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DESIGN, SYNTHESIS AND MOLECULAR DOCKING OF AMINOACETYLENIC-4,4-DIMETHYLGLUTARIMIDE AS NOVEL CYCLOOXYGENASE (COX) INHIBITORS

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ABSTRACT

Objective: Design and synthesize a new Aminoacetylenic-4,4-dimethylglutarimide derivatives and investigate their selective inhibitory activity to COXs.

Methods: Aminoacetylenic-4,4-dimethylglutarimide derivatives were synthesized by alkylation of 4,4-dimethylglutarimide with propargyl bromide afforded 4,4-dimethyl-1-(prop-2-yn-1-yl)piperidine-2,6-dione. The alkylated4,4-dimethylglutarimide was subjected to Mannich reaction afforded the desired Aminoacetylenic-4,4-dimethylglutarimides (**ZS-1 to ZS-8**). The elemental analysis was indicated by the Euro EA elemental analyzer (Jordan University) and chemical structures were investigated via IR, ^{1}H-NMR, ^{13}C-NMR, DSC (Star system, Switzerland) with the aid of Bruker FT-IR and Varian 300 MHz spectrometer and DMSO-d6 as a solvent, molecular docking was done using the Autodock Tool software (version 4.2). ChemBioDraw was used in the drawing of our schemes.

Results: The IR, 1H-NMR, 13C-NMR, DSC and elemental analysis were consistent with the assigned structures. The design of these compounds as COXs inhibitors were based on the rationalization of the important π–interaction or aromaticity criteria that provide effective inhibitory with COXs–enzymes.

Conclusion: Requirement of aromaticity in binding affinity to COXs enzymes was very essential.

Keywords: Aminoacetylenic, 4,4-Dimethylglutarimide, Molecular modelling, Cyclooxygenase inhibitors, Anti-inflammatory

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly used classes of medicines in the world, accounting for approximately 5% of all prescribed medications. An inhibitory effect of NSAIDs on cyclooxygenase (COX) activity are responsible for their anti-inflammatory actions these are due to COXs are enzymes essential for the synthesis of prostaglandins (PGs), such as PGE2, which have a strong capability to induce inflammation. [1]

Nearly all mammalian cells metabolize arachidonic acid converted via the cyclooxygenase enzymes pathway to prostaglandins and thromboxane [2].

There are at least two isoforms of COX namely COX-1and COX-2 [3] which are considered as significant pharmacological targets due to their various patho physiological effects. [4]

COX-1is a "housekeeping" enzyme expressed constitutively in many tissues, and PGs produced by COX-1 mediate vital functions such as cytoprotection of gastric mucosa [5] in addition to its role in regulation of renal blood flow [6]. The presence of COX-1 in platelet leads to thromboxane A2 (TXA2) production that causes platelet aggregation, so it is useful in prevention of an inappropriate bleeding [7]. COX-2is an inducible enzyme, rapidly expressed in several cell types in response such as inflammation [8].

However, NSAID administration is related with gastrointestinal complications, such as gastric ulcers and bleeding, which sometimes become life-threatening diseases. About 15-30% of chronic users of NSAIDs have gastrointestinal ulcers, bleedings and to less extent kidney damages [1]. Also other complication as the cardiovascular (CV) toxicity associated with COX-2 inhibitors and some other NSAIDs may be due to imbalance of Thromboxane A2/PGI2 [9, 10].

The therapeutic effect of conventional NSAIDs are induced by inhibition of COX1 and COX2 enzymes at the same time are associated with the adverse effect occurs as a results of inhibition of COX-1 enzyme.

To overcome or to minimize COX inhibitors side effects, it was imperative to design and synthesis conformational constrained selective COX inhibitors. Based on our previous works associated with2-[4-(t-amino)-2-but-1-yl]isoindoline-

2,6-dione, that exert non-selective COX-1 and COX-2 with moderate activity[11], the second series of compounds Amino-acetyl enictetra hydro phthalimide [12] with the lack of one double bond relative to the first series, showed the lack ofCOX-2activity while showed COX-1 inhibitory activity. In this paper we envision the design and synthesis a rigid but not flexible structure that lacking aromaticity. The results showed less activity relative to used COX-1 and COX-2inhibitory activity. None-selective, better binding affinity toward COX-2, in addition the requirement of aromaticity for better binding affinity towards COXs enzymes.

MATERIALS AND METHODS

Chemicals

The following chemicals and materials were used:4,4-dimethylglutarimide 99%, (Sigma-Aldrich, St. Louis, USA), propargyl bromide (Sigma-Aldrich, St. Louis, USA), piperidine 99% reagent plus (Sigma-Aldrich, St. Louis, USA), 2-methylpipera 99% (alpha Aesar), 2,6-dimethyleneimine 98% (Sigma-Aldrich, St. Louis, USA), N-methyl piper a 99% (Sigma-Aldrich, St. Louis, USA), hexa methylene diamine 98% (Sigma-Aldrich, St. Louis, USA), pyrrolidine 99%, 2-methyl-lindoline, morpholine, ethanol (Giant and chemical company), 1,4-dioxan (Full time Chemicals, Anqing, China), chloroform (BDH chemicals, Pennsylvania, USA), paraformaldehyde (BDH chemicals, Pennsylvania, USA), cuprous chloride (BDH chemicals, Pennsylvania, USA), colorimetric COX (ovine/human) inhibitor screening assay Kit (No. 560131, Cayman, USA). .

Instrumentals

Melting points were determined by using a Gallen Kamp melting point apparatus. DSC Differential Scanning Colorimetry using Mettler Toledo DSC1 Stare system, Switzerland. Infrared spectra (IR) using FTIR Bruker. 1H and 13C-NMR were acquired with the aid of Varian 300 MHz spectrometer and DMSO-d6 as a solvent, and TMS as standard. The analysis was indicated by Euro EA elemental analyzer. The result obtained had a maximum deviation of ± 0.4.

Molecular docking studies for ZS-1 to ZS-8

COX-1 and COX-2 were downloaded from the protein data bank (PDB, ID: 3N8Z [13] and 3NT1 [14]). Then the co-crystallized ligand and all water molecules were removed from the protein structure. The protein structure was prepared by MOE using the protein preparation module [15]. Then, it was processed by the Maestro protein preparation module to set up partial charges on each atom and protonation states on each ionizable group [16]. The binding site of the COX enzymes was identified by its own co-crystallized ligand

then a grid box was created using the Receptor Grid Generation module in Glide [17].

Compounds were built then were energy minimized via the Maestro program [16] and the OPLS force field [16], respectively. Next, ligands were docked into the previously identified binding site using the Glide docking tool [17, 18], where the extra-precision (XP) Algorithm was used for conformational sampling [19]. Next, produced poses were giving scores via the Glide_XP scoring function which includes terms for van der Waals, hydrogen bond, electrostatic interactions, desolvation penalty and penalty for intra-ligand contact [19].

Synthesis

Synthesis of4,4-dimethyl-1-(prop-2-yn-1-yl)piperidine-2,6-dione (ZS-0)

Propargyl bromide in 10 ml actonitril was added to a mixture of 4,4-Dimethylglutarimide (1.41 g) and potassium carbonate K2CO3 (2.18 g), in 20 ml actonitril, refluxed stirred for 80 min after 80 min, cooled and filtered. The evaporated residue, in CHCL3 (30 ml) was washed with water (20 ml). Drying, evaporation and chromategraphy afforded the desired **ZS-0** compound as white powder: IR vmax 3300 (acetylenic C-H stretch), 2123 (C-C triple bond stretch), 1731 (C=O stretch), 1600 (Ar C=C stretch), 1200 cm-1 (N-C stretch). NMR δH ((CD3)2SO: δH 0.93(s, 6H), 2.51(s, 4H), 3.00(s, 1H), 4.3(s, 2H). Anal. Calcd, ($C_{11}H_{11}N_1O_2$): C, 67.02%; H, 7.31 %; N, 7.82 %. Found: C, 67.14 %; H, 7.51 %; N,8.0 %.

Synthesis of amino acetylenic compounds (ZS-1 to ZS-8)

A mixture of 4,4-dimethyl-1-(prop-2-yn-1-yl)piperidine-2,6-dione (2 g), paraformaldehyde (0.5 g), cyclic amines (around 0.01 mol) and cuprous chloride catalytic amount (0.03 g), in peroxide-free dioxin 35 ml was refluxed for 1 h. filtered and evaporated under reduced pressure afforded compounds (**ZS-1 to ZS-8**).

Synthesis of 4,4-dimethyl-1-[4 (morpholin-4-yl)but-2-yn-1- yl] pipe ridine-2,6-dione (ZS-1)

The titled compound was prepared following the general procedure for synthesis of aminoacetylenic compounds 1-8, yielded 3 g (95.59%). IR: 2955 (C-H stretch). 2830 (C-H stretch), 1725 (Ar C=O stretch), 1289 (Ar C-N stretch). 1H-NMR (DMSO-d6): δ0.98(s, 6H, CH_3-imide), 2.36(s, 4H, CH_2-N morpholin), 3.78(s, 4H, CH_2-O morpholin), 2.57(s, 4H, CH_2-c=o), 3.39(s, 2H, -CH_2-morpholin), 4.40(s, 2H, -CH_2-imide). Anal. Calcd, ($C_{19}H_{26}N_2$): C, 64.73 %; H, 7.97 %; N, 10.06 %. Found: C, 64.52 %; H, 7.81 %; N, 9.98 %.

Synthesis of 2-{1-[4-(2,6 dimethylpiperidin-1-yl)but-2-yn-1-yl]-4,4-dimethylpiperidine-2,6-dione] (ZS-2).

The titled compound was prepared following the general procedure for synthesis of aminoacetylenic compounds 1-8, yielded 2.85 g (95%). IR: 2925 (C-H stretch), 2852 (C-H stretch), 1722 (Ar C=O stretch), 1324 (Ar C-N stretch). 1H-NMR (DMSO-d6): δ,0.96(d, 6H, CH_3-piperdine), 1.00(s, 6H, CH_3-imide), 1.16-1.60(m, 8H, protons of piperdine), 2.56(s, 4H, CH_2-c=o), 3.49(s, 2H, -CH_2-piperdine), 4.4(s, 2H, -CH_2-imide). Anal. Calcd, ($C_{19}H_{26}N_2$): C, 71.02 %; H, 9.27 %; N, 9.20 %. Found: C, 71.20 %; H, 9.41 %; N, 9.53 %.

Synthesis of [4,4-dimethyl-1-[4-(4-methyl piperazin-1-yl)but-2-yn-1- yl]piperidine-2,6-dione](ZS-3)

The titled compound was prepared following the general procedure for synthesis of aminoacetylenic compounds 1-8, yielded 2.7 g 94.4%. IR: 2933 (C-H stretch), 2803 (Ar C-H stretch), 1724 (Ar C=C stretch), 1190 (Alk N-C stretch). 1H-NMR (DMSO-d6): δ,0.99(s, 6H, CH_3-imide), 2.18(s, 3H, CH_3-piperazin), 2.37-2.43(m, 8H, protons of piperazin), 2.57(s, 4H, CH_2-c=o), 3.17(s, 2H, -CH_2-piperazin), 4.40(s, 2H, -CH_2-imide). Anal. Calcd, ($C_{18}H_{24}N_2O_2$): C, 65.95 %; H, 8.65 %; N, 14.42 %. Found: C, 65.78 %; H, 8.54 %; N, 14.62%.

Synthesis of {4,4-dimethyl-1-[4 (pyrrolidin-1- yl) but-2-yn-1-yl] piperidine- 2,6-dione} (ZS-4)

The titled compound was prepared following the general procedure for synthesis of aminoacetylenic compounds 1-8, yielded 2.9 g 96.34%. IR: 2933 (C-H stretch), 2803 (Ar C-H stretch), 1724 (Ar C=C stretch), 1288 (Alk N-C stretch). 1H-NMR (DMSO-d6): δ,0.99(s, 6H, CH_3-imide), 1.65(s, 4H, CH_2-CH_2 in pyrrolidin), 2.43(s, 4H, CH_2-N in pyrrolidin), 2.56(s, 4H, CH_2-c=o), 3.41(s, 2H, -CH_2-pyrrolidin), 4.39(s, 2H, -CH_2-imide). Anal. Calcd, ($C_{18}H_{24}N_2O_2$): C, 68.67 %; H, 8.45 %; N, 10.68 %. Found: C, 68.58 %; H, 8.48 %; N, 10.88 %.

Synthesis of {1-[4-(azepan-1-yl)but-2-yn-1-yl]-4,4-dimethylpiperidine-2,6-dione}(ZS-5)

The titled compound was prepared following the general procedure for synthesis of aminoacetylenic compounds 1-8, yielded 2.6 g 95.58%. IR: 2931 (C-H stretch), 2863 (Ar C-H stretch), 1723 (Ar C=C stretch), 1270 (Alk N-C stretch). 1H-NMR (DMSO-d6): δ, 0.99(s, 6H, CH_3-imide), 1.5-2.53(m, 12H, protons of azepan) , 2.57(s, 4H, CH_2-c=o), 3.25(s, 2H, -CH_2- azepan), 4.39(s, 2H, -CH_2-imide) . Anal. Calcd, ($C_{18}H_{24}N_2O_2$): C, 70.31 %; H, 9.02 %; N, 9.65 %. Found: C, 70.52 %; H, 9.20 %; N, 9.66 %.

Synthesis of [2{4,4-dimethyl-1-[4-(2 methyl piperidin-1-yl)but-2-yn-1- yl]piperidine-2,6-dione}] (ZS-6)

The titled compound was prepared following the general procedure for

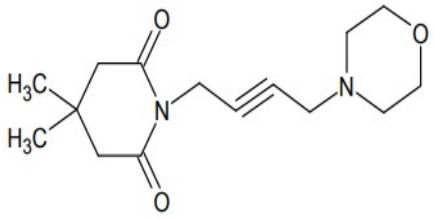
synthesis of aminoacetylenic compounds 1-8, yielded 2.9 g 96.34%. IR: 2934 (C-H stretch), 2871 (Ar C-H stretch), 1723 (Ar C=C stretch), 1297(Alk N-C stretch). 1H-NMR (DMSO-d6): δ,0.91(d, 3H, CH_3-piperdine), 0.99(s, 6H, CH_3-imide), 1.10-1.60(m, 9H, protons of piperdine), 2.57(s, 4H, CH_2-c=o), 3.40(s, 2H, -CH_2-piperdine), 4.39(s, 2H, -CH_2-imide). Anal. Calcd, ($C_{18}H_{24}N_2O_2$): C, 70.31 %; H, 9.02 %; N, 9.65%. Found: C, 70.51 %; H, 8.89 %; N, 9.56 %.

Synthesis of {4,4-dimethyl-1-[4-(2- methyl pyrrolidin-1-yl)but-2-yn-1-yl] piperidine-2,6-dione}.(ZS-7)

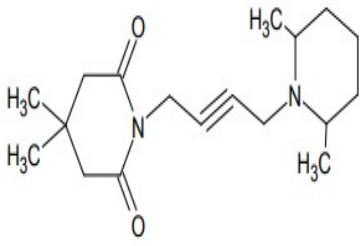
The titled compound was prepared following the general procedure for synthesis of aminoacetylenic compounds 1-8, yielded 3 g (95.59%). IR: 2957 (C-H stretch), 2872 (Ar C-H stretch), 1721(Ar C=C stretch), 1290(Alk N-C stretch). 1H-NMR (DMSO-d6): δ,0.99(s, 6H, CH_3-imide), 0.94(d, 3H, CH_3-pyrrolidin), 1.29-2.32(m, 7H, protons of pyrrolidin), 2.57(s, 4H, CH_2-c=o), 3.4 (s, 2H, -CH_2-pyrrolidin), 4.39(s, 2H, -CH_2-imide). Anal. Calcd, ($C_{18}H_{24}N_2O_2$): C, 69.53 %; H, 8.75 %; N, 10.14 %. Found: C, 69.66 %; H, 8.56%; N, 10.26 %.

Synthesis of [4,4-dimethyl-1-[4-(piperidin-1-yl)but-2-yn-1-yl]piperidine-2,6-dione}(ZS-8)

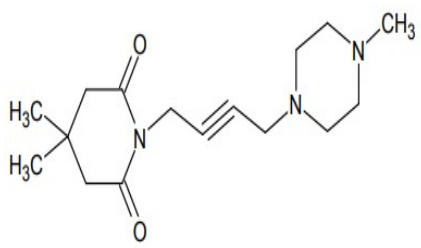
The titled compound was prepared following the general procedure for synthesis of aminoacetylenic compounds 1-8, yielded 2.7 g 94.4%. IR: 2949 (C-H stretch), 2824 (Ar C-H stretch), 1725(Ar C=C stretch), 1269(Alk N-C stretch). 1H-NMR (DMSO-d6): δ, 0.99(s, 6H, CH_3-imide), 1.37-1.75(m, 10H, protons of piperdine), 2.57(s, 4H, CH_2-C=O), 3.42(s, 2H, -CH_2-piperdine), 4.42(s, 2H, -CH_2-imide). Anal. Calcd, ($C_{18}H_{24}N_2O_2$): C, 69.53 %; H, 8.75 %; N, 10.14%. Found: C, 69.33 %; H, 8.82 %; N, 10.24 %.



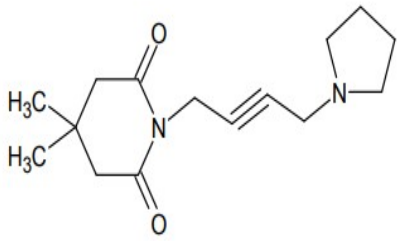
ZS-1



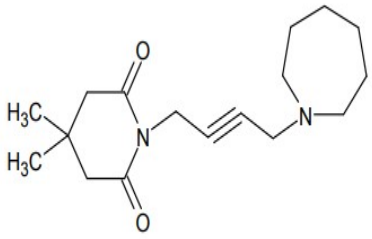
ZS-2



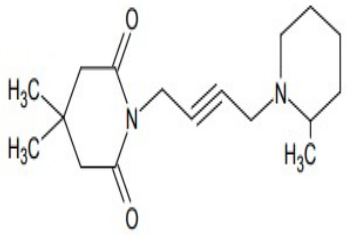
ZS-3



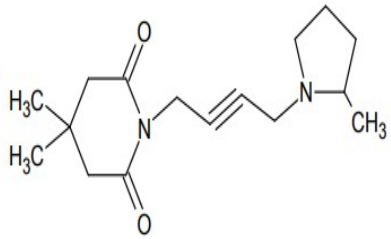
ZS-4



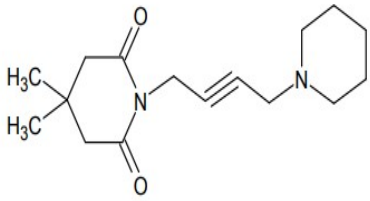
ZS-5



ZS-6



ZS-7



ZS-8

Figure 1: Structural representation of the prepared compounds (ZS-1 to ZS-8)

RESULTS AND DISCUSSION

Chemistry

The designed compounds were prepared as shown in schemes 1 and 2. Scheme 1 involved the alkylation of 4,4-Dimethylglutarimide with 3- bromo prop-1-yne (propargyl bromide) in the presence of acetonitrile as a solvent under basic conditions. The reaction involves direct displacement of the anionic nitrogen of 4,4-dimethylglutarimide on the propargyl bromide to generate 4,4-dimethyl-1-(prop-2-yn-1-yl)piperidine-2,6-dione (**ZS-0**) .

Compounds **ZS-1 to ZS-8** were generated through Mannich reaction of 4,4-dimethyl-1-(prop-2-yn-1-yl)piperidine-2,6-dione (**ZS-0**) with formaldehyde, appropriate cyclic amine and a catalytic amount of cuprous chloride in peroxide-free 1,4-dioxane was heated to 80 °C to yield the designed compounds (**ZS-1 to ZS-8**). The yield obtained ranged from 52.4-60.75%. The proposed mechanism for Mannich reaction is shown in scheme 2, in order for Mannich reaction to proceed, a reactive immonium cations intermediates should be

formed from the condensation of the formaldehyde and the appropriate amine (Schiff base formation). The attack of the carbanion in 4,4-dimethyl-1-(prop-2-yn-1-yl)piperidine-2,6-dione cuprous salt on the Schiff base generates the desired Mannich products (**ZS-1 to ZS-8**). The structures were verified by IR, 1H-NMR, 13C-NMR and elemental analysis, and were consistent with the assigned structures.

Molecular modeling

The synthesized compounds were investigated for their docking binding with COXs structures and their ability to inhibit COX activity as reflected in the removal of the double bond in 4,4-Dimethylglutarimide. According to Duggan and his co-workers [19], NSAIDs bind to two key groups of amino acids in the COX-1 and COX-2 active site, Ser530 and Tyr385 in the top of the catalytic pocket or Arg120 and Tyr355 in the bottom of the pocket. For instance, diclofenac binds to the first group residues (top) and flurbiprofen interacts to the latter group residues (bottom), mainly via electrostatic interactions that are made between polar heads of such residues and the carboxylate group in these NSAIDs structures. The NSAIDs hydrophobic groups also have a role in the binding via making van der Waals interactions with the hydrophobic residues lining the active pocket [19]. Binding energies of the best docked pose of all eight compounds are shown in Table 1 this table shows the binding energies of our eight compounds docked into the COX-1 and COX-2 binding site along with the flurbiprofen and celecoxib scoring as a reference (flurbiprofen -8.7 kcal/mol in COX-1, -8.0 kcal/mol in COX-2, celecoxib -8.5 kcal/mol in COX-1, -10.6 kcal/mol in COX-2). All compounds are predicted to have favorable binding energies, where most of them showed better affinities to COX-2 than COX-1.

ZS-1was predicted to have the best docking score (-6.75 kcal/mol) for the COX-2 enzyme. As shown in Table 1, **ZS-1** forms hydrogen bonding with the Tyr355, Gly526 and Val523 along with multiple van der Waals contacts with the surrounding hydrophobic residues.

These interactions were made by ligand protonated amino group and a cyclic carbonyl group. Obviously, these interactions were assisted by the existence of the acetylenic group which acted as an anchor; via placing these two polar groups in the correct position for binding. In addition to these electrostatic interactions, extensive hydrophobic interactions were made between the ligand carbon atoms and the side chains of Gly526, Val523, Tyr355.

Table 1: Docking results of tested compounds into the COX-1 and COX-2 binding sites

Compound code	COX-1		Cox-2		Lipinski's druglikeness	logP (o/w)	Molecular weight (g/mol)
	Glide_XP (kcal/mol)	Ligand efficiency	Glide_XP (kcal/mol)	Ligand efficiency			
ZS_1	-4.606	-0.230	-6.757	-0.337	1	0.68	278.35
ZS-2	-3.059	-0.144	-5.261	-0.238	1	3.01	304.43
ZS-3	-20472	-0.105	-5.245	-0.184	1	0.64	291.39
ZS-4	-5.707	-0.277	-6.468	-0.317	1	1.64	262.35
ZS-5	-3.059	-0.144	-5.428	-0.178	1	2.53	290.4
ZS-6	-1.927	-0.088	-5.268	-0.249	1	2.55	290.4
ZS-7	-6.750	-0.315	-5.134	-0.238	1	2.1	276.38
ZS-8	-6.542	-0.242	-5.277	-0.179	1	2.08	276.38

Table 2: ZS-1 interactions with COX-2 binding site

Ligand (ZS-1)	Receptor (COX-2)	Interaction	Distance (Å)
C	Gly526-O	H-donor	3.28
O	Val523-C	H-acceptor	3.51
N	Tyr355-C	H-acceptor	3.42
N	Tyr355-OH	H-acceptor	3.58

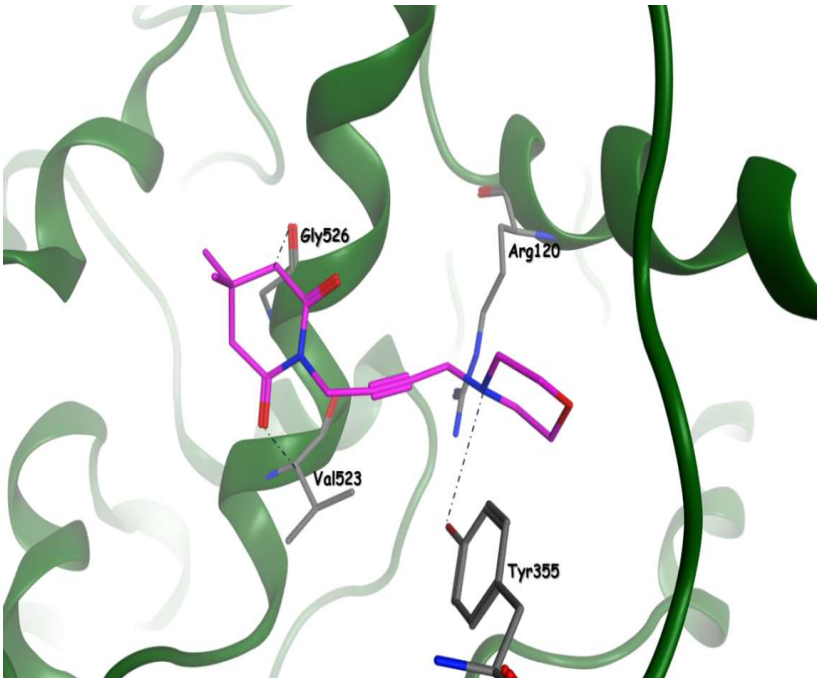
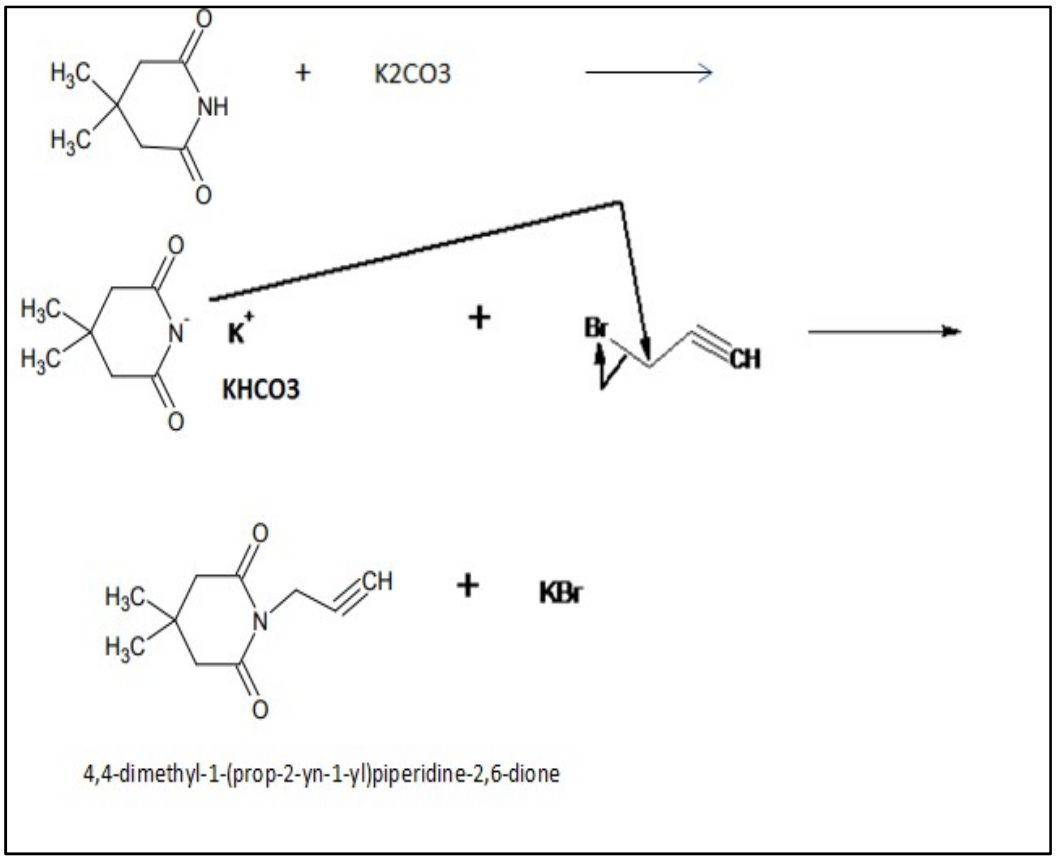
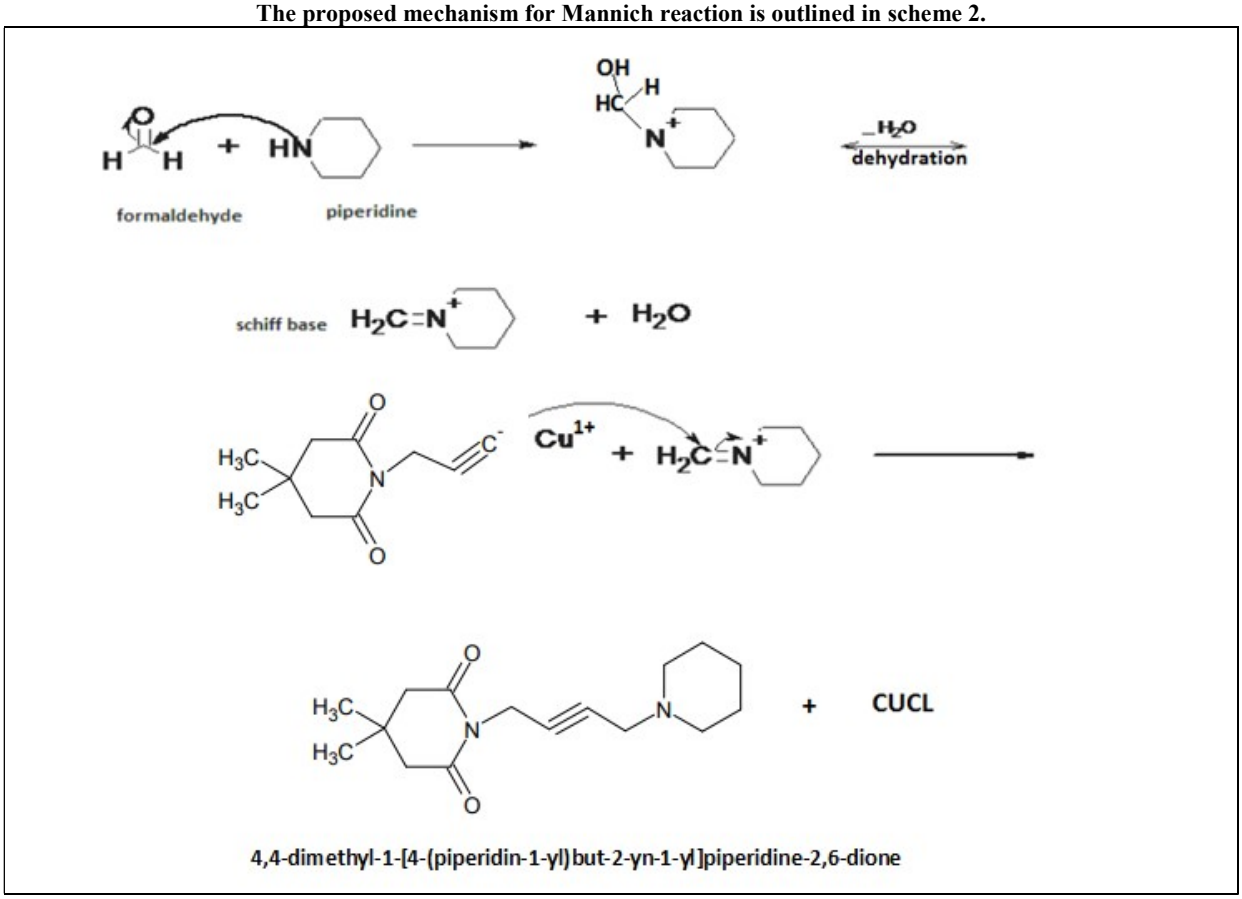


Figure 2 Docked pose of compoundZS-1 into the COX-2 binding site



Scheme 1: Alkylation reaction of 3,3-dimethylglutarimide moiety

The proposed mechanism for Mannich reaction is outlined in scheme 2.



Scheme 2 proposed Mannich reaction

The in silico findings presented in this work indicate that the synthesized compounds have the required complementary shape and electrostatics interaction needed for COX inhibition. But shows weak binding affinity to either COX enzymes than our previous synthesized compounds (Aminoacetylenic isoindolinedione and Aminoacetylenic tertrahydrophthalimide) that's prove the importance of aromaticity in the binding of and potency to these enzymes.

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CONFLICT OF INTERESTS

The authors have declared no conflict of interest.

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