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Research Article

Medicinal chemistry

Synthesis of Isoindoline-1,3-Dione Derivatives as Cyclooxygenase (Cox) S Inhibitors

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Abstract: Inflammation is the vital part of the immune system's response to injury and infection. It is the body's way of signaling the immune system to heal and repair damaged tissue. The objective of this paper is to design and synthesize a new isoindoline 1,3-dinoe derivative and investigate their selective anti inflammatory activity to COXs. As a potential anti-inflammatory compound, Isoindoline-1,3-dione derivatives were synthesized from the addition reaction of phthalimide, formaldehyde, catalytic amount of potassium hydroxide and cyclic amine in ethanol yielded the desired Isoindoline-1,3-dione compounds (ZJ1-ZJ6. ^{1}H-NMR, ^{13}C-NMR, FT-IR and elemental analysis were consistent with the assigned structures. Isoindoline-1,3-dione derivatives exhibited good inhibitory activity against the COX enzymes. To explain the result of our investigation to COX-1 and COX-2 and the selectivity of our compounds to either COX-1 or COX-2, the rationalization in COX-1, the amino group participate more effectively in binding with the ligand while in COX-2, the aryl group is more effective in binding to the ligand. The amino acetylenic compounds behave differently toward COXs from our compound. ZJ4 have shown some selective COX-1 ligand efficiency while ZJ1 promised a potent blockage and ligand efficiency toward the COX-2 enzyme which was found to be higher than the marketed drug Indomethacin and near potency score of Celecoxib. For the first time, this indicates the requirement of investigating the removal of acetylenic group in this study showed that it might be a different binding site in COXs which may result in effective compounds.

Keywords: Inflammation, COXs Inhibitors, amino acetylenic isoindoline, Molecular Docking.

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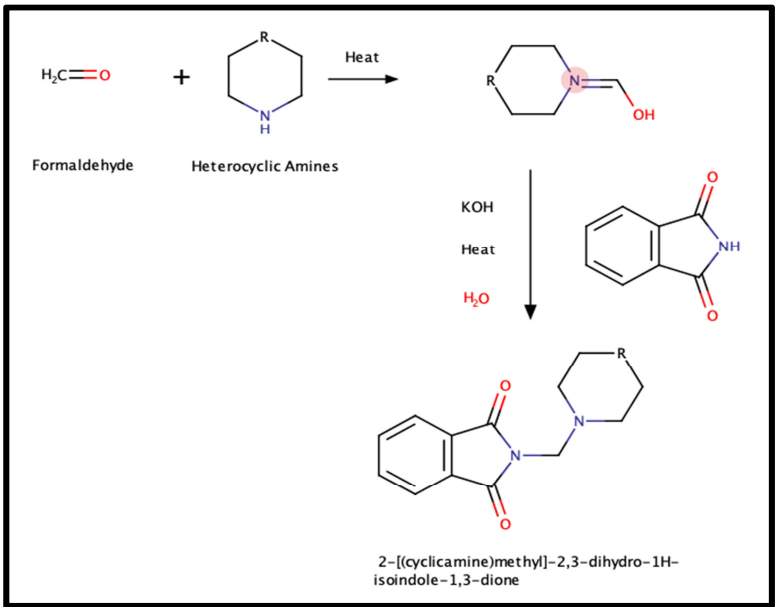
1. INTRODUCTION

Infection, tissue injury, or cardiac infarction are some various pathogenic factors that can induce inflammation by causing tissue damage[1] A multifactorial network of chemical signals initiates when tissue injury takes place and maintain a host response intended to 'heal' the affected tissues, which include the activation and directed migration of all types of leukocytes (neutrophils, monocytes and eosinophils) from the venous system to the site of damage. The protective mechanism that is responsible for removing all foreign substances, toxins, microbes is what we refer to as inflammation.[2] Prostaglandins (PG) are a group of physiologically active lipid compounds called eicosanoids, having diverse hormone-like effects. Prostaglandins have been found in almost every tissue in humans and other animals. They are derived enzymatically from the fatty acid arachidonic acid.[3] Prostaglandins (PGs) has been recognized for several years among the biologically active compounds synthesized by the gastrointestinal musculature. The endogenous synthesis of PGs inhibits phasic contractile activity in the distal stomach and generates tonic contraction in the proximal stomach. Arachidonic acid, most commonly liberated from membrane phospholipids by phospholipase A2, is the precursor for PG synthesis. Arachidonic acid is converted to PGG2 and PGH2 by cyclooxygenase enzymes (COX) that convey both cyclooxygenase and peroxidase activities. PGH2 can be metabolized by different enzymatic pathways to generate several products that have potent biological effects.[4] Prostaglandins play important and diverse roles in the CNS. The first step in prostaglandin synthesis involves enzymatic oxidation of arachidonic acid, which is catalyzed by prostaglandin H(PGH) synthase, also referred to as cyclooxygenase.[5] From arachidonic acid synthesis the 20-carbon chain unsaturated fatty acids (eicosanoids) which is called then the prostaglandins was synthesized via the enzymatic action of phospholipases and cyclooxygenase (COX). Prostaglandin synthesis and activation in gestational tissues is now recognized as one of the fundamental signals responsible for labor.[6] Prostaglandins and leukotrienes which are the metabolites of arachidonic acid are now considered as intracellular messengers. Arachidonic acid is a component of membrane phospholipids released either in a one-step process, after phospholipase A2 (PLA2) action, or a two-step process, after phospholipase C and DAG lipase actions. Arachidonic acid is then metabolized by cyclooxygenase (COX) and 5-lipoxygenase, resulting in the synthesis of prostaglandins and leukotrienes, respectively. These intracellular messengers play an important role in the regulation of signal transduction implicated in pain and inflammatory responses.[7] The cyclooxygenases are heme-containing enzymes that convert arachidonic acid to prostaglandin H2. Cytokines, growth factors, glutamate, PAF and others is the mediators responsible for inducing COX-2 enzyme, while COX-1 is a constitutive one which does not need to be inducted. [8] In the brain, COX-2 has both constitutive and inducible functions.[9] As a part of our investigation for the structure relationship activity (SAR) for amino acetylenic isoindoline-1,3- dione as anti-inflammatory agent, in this paper; the acetylenic moiety was removed to generate isoindoline-1,3- dione derivatives of potential COXs inhibitors.[10,11,12]

2. MATERIALS AND METHODS

2.1 Synthesis of 2-[(cyclic amino)methyl]-2,3-dihydro-1H-isoindole-1,3-dione (ZJ1-ZJ6) [11]

A mixture of Formaldehyde (39%, 30.1 mL), Heterocyclic amine e.g. 2,6 dimethylpiperidine (1.7 g, 0.01 mole) and 50ml ethanol was heated and stirred under reflux for 30 minutes at a temperature of 70°C. at the same time a mixture of Phthalimide (2.94 g, 0.0067 mole) and Potassium Hydroxide (1.12 g) and 50ml ethanol was heated and stirred under reflux for 30 minutes at a temperature of 70°C in another beaker. Then the two solutions were mixed and heated at 70 C° for 3 hours. At the end of the reaction the mixture was filtered and kept in the refrigerator overnight, filtered the yielded crystals on the filter paper was weighed and confirmed structurally by ^{1}H-NMR, ^{13}C -NMR, FT-IR and elemental analysis as mentioned in the results.



Scheme I

2.2 *Chemicals*

The following materials and chemicals were used, 2-methylpiperidine 99% (Alpha Aesar), 1-methylpiperazine 99% (Sigma-Aldrich, St. Louis, USA), cis 2,6 dimethyl-piperidine 98% (Sigma-Aldrich, St. Louis, USA), pyrrolidine 99% (Sigma-Aldrich, St. Louis, USA), hexamethylenediamine 99% ((Sigma-Aldrich, St. Louis, USA), morpholine (Sigma-Aldrich, St. Louis, USA), Formaldehyde solution(BDH chemicals, Pennsylvania, USA). Potassium Hydroxide (Gialand chemical company GCC,UK). Solvents: Ethanol 99.9% (PanReAC Química SA, EU), 1,4Dioxane (Full time, China), Chloroform extra pure (Tedia, USA), Diethyl-ether (Lonover , England), Acetone 99% (Scharlau, Spain), Absolute Ethanol 99.9% (Super Chem) , Distilled water.

2.3 *Instrumentation*

Hot plate with magnetic stirrer (Dragon MS7-H55-S, China) was used for the synthesis, Analytical balance with a precision of 0.01mg (Phoenix instrument, USA), Rotary evaporator 0-100Kpa/0-700mmHg (Rocker 600, Germany) with digital water bath RF300DB (Stuart, Germany). Gallenkamp Melting Point Apparatus (U.S.A). DSC (Mettler Toledo, Int Co.). NMR Bruker 500 MHz – Avance III . Bruker FT-IR spectrophotometer 7800 to 400cm-1 (Evisa, Poland). Elemental Analyzer with variation range (±0.4) (Euro Vector, Italy).

2.4 *Molecular docking studies*

The COX-1 and COX-2 with HEM complex target was selected from RCSB databank.[13] The COX-1 complexed with Flurbiprofen having PDB id 1EQH was downloaded for study. [14] The HEME is an important cofactor in COX-1 and COX-2 activity. Thus, the enzyme complex with COX-1 and COX-2 was extracted. The complex was then used for minimizing the structure. The COX-2 complexed with celecoxib having PDB id 3LN1 was downloaded for study. [15] The GROMACS [16], Linux based software was used for this complex minimization. The COX-1 and COX-2 complexes with cofactor structure were used as a docking target enzyme. The ligand structure was constructed using ChemDraw 2D. [17] Then it was used to get three-dimensional structures of ligand using Chem3D. Also, the ligand was energy minimized using MM2 force field present in Chem3D. Then, ligands and enzymes were prepared for docking using AutoDock Tools. [18] The grid for docking was prepared using the active site from template structure. The Lamarkin GA algorithm was chosen to perform the docking. The docking was performed for 10 conformations and done using AutoDock 4.2. [18] The results were then analyzed using PyMOL and Chimera visualization software.

3. RESULTS

3.1 *2-[(2,6-dimethyl piperidin-1-yl)methyl]-2,3-dihydro-1H-isoindole-1,3-dione* [11]

The titled compound (Fig 1) was prepared following the general procedure for synthesis of 2-[(cyclic amino)methyl]-2,3-dihydro-1*H*-isoindole-1,3-dione (ZJ1-ZJ6), yielded 54.9 %. FT-IR: 1295 (C-N stretch), 1623 (C=O stretch), 1693 (C=O stretch), 3160 (C-H aromatic stretch). ^{1}H-NMR (DMSO, d6) : 0.983 (d, 6H, C19-C20), 1.476 (m, 2H, C15-C16-C17), 1.60 (m, 2H, C14-C18), 3.44 (s, 2H, C12), 7.322 (m, 2H, Aromatic) **^{13}C** -NMR (DMSO, d6): δ, 18.37 (C19-C20), 28.54 (C16), 29.82 (C15-C17), 32.73 (C14-C18), 42 (C12), 78.52 (Aromatic), 109.94 (C7-C9). Anal. Calcd, ($C_{16}H_{20}N_2O_2$): C, 67.02%; H, 7.31%; N, 7.82%. Found: C, 66.84%; H, 7.54%; N, 8.01%.

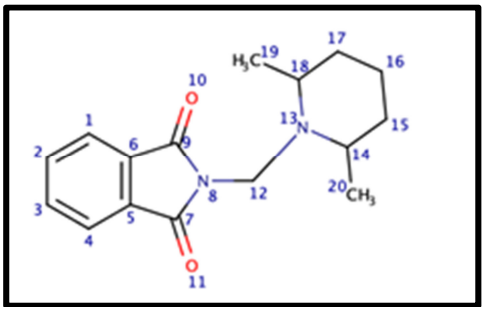


Fig 1. ZJ1

3.2 *[(azepan-1-yl)methyl]-2,3-dihydro-1H-isoindole-1,3-dione* [11]

The titled compound (Fig 2) was prepared following the general procedure for synthesis of 2-[(cyclic amino)methyl]-2,3-dihydro-1*H*-isoindole-1,3-dione (ZJ1-ZJ6), yielded 41.3%. FT-IR: 1263 (C-N stretch), 1621 (C=C aromatic stretch), 1693 (C=O stretch), 3156 (C-H aromatic stretch). ^{1}H-NMR (DMSO, d6) : 1.06 (m, 4H, C16-C17), 1.55 (m, 4H, C15-C18), 2.66 (t, 4H, C14-C19), 3.34 (s, 2H, C12), 7.31 (m, 2H, Aromatic). **^{13}C** -NMR (DMSO, d6): δ, 19.65 (C16-C17), 21.76 (C15-C18), 26.95 (C14-C19), 39.99 (C12), 82.51 (Aromatic), 107.49 (C7-C9). Anal. Calcd, ($C_{15}H_{18}N_2O_2$): C, 69.74%; H, 7.02%; N, 10.84%. Found: C, 69.63%; H, 7.04%; N, 10.72%.

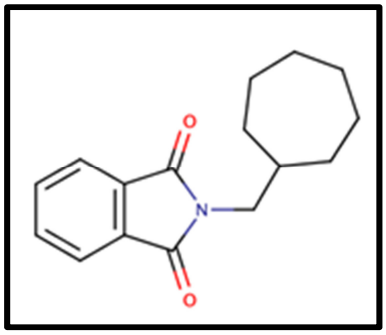


Fig 2. ZJ2

3.3 *2-[(4-methylpiperazin-1-yl)methyl]-2,3-dihydro-1H-isoindole-1,3-dione* [11]

The titled compound (Fig 3) was prepared following the general procedure for synthesis of 2-[(cyclic amino)methyl]-2,3-dihydro-1*H*-isoindole-1,3-dione (ZJ1-ZJ6), yielded 50.8%. FT-IR: 1297 (C-N stretch), 1621 (C=C aromatic stretch), 1693 (C=O stretch), 2951 (C-H alkane stretch), 3156 (C-H aromatic stretch). ^{1}H-NMR (DMSO, d6) : 0.88 (s, 3H, C19), 2.51 (m, 4H, C15-C17), 2.67 (m, 4H, C14-C18), 3.45 (s, 2H, C12), 7.33 (m, 2H, Aromatic) ^{13}**C** -NMR (DMSO, d6): δ, 19.64 (C19), 21.49 (C14-C18), 25.18 (C15-C17), 39 (C12), 79.09 (Aromatic), 109.48 (C7-C9) Anal. Calcd, ($C_{14}H_{17}N_3O_2$): C, 64.85%; H, 6.61%; N, 16.2%. Found: C, 64.73%; H, 6.75%; N, 16.31%.

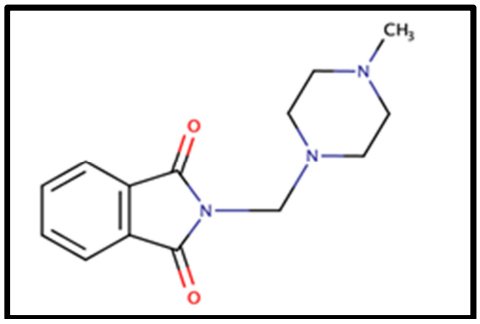


Fig 3. ZJ3

3.4 *2-[(2-methylpiperidin-1-yl)methyl]-2,3-dihydro-1H-isoindole-1,3-dione* [11]

The titled compound (Fig 4) was prepared following the general procedure for synthesis of 2-[(cyclic amino)methyl]-2,3-dihydro-1*H*-isoindole-1,3-dione (ZJ1-ZJ6), yielded 60%. FT-IR: 1250 (C-N stretch), 1623.77 (C=C aromatic stretch), 1693.19 (C=O stretch), 900 (C-H alkane stretch), 3156.90 (C-H aromatic stretch). ^{1}H-NMR (DMSO, d6) : 1.04 (d, 3H, C19), 2.50 (m, 6H, C15-C16-C17), 3.37 (m, 3H, C14-C18), 3.60 (s, 2H, C12), 7.31 (m, 2H, Aromatic) ^{13}**C** -NMR (DMSO, d6): δ, 18.64 (C19), 19.91 (C16), 21.19 (C15), 22.47 (C17), 22.75 (C14), 24.30 (C15), 41.30 (C12), 77.50 (Aromatic), 108.53 (C7-C9). Anal. Calcd, ($C_{15}H_{18}N_2O_2$): C, 69.74%; H, 7.02%; N, 10.84%. Found: C, 69.54%; H, 6.93%; N, 11.01%.

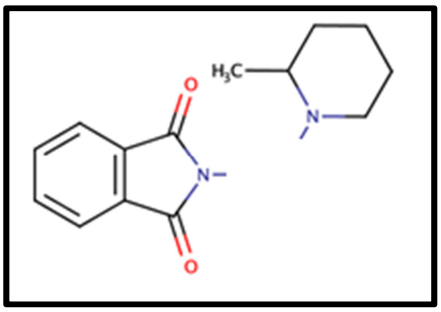


Fig 4. ZJ4

3.5 *2-[(pyrrolidin-1-yl)methyl]-2,3-dihydro-1H-isoindole-1,3-dione* [11]

The titled compound (Fig 5) was prepared following the general procedure for synthesis of 2-[(cyclic amino)methyl]-2,3-dihydro-1*H*-isoindole-1,3-dione (ZJ1-ZJ6), yielded 51.2%. FT-IR: 1261.22 (C-N stretch), 1623.77 (C=C aromatic stretch), 1693.19 (C=O stretch), 2836 (C-H alkane stretch), 3156.90 (C-H aromatic stretch). ^{1}H-NMR (DMSO, d6): 1.50 (m, 4H, C15-C16), 2.35 (m, 4H, C14 -C17), 2.97 (s, 2H, C12), 7.30 (m, 2H, Aromatic) ^{13}**C** -NMR (DMSO, d6): δ, 18.65 (C15-C16), 21.32 (C14-C17), 40 (C12), 81.76 (Aromatic), 105.44 (C7-C9). Anal. Calcd, ($C_{13}H_{14}N_2O_2$): C, 67.81%; H, 6.13%; N, 12.17%. Found: C, 67.74%; H, 6.05%; N, 12%.

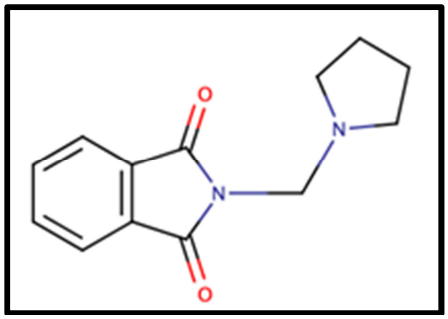


Fig 5. ZJ5

3.6 *2-[(morpholin-4-yl)methyl]-2,3-dihydro-1H-isoindole-1,3-dione* [11]

The titled compound (Fig 6) was prepared following the general procedure for synthesis of 2-[(cyclic amino)methyl]-2,3-dihydro-1*H*-isoindole-1,3-dione (ZJ1-ZJ6), yielded 57.9%. FT-IR: 1263.15 (C-N stretch), 1623.77 (C=C aromatic stretch), 1687.41 (C=O stretch), 2786.53 (C-H alkane stretch), 3164.61 (C-H aromatic stretch). ^{1}H-NMR (DMSO, d6): 1.51 (m, 4H, C14-C18), 2.37 (m, 4H, C15 -C17), 2.60 (s, 2H, C12), 7.23 (m, 2H, Aromatic) **^{13}C** -NMR (DMSO, d6): δ, 20.63 (C14-C18), 22.98 (C15-C17), 38 (C12), 79.72 (Aromatic), 106.95 (C7-C9). Anal. Calcd, ($C_{13}H_{14}N_2O_3$): C, 63.4%; H, 5.73%; N, 11.38%. Found: C, 63.10%; H, 5.54%; N, 11.24%.

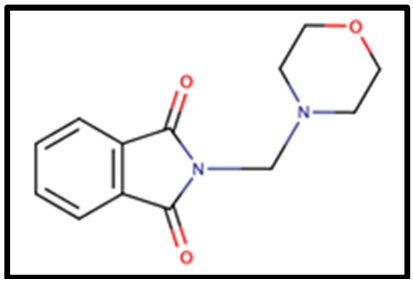


Fig 6. ZJ6

Table 1. Compounds binding energy (in kcal/mol) after docking with COX-1 and HEM complex.

Ligand Name	Binding Energy (in kcal/mol)	Ligand efficiency (in kcal/mol)
ZJ1	-8.1	-0.426
ZJ2	-7.7	-0.405
ZJ3	-5.7	-0.3
ZJ4	-8.3	-0.437
ZJ5	-7.6	-0.447
ZJ6	-7.6	-0.422
Indomethacin	-1.7	-0.068
Celecoxib	-3.5	-0.135

Table 2. Compounds binding energy (in kJ/mol) after docking with COX-2 and HEM complex

Ligand Name	Binding Energy (in kcal/mol)	Ligand efficiency (in kcal/mol)
ZJ1	-9.5	-0.5
ZJ2	-8.9	-0.469
ZJ3	-8.4	-0.442
ZJ4	-8.9	-0.469
ZJ5	-7.9	-0.465
ZJ6	-8.1	-0.45
Indomethacin	-9.2	-0.368
Celecoxib	-12.6	-0.485

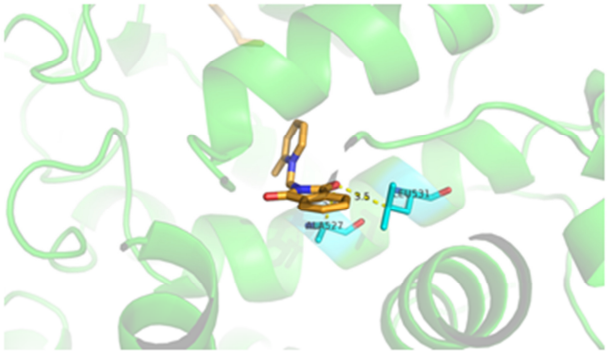


Fig 8. ZJ4 docked with COX-1 and HEM complex.

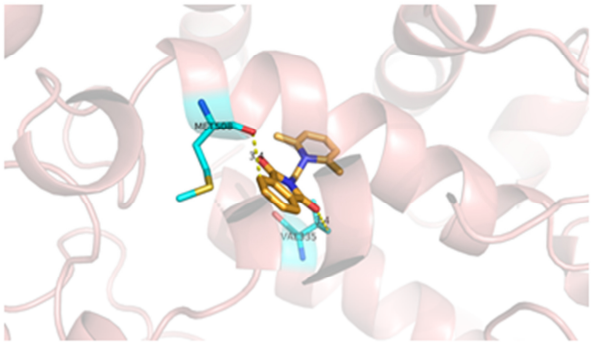


Fig 7. ZJ1 docked with COX-2 and HEM complex.

Table 3. Interaction of ZJ4 with COX-1 and HEM complex

Ligand	Atom name	Chain	Atom no	Residue	Residue no	Atom name	Chain	Distance (in Å)	Interaction role of ligand atom
ZJ4	O1	A	53	ALA	527	CA	A	3.24703	H-acceptor
ZJ4	O1	A	53	LEU	531	CG	A	3.4679	H-acceptor

Table 4. Interaction of ZJ1 with COX-2 and HEM complex

Ligand	Atom name	Chain	Atom no	Residue	Residue no	Atom name	Chain	Distance (in Å)	Interaction role of ligand atom
ZJ1	C4	A	47	MET	508	O	A	3.35014	H-donor

Table 5. Interaction of ZJ3 with COX-1 and HEM complex

Ligand	Atom name	Chain	Atom no	Residue	Residue no	Atom name	Chain	Distance (in Å)	Interaction role of ligand atom
ZJ3	C4	A	47	MET	522	O	A	2.97922	H-donor
ZJ3	O1	A	53	VAL	349	CG2	A	3.15784	H-acceptor
ZJ3	O2	A	54	ILE	523	CG1	A	3.13046	H-acceptor
ZJ3	C14	A	61	ARG	120	NE	A	3.00161	H-donor

4. DISCUSSION

4.1 *Chemistry*

The designed compounds were prepared as 2-[(cyclic amino)methyl]-2,3-dihydro-1*H*-isoindole-1,3-dione, through the addition of formaldehyde and cyclic amine in ethanol. In other containers potassium phthalimide in ethanol. The mixture was heated at 70 C° for 3 hours to generate the desired derivatives. The mechanism as outlined in (scheme 1). The first step was the formation of the Schiff base resulting from the condensation of cyclic amine and formaldehyde. The second step was the attack of the anion of phthalimide on the Schiff base result in the formation of the desired products. The structures were verified through ^{1}H-NMR, ^{13}C-NMR, FT-IR and elemental analysis for the compounds and found to be consistent with the assigned structures. In the designing of these compound, we took in consideration the appropriate distance between the functional groups related to COXs. [19] The Aryl group that could selectively differentiate between COX-1 and COX-2 inhibitory activity of aminoacetylenic analogues. [10,11,12] [in] our study we suggest that the removal of the acetylenic group in this study showed that it might be a different binding site in COXs which may result in effective compounds. there is no precise or specific pattern observed at COXs binding sites [23]

4.2 *Docking*

In the present study, to understand the interaction between the ligand of the synthesized compounds (ZJ 1 – 6) and COXs. To explore their binding mode, docking study was performed using AutoDock 4.2 [18]. The results were then analyzed using PyMOL and Chimera visualization software. The amino group, cyclic carbonyl group and the aryl group are the key functional groups in molecular docking of our compound binding with COX enzymes as outlined in table (1,2). The position of these groups should be in appropriate locations relative to COX. [19,20] The amino group contributes to ionic bonding or hydrogen bonding with the ionic ligand of the opposite group. The carbonyl group will accept protons from the appropriate ligand or coordinates with an electron deficient group (20), additional requirement is the aryl group where it provides a Pi Overlap. [19] To sum up, the *in-silico* findings presented in this work indicated that the synthesized compounds have the required complementary shape and electrostatic interaction needed for COX inhibition. The previous amino acetylenic compounds as COX inhibitors were based on the rationalization for the importance of the amino, carbonyl and acetylenic group were overlapped effectively with COX enzymes. In our new compound, the removal of the acetylenic group indicated the more

importance of the amino and the carbonyl group in binding to COX as outlined in the (tables 1,2). Molecular docking showed the important residues interacting in COX-1 (LEU 93, ARG 120, VAL 349, LEU 352, SER 353, TYR 355, TYR 385, TRP 387, PHE 518, MET 522, ILE 523, GLY 526, ALA 527, SER 530 and LEU 531). This indicates that the more effective residues are the amino groups.[22] The molecule Celecoxib and Indomethacin has shown several interactions, but their interaction energy and ligand efficiency is very low. The ZJ4 has shown lowest binding energy amongst all selected molecules and has highest ligand efficiency too (table 3). Thus, it is a potent molecule with higher activity to COX-1 enzyme. The important residues found interacting in COX-2 were HIS 75, ARG 106, GLN 178, VAL 335, LEU 338, SER 339, TYR 341, LEU 345, LEU 370, TRP 373, ARG 499, PHE 504, MET 508, VAL 509 and ALA 513, SER 516. The molecule ZJ1, Indomethacin and Celecoxib has binding energy more than 9 kcal/mol and ZJ2 and ZJ4 has binding energy near to 9 kcal/mol. Celecoxib has shown lowest binding energy amongst all selected molecules. However, molecule ZJ1 has the highest ligand efficiency. Thus, Celecoxib and ZJ1 are potent molecules with higher activity to COX-2 enzymes (table 4). From COX 2 interaction with our compound, the need of the aromatic group was essential, and has great importance to overlap effectively to COX 2. [21] the JZ3 ligand is overlapping effectively with COX enzymes with the amino, carbonyl and acetylenic groups same as the other ligands with no conformational advantage. But the existence of the nitrogen in this ligand on the N-4 Position increased the lipophilicity to the docking. ZJ3 interacted in molecular docking with COX-1 enzymes (MET, VAL, ILE and ARG) (table 5) compared to ZJ4 which interacted with ALA and LEU only (table 6). In COX-2 molecular docking studies, ZJ3 showed a strong interaction with multiple amino acids which promised a potent blockage activity for this compound.

5. CONCLUSION

Isoindoline-1,3-Dione derivatives exhibited good inhibitory against the COXs enzyme. after the removal of the acetylenic group in this study showed that it might be a different binding site in COXs which may result in effective compounds. In our prepared series. ZJ4 have some selective COX-1 ligand efficiency while ZJ1 promised a potent blockage toward COX-2 enzyme higher than the marketed drug Indomethacin and near the potency score of Celecoxib. Such results strengthen the use of such compounds, but more pharmacokinetic and pharmacodynamic studies are warranted.

6. ACKNOWLEDGEMENTS

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7. AUTHOR CONTRIBUTION STATEMENT

Prof. Zuhair Muhi-eldeen conducted and conceived the design of the compounds and supervised the reaction of synthesis. Sadeq Al-tameemi and Rand Al-Qazweeny participated in the explanation of the molecular docking. Jaafar Al Husseini carried out the chemical reaction and the draft writing.

8. CONFLICT OF INTEREST

Conflict of interest declared none

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