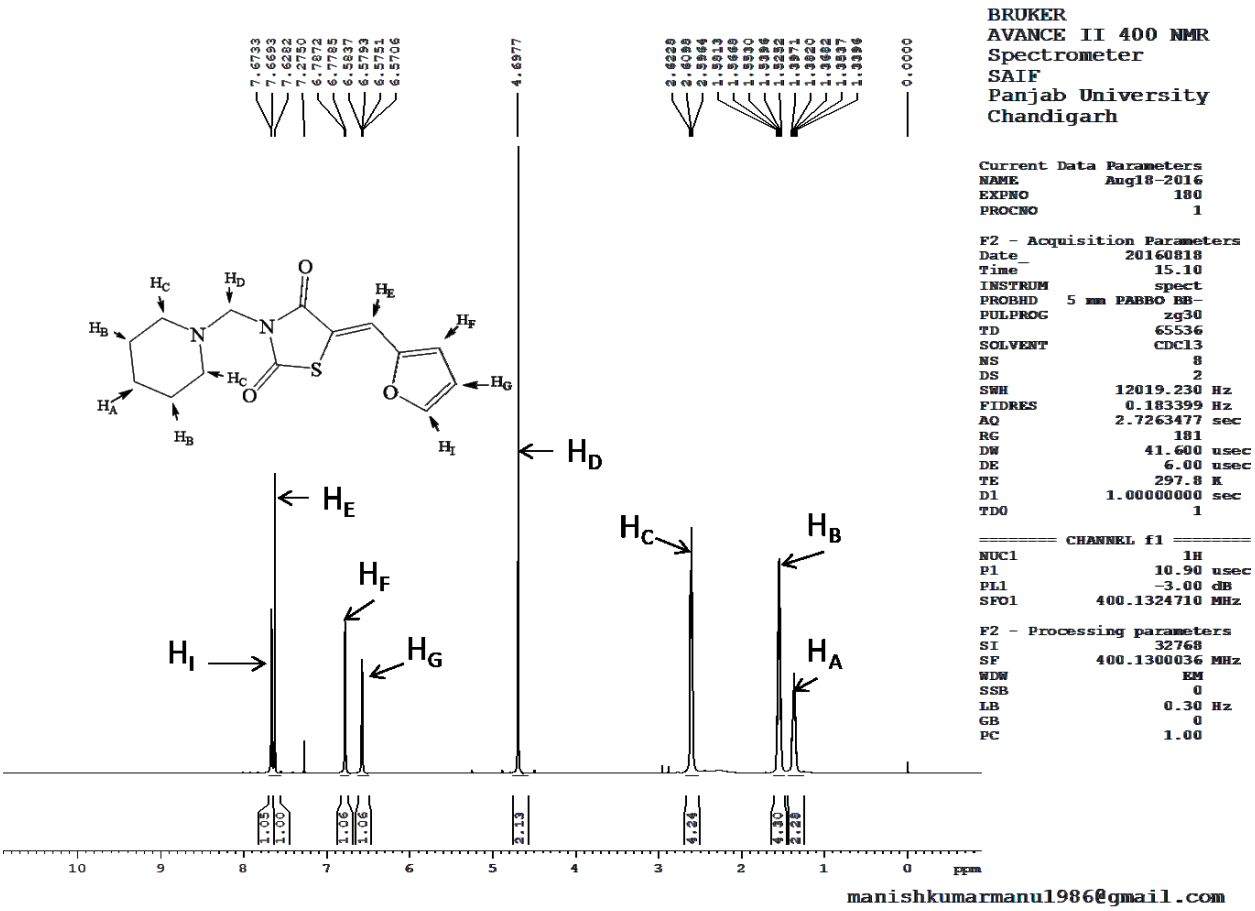

Figure 2: ^{1}H NMR spectrum of 5-(furan-2-ylmethylene)-3-(piperidin-1-ylmethyl)thiazolidine-2,4-dione **(4a).**

The mass spectra further confirmed the structures of the new compounds **(4a-e)**. In a typical example, the mass spectrum of 5-(furan-2-ylmethylene)-3-(piperidin-1-ylmethyl)thiazolidine-

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2,4-dione **(4a) (Figure 3)** showed molecular ion peak at m/z = 292 (M^+) which is in conformity with its molecular formula $C_{14}H_{16}N_2O_3S$.

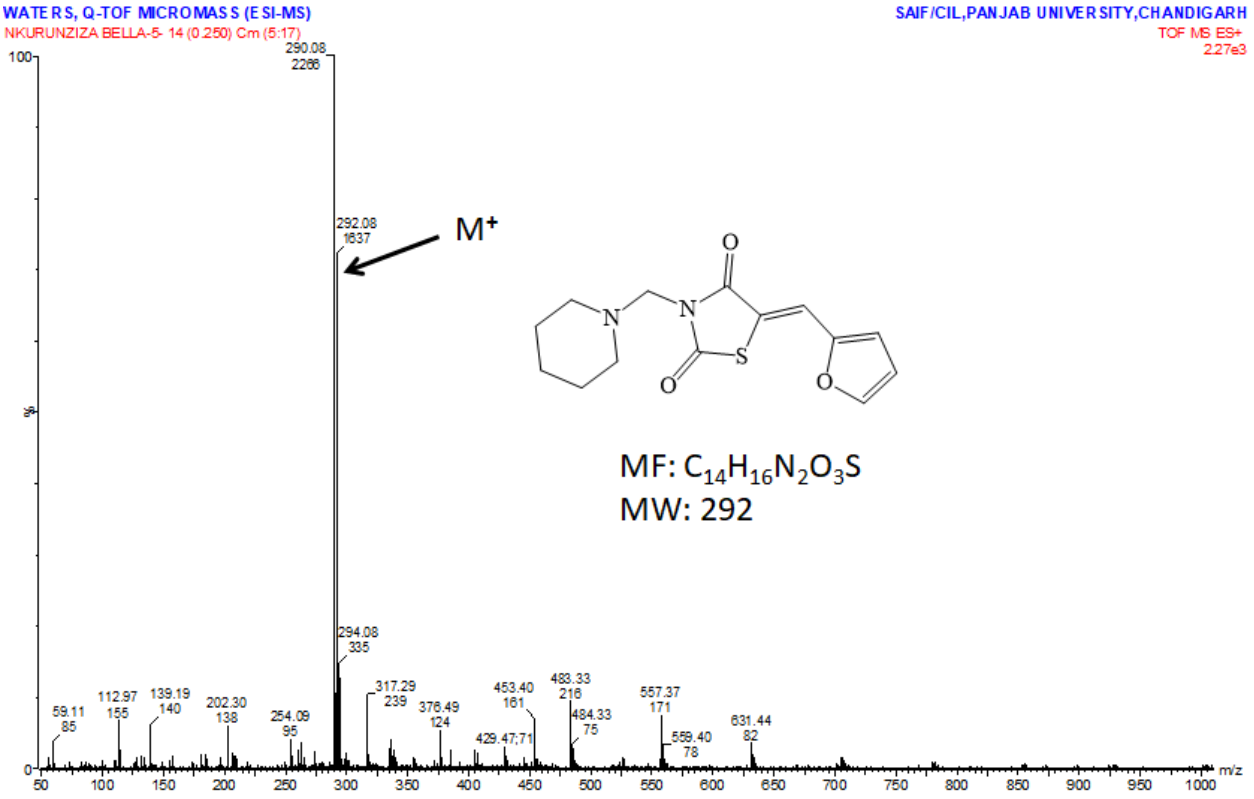

Figure 3: Mass spectrum of of 5-(furan-2-ylmethylene)-3-(piperidin-1-ylmethyl)thiazolidine-2,4-dione **(4a)**

The spectral data of other newly synthesized compounds prepared according to the general procedure presented in section 2.2 are given below:

4b) 3-(Piperidin-1-ylmethyl)-5-(thiophen-2-ylmethylene)thiazolidine-2,4-dione

IR (KBr, γ/cm^{-1}): 3074, 2985 (C-H stretch), 1633, 1573 **(**C=O stretch), **^{1}H-NMR** (400 MHz, $CDCl_3$): δ (ppm) 1.34-1.40 (quintet, 2H at 4th position piperidine), 1.52-1.58 (quintet, 4H at 3rd position of piperidine), 2.60-2.63 (t, 4H at 2nd position of piperidine), 4.71 (s, 2H, N-CH_2-N), 7.17-7.20 (t, 1H, furan-4H), 7.39-7.40 (d, *J*=3.64 Hz, 1H, furan-3H), 7.64-7.66 (d, *J*=5.08 Hz, 1H, furan-5H), 8.04 (s, 1H, C=CH). LC-MS (m/z): 309 (M^+ + 1).

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4c) 3-(Morpholinomethyl)-5-(thiophen-2-ylmethylene)thiazolidine-2,4-dione

IR (KBr, γ/cm^{-1}): 3111, 2964 (C-H stretch), 1651, 1589 **(**C=O stretch), **^{1}H-NMR** (400 MHz, $CDCl_3$): δ (ppm) 2.66-2.68 (t, 4H adjacent to N-morpholine), 3.66-3.68 (t, 4H adjacent to O-morpholine), 4.70 (s, 2H, N-CH_2-N), 7.18-7.21 (t, 1H, furan-4H), 7.40-7.41 (d, *J*=3.68 Hz, 1H, furan-3H), 7.66-7.67 (d, *J*=5.04 Hz, 1H, furan-5H), 8.06 (s, 1H, C=CH). LC-MS (m/z): 310 (M^+).

4d) 5-(furan-2-ylmethylene)-3-((4-methylpiperazin-1-yl)methyl)thiazolidine-2,4-dione

IR (KBr, γ/cm^{-1}): 3057, 2978 (C-H stretch), 1649, 1587 (C=O stretch), **^{1}H-NMR** (400 MHz, $CDCl_3$): δ (ppm) 2.25 (s, 3H, N-CH_3), 2.41 (s, 4H of piperazine moiety), 2.72 (s, 4H of piperazine moiety), 4.73 (s, 2H, N-CH_2-N), 7.18-7.20 (t, 1H, furan-4H), 7.39-7.40 (d, *J*=3.72 Hz, 1H, furan-3H), 7.65-7.66 (d, *J*=5.00 Hz, 1H, furan-5H), 8.03 (s, 1H, C=CH). LC-MS (m/z): 323 (M^+).

4e) 5-(furan-2-ylmethylene)-3-(morpholinomethyl)thiazolidine-2,4-dione

IR (KBr, γ/cm^{-1}): 3082, 2985 (C-H stretch), 1637, 1577 (C=O stretch), **^{1}H-NMR** (400 MHz, $CDCl_3$): δ (ppm) 2.65-2.68 (t, 4H adjacent to N-morpholine), 3.66-3.68 (t, 4H adjacent to O-morpholine), 4.68 (s, 2H, N-CH_2-N), 6.58-6.59 (m, 1H, furan-4H), 6.78-6.79 (d, *J*=3.56 Hz, 1H, furan-3H), 7.64 (s, 1H, C=CH), 7.64-7.68 (d, *J*=4.52 Hz, 1H, furan-5H). LC-MS (m/z): 294 (M^+).

The plausible mechanism for the formation of the above new Mannich base products probably involved the formation of an alcohol intermediate (OH-intermediate) rather than imine from the reaction between thiazolidine-2,4-dione derivatives **(3)** with formaldehyde. This intermediate product then condensed with secondary amines to furnish the title compounds **(4)** in the reaction that has not required a catalyst **(Scheme 2).**

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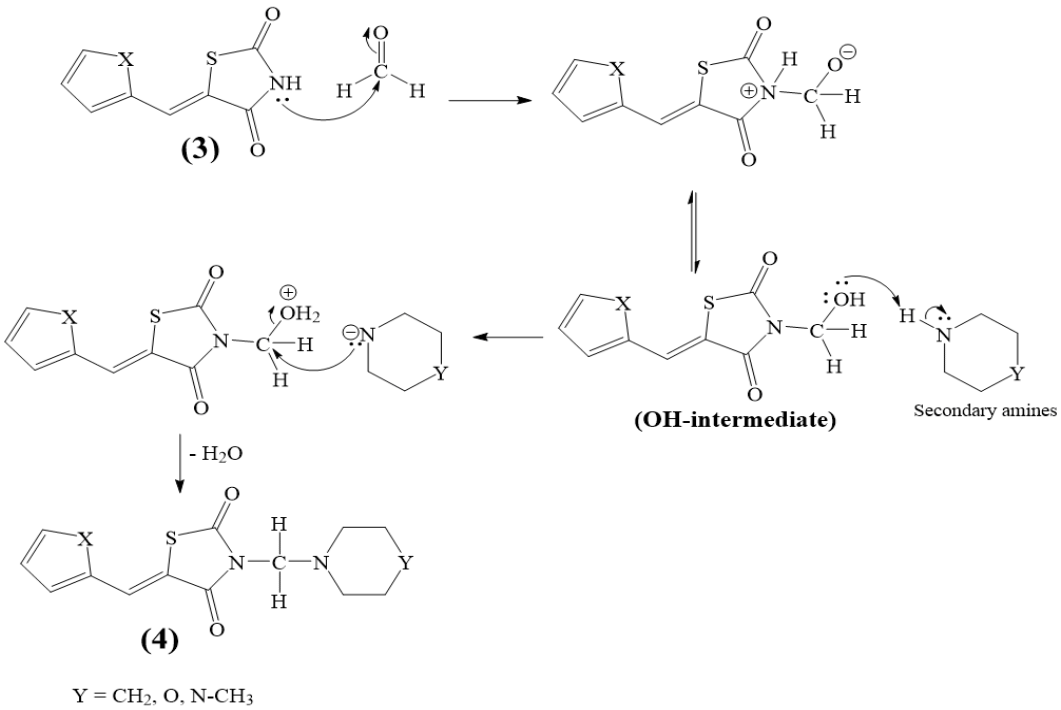

Scheme 2: Mechanism for the formation of Mannich bases **(4a-e)**

3.2. Molecular Docking Study

In silico anti-inflammatory activity of compounds **4a-e** was undertaken by studying the binding and inhibition effects of ligands **(4a-e)** to the target COX-2 protein (PDB code: 1CX2) in which the co-crystallized structure **SC-558** was carefully removed using Discovery studio 2020 suite. The docking results of the synthesized compounds **(4a-e)** and diclofenac used as the reference drug are presented in **Table 2**.

Table 2. Docking results of thiazolidinedione-based Mannich base bearing furan/thiophene moiety (4a-e).

Compound No.	Binding energy	Inhibitory constant (μM)	No. of H-bonds	H-Bond
4a	-7.61	2.65	1	A:ARG120:HH::UNK0:O
4b	-7.59	2.75	0	-
4c	-6.64	13.53	1	A:TYR385:HH::UNK0:O
4d	-6.72	11.81	0	-

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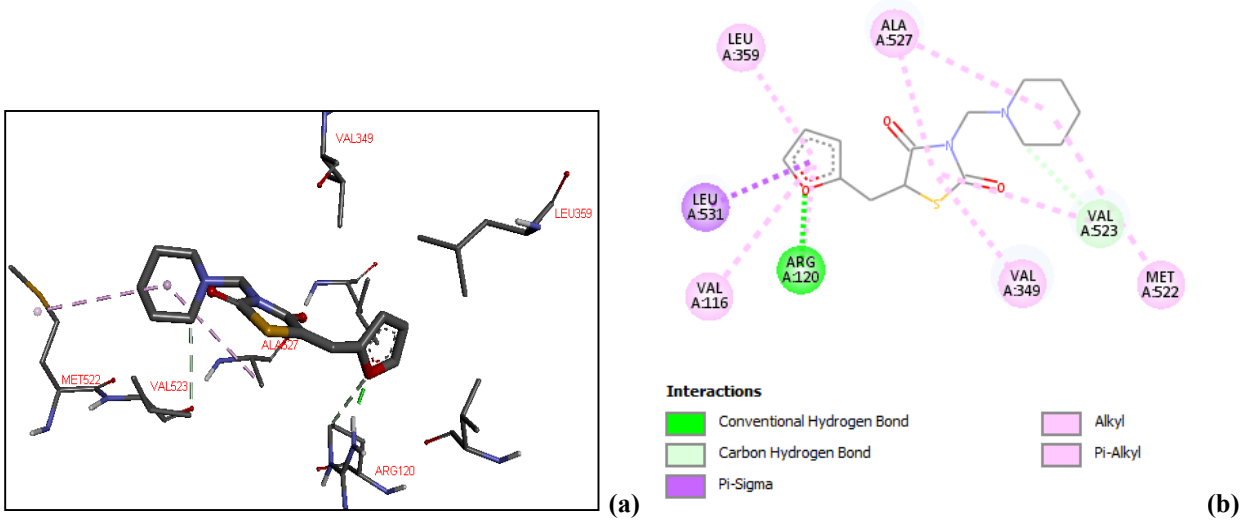
4e	-6.95	8.03	1	A:ARG120:HH::UNK0:O
Diclofenac	-7.63	2.53	1	A:ARG120:HH::UNK0:O

The above results showed that two compounds **4a** and **4b** displayed good binding energy of -7.61 kJ mol^{-1} and -7.59 kJ mol^{-1} respectively, which are comparable to the reference drug diclofenac with -7.63 kJ mol^{-1}. In addition to one conventional hydrogen bond interaction between the oxygen atom of furan moiety in the compound **4a** with NH of ARG 120 and one carbon-hydrogen bond between the nitrogen atom of piperidine moiety with a CH group of VAL 523, the observed high binding affinity of compound **4a** has been attributed to strong hydrophobic interactions between **4a** ligand with VAL 116, VAL 349, LEU 359, LEU 531, MET 522 and ALA 527 amino acids that maximized its interactions with the target binding site (**Figure 4a and 4b**).



(a) **(b)**

Figure 4(a): Docked complex between the protein 1CX2 and ligand 4a; Figure 4(b): Interacting residues between the protein 1CX2 and ligand 4a. The hydrogen bonds between one of the O-atoms of the ligand with ARG 120 is shown in green dotted line.

The **1CX2-Diclorofenac complex** is given in **Figure 5(a) and the interacting residues in the same complex are shown in Fig 5(b)**. Diclofenac displayed one conventional hydrogen bond between the oxygen atom of the ligand with NH of ARG 120, and also showed strong

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hydrophobic interactions with VAL 349, VAL 523, LEU352 and ALA 527 amino acids of the target active site.

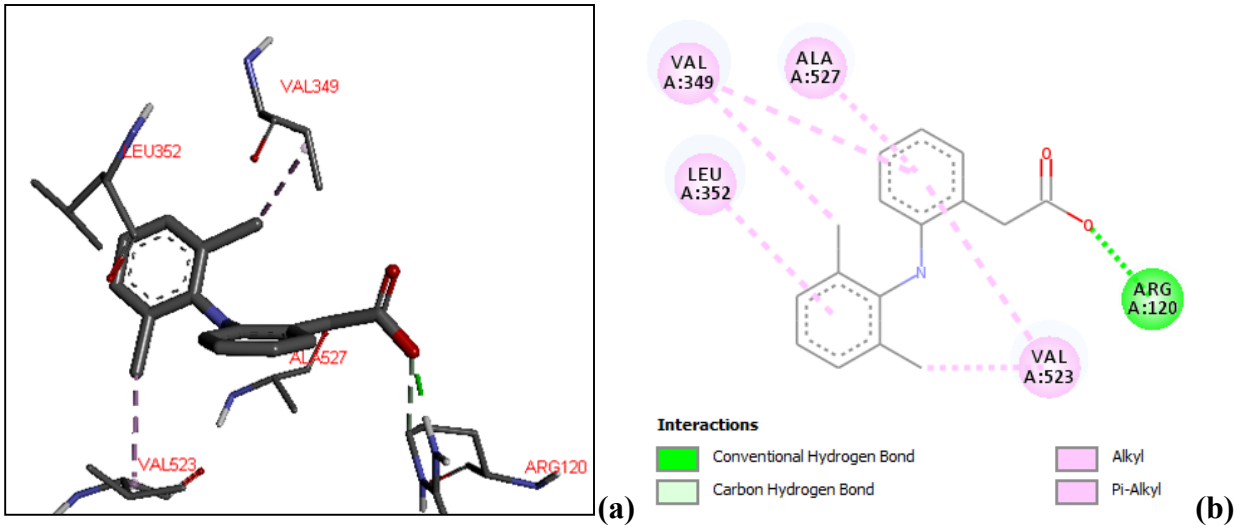

Figure 5(a): Docked complex between protein 1CX2 and diclofenac ligand; **Figure 5(b)**: Interacting residues in 1CX2-Diclofenac complex. The hydrogen bond between one of the O-atoms of the ligand with ARG 120 is shown in green dotted line. The observed results are in line with Mousa et al. (2019) experiment in which Diclofenac inhibited the 1CX2 enzyme by binding on ARG 120. Furthermore, molecular docking study results showed that each ligand molecule displayed its own conformation, related to its IR spectrum that has fitted within the active site to some extent. As a typical example, the IR spectrum of compound **4a** showed the IR band at 1273 cm^{-1} for C-O-C (stretching) of the furan moiety. This furan-oxygen atom displayed one H-bond with ARG 120 of the 1CX2 target protein. However, compound **4b** which is lacking such a C-O-C group of atoms did not display such IR band, hence unable to display any hydrogen bond with the protein active site.

4. Conclusion

We successfully achieved the synthesis of novel series of thiazolidine-2,4-dione-based Mannich base bearing furan/thiophene moiety **(4a-e)** in a reaction that did not require any acidic catalysts. *In silico* docking studies of compounds **(4a-e)** on particular cyclooxygenase COX-2 enzyme (PDB ID: 1CX2) have been evaluated in comparison with Diclofenac used as a reference drug. The compounds **4a** (5-(furan-2-ylmethylene)-3-(piperidin-1-ylmethyl)thiazolidine-2,4-dione) and **4b** (3-(Piperidin-1-ylmethyl)-5-(thiophen-2-ylmethylene)thiazolidine-2,4-dione) displayed

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comparable docking energy to that of standard drug Diclofenac, and the present molecular docking studies suggested that these compounds **4a** and **4b** are candidate ligands for restoring inflammation and pain in conditions such as osteoarthritis, rheumatoid arthritis.

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Conflict of interest

The authors declare no conflict of interest

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