Available online on www.ijpqa.com
International Journal of Pharmaceutical Quality Assurance 2018; 9(2); 102-108
doi: 10.25258/ijpqa.v9i2.13630
ISSN 0975 9506

Research Article

Synthesize of New Ibuprofen and Naproxen Sulphonamide Conjugate with Anti-Inflammatory Study and Molecular Docking Study

Tagreed N-A Omar[1*], Monther F Mahdi[2], May Mohammed Jawad Al-Mudhafar[1], ZainabBassim[3]

[1]*Department of Pharmaceutical Chemistry, College of Pharmacy, University of Baghdad, Baghdad, Iraq.*
[2]*Dean of Collage of Pharmacy, Mustansiriyah University, Baghdad, Iraq*
[3]*Ministry of Health. Baghdad, Iraq*

Received: 11th Mar, 18; Revised: 2nd Apr, 18, Accepted: 22nd May, 18; Available Online: 25th Jun, 2018

ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) contain free –COOH which thought to be responsible for the GI irritation associated with all traditional NSAIDs. The esterification of this group is one of an approach to ultimate aim for reduce the gastric irritation; so in this study we synthesized and preliminarily evaluated new ester compounds as new analogues with expected selectivity toward COX-2 enzyme. Synthetic procedures have been successfully developed for the generation of the target compounds (III a and b). The synthetic approach involved multi-steps procedures which include: Synthesis of 4-hydroxy benzene sulphonamide (I b), synthesis of Naproxen and Ibuprofen acyl chloride and then reacting them with 4-hydroxy benzene sulphonamide to form final compounds (III a-b) .The structures of these compounds were identified and characterized using (TLC), infrared spectroscopy (FT-IR), 1H NMR data and microanalysis (CHN).Pharmacological study as anti-inflammatory activities for the final compounds were studied in rats by induced edema type of inflammation. Moreover, the results of a docking study of compounds III a-b into the COX-2 binding site revealed that its mechanism was possibly similar to that of naproxen, a COX-2 inhibitor. The effect of them on COX-2 antibody was showed it could significantly inhibit COX-2 activity.

Keywords: anti-inflammatory; naproxen derivatives, ibuprofen derivatives.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are within the common uses drugs by many patients in the world. They are very effective in the reduction of pain, fever and inflammation[1]. Their anti-inflammatory effect is exertion by inhibit the activity of cyclooxygenase which catalyzes the biotransformation of arachidonic acid.NSAIDs works by hindering the formation of prostaglandins (PGs) which are a family of chemicals that produced by the cells of the body and have several important functions. They play an action role in the inflammation response of the body through producing chemical signals which promote its effect on immune system[2].

The cyclooxygenase affects the production of prostaglandins and it have an effect on platelets function, three types of cyclooxygenase[1,2] have been discovered[3]. COX-1 has function as "housekeeping", its importance through controlling gastric mucosal integrity and maintaining renal function[4]. COX-2 is highly cause settings of inflammation by cytokines and mediators of inflammatory or stress physiological effect[5,6]. Selective COX-2 inhibitors are different from traditional NSAIDs they do not cause inhibition for platelet function[7], they lead to less damage to GI and bleeding than original NSAIDs[8,9]. Ibuprofen and naproxen are the most uses NSAIDs for t headache, rheumatoid arthritis, and colon cancer[10,11]. The derivitization of the carboxylate moieties in NSAIDs may lead to the generation of potent and selective inhibitors of COX-2[12].

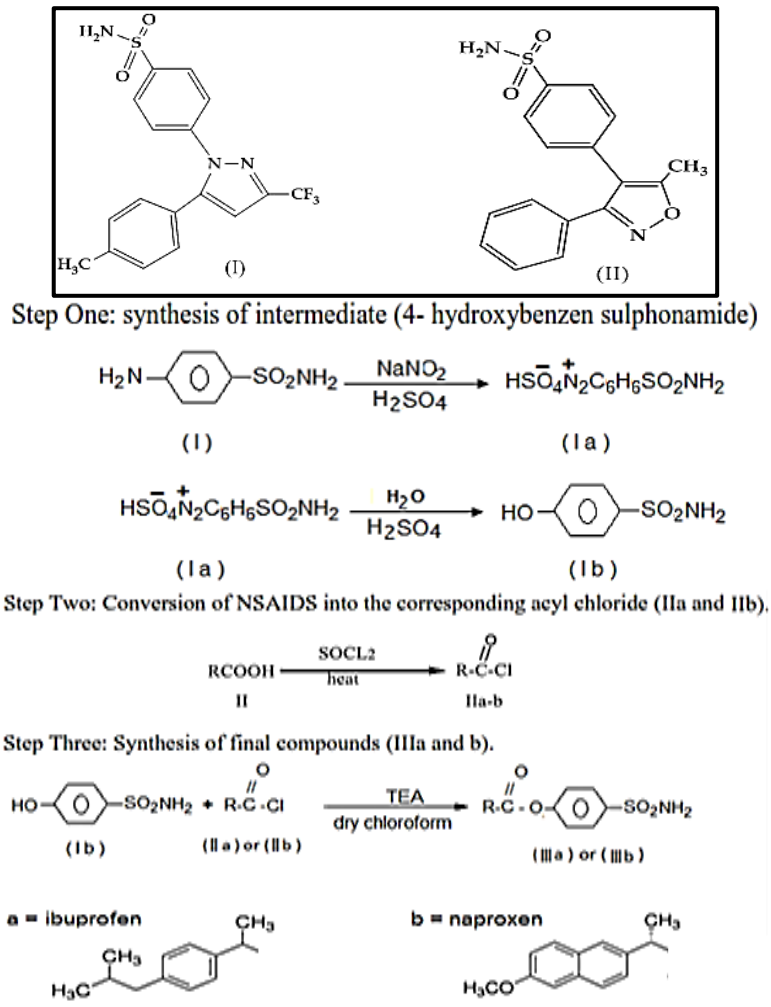
Preferential inhibition of COX-2 is thought to be due to the extra space in the COX-2 lipophilic channel, in addition to the presence of a side pocket in the channel[13]. This side pocket can discriminate the selective NSAIDs, like celecoxib (I)[14], valdicoxib(II)[15], which contain derivatives of aminobenzene sulfonamide that occupied that side pocket[16], from nonselective agents.

This study was foxing on the esterfication and preliminary evaluation of Ibuprofen and naproxen with hydroxyobenzene sulfonamide as new agents of NSAIDs with an expectation to have selectivity towards COX-2 enzyme.

EXPERIMENTAL SECTION

The determination of melting points is done by using electro thermal apparatus for melting point (Stuart, Germany). The completing of reaction and the purity of the compounds are tested on aluminum coated TLC plates 60 F245 (E. Merck) using Methanol: Acetic acid: Ether: Benzene (05:15:60: 20)[17]. As the mobile phase and visualized under iodine vapor. FT-IR spectra were done by KBr discs using Shimadzu FT-IR 8400S

**Author for Correspondence: tagreed1422@gmail.com*



Scheme 1: The synthetic procedures for generation of intermediate Ib and final compounds III a-b:

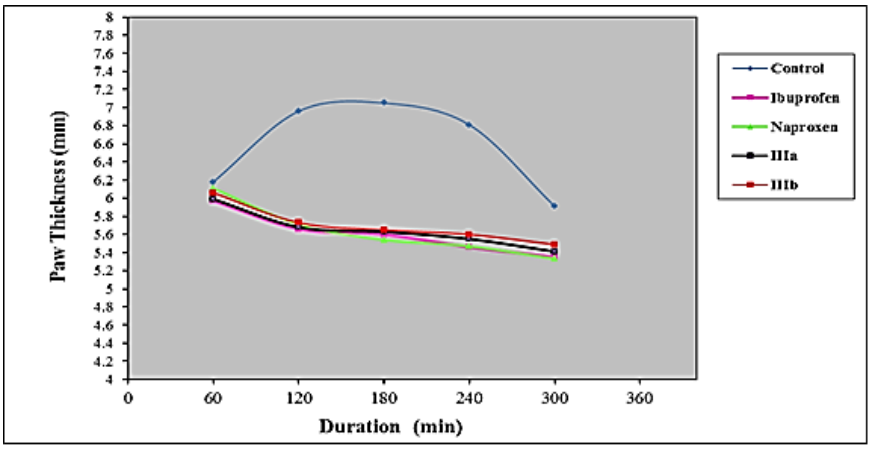


Figure 1: ibuprofen, Naproxen propylene glycol and tested compounds (III a-b) ;their effect on egg-white induced paw edema in rats. Results were representing as Mean ± SEM (n=6).Time (30) is the time of egg-white injection.

spectrophotometer, 1HNMR spectra were recorded on Bruker 500 MHz -Avanc III in University of Jordan, Faculty of Science, and Department of Chemistry, Jordan. CHNS microanalysis was done using a Euro-Vector EA3000 (Italy) in College of Science, Al-MustansiriyahUniversity. Different chemical tests are performing to the intermediate and target compounds as diazonium salts, carboxylic group and phenolic hydroxyl tests.Diazonium salts synthesis[18] Sodium bicarbonate test[18] Ferric chloride test:[18]

Chemistry

The synthetic pathways for the designed target compounds (I-III a-b) are illustrated in scheme (1).

Synthesis of 4-hydroxy benzene sulphonamide (I b)[11,1]

4- aminobenzensulphonamide (1.72g, 0.01mmole) was dissolved in distilled water(15mL) with heating,

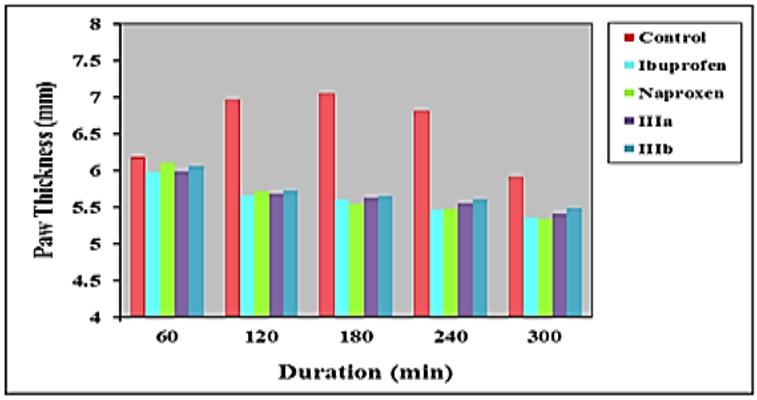


Figure 2: Effect of ibuprofen,Naproxen propylene glycol and tested compounds (III a-b)on egg-white

Table 1: Anti-inflammatory effect od final compounds III a-b.

Paw thickness(mm)/ n=6	Time (min)						
	0	30	60	120	180	240	300
Control	4.40±0.08	5.43±0.10	6.18±0.09	6.96±0.06	7.05±0.10	6.81±0.05	5.91±0.04
Ibuprofen	4.34±0.10	5.41±0.05	5.97±0.09	5.66±0.04*	5.60±0.06*	5.46±0.05*	5.35±0.07*
Naproxen	4.36±0.07	5.48±0.08	6.11±0.10	50771±0.08*	5.54±0.05*	5.47±0.10*	5.33±0.05*
III a	4.40±0.06	5.40±0.10	5.99±0.04	5.68±0.07*	5.63±0.09*	5.55±0.05*	5.41±0.08*
III b	4.38±0.05	5.42±0.04	6.06±0.06	5.73±0.10*	5.65±0.08*	5.60±0.09*	5.49±0.10*

concentrated sulphric acid (3ml) was added to the solution and cold in ice bath. Then solution of sodium nitrate (1.379g, 0.02mmole) in distilled water (7 mL) was added drop by drop with continuous stirring until get yellow or pale orange clear solutions. Concentrated sulphric acid (8.1mL) in (24.3mL) water was adds drop by drop to the pale orange solution in the conical flask until get yellow to orange solution. Then transfer the solution to the round flask for gentle heating and refluxed for 90min. cooled at room tempera-ture and added small amount of activated charcoal. The mixture is heated to boiling then filtrated, sodium bicarbonate (10%) is added to the filtrate in a portion with continuous stirring until solution become red color (neutral solution), cool by an ice bath, filtrate it then evaporated the solvent to yield compound(Ib).

Synthesis of Acid Chloride Derivatives of ibuprofen and naproxen. (IIa and IIb)

NSAIDs either (ibuprofen or naproxen) (0.01mmole)was dissolved in dry chloroform (25mL) and Thionyl chloride (0.725mL, 0.01mmole) was added drop wise over a period of 15min. with cooling on ice bath.The mixture was refluxed for 3hours at 65ºc with continuous stirring and monitored by evolution of excess HCl gas which is detected by changing the color of pH graduated litmus paper into reddish of 1-1.5 pH when placed on the top of the condenser and changing the color of the solution from colorless to white color for ibuprofen and to yellow for naproxen .The excess of thionyl chloride and solvent was removed under reduced pressure and re-dissolving in dry chloroforms (15mL) and re-evaporated .

General procedure for synthesis of the final compound (4-hydroxy benzene sulphonamide with NSAIDs-ibuprofen and naproxen) (III a and b)

Compound (Ib) was dissolved in dry chloroform (40mL) in 100mL round flask container and TEA (1.39mL, 0.01mmole) was added drop wise with stirring for 10 min. using ice path. Then the compound of II a or II b was added slowly dropped for 50min. with continues stirring in ice bath then continuous stirring at room temperature overnight, then the solvent was removed under reduced pressure using rotary evaporator. The resulting product was re-dissolved in ethyl acetate (20mL), washing with 5% sodium bicarbonate solution (20mL), 5% HCl and distilled water (20mL). The organic layer dried using magnesium sulphateanhydrous, filtrated and solvent was evaporated under reduced pressure to give the final compounds III a-b.

Characterization

(R)-4-sulfamoylphenyl-2-(4-isobutylphenyl) propanoate (III a)

yield: 82%; melting point: 110 °C; Rf = 0.67(ethanol: petroleum ether: ethyl acetate) (2:2:6); IR (KBr) (cm-1): 3483 & 3329 (NH stretching vibration of 1º sulfonamide), 2928 & 2850 (CH stretching vibration of CH&CH3), 1728 (C=O stretching vibration of ester), 1602,1585 &1502 (C=C stretching vibration of Aromatic)1346 & 1153 O = S = O (stretching vibration of sulfone).1HNMR (500 MHz, DMSO) (δ): 0.91(d,6H, CH3, iso-but); 1.56 (3H CH3, prop); 1.82(m,1H, CH of iso-but); 2.43(d,2H, CH2 of isobut); 3.78(1H, CH,prop); 5.42(s,2H,NH2); (7.11(2H,d,at 2 &6 positions ,Ar); 7.74(2H, d, at 3 & 5 positions of Ar). Anal. calcd. For C19H23NO4S: C,63.13; H, 6.41; N, 3.88; O, 17.71; S, 8.87, found, C, 63.00; H, 6.38; N, 3.86; O, 17.89; S, 8.75.

(S)-4-sulfamoylphenyl 2-(6-methoxynaphthalen-2-yl) propanoate(III b)

yield: 84%; melting point: 115 °C; Rf = 0.78(ethanol: petroleum ether: ethyl acetate) (2:2:6); IR (KBr) (cm-1):

Table 2: The observed docking score for compounds III a-b.

III a

Docking pose	Docking score		
#1	-9.2	VISUALIZE POSE	DOWNLOAD POSE
#2	-8.4	VISUALIZE POSE	DOWNLOAD POSE
#3	-8.0	VISUALIZE POSE	DOWNLOAD POSE
#4	-7.7	VISUALIZE POSE	DOWNLOAD POSE

III b

Docking pose	Docking score		
#1	-9.7	VISUALIZE POSE	DOWNLOAD POSE
#2	-9.2	VISUALIZE POSE	DOWNLOAD POSE
#3	-9.0	VISUALIZE POSE	DOWNLOAD POSE
#4	-8.8	VISUALIZE POSE	DOWNLOAD POSE

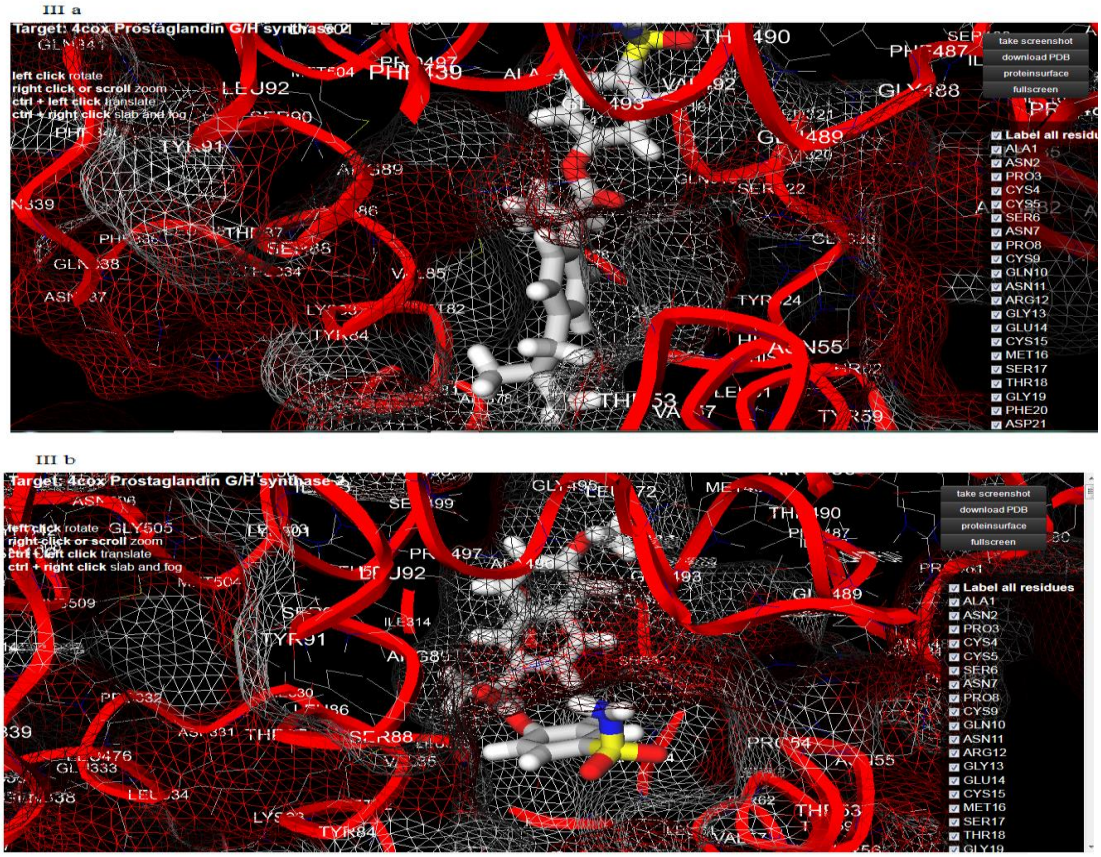
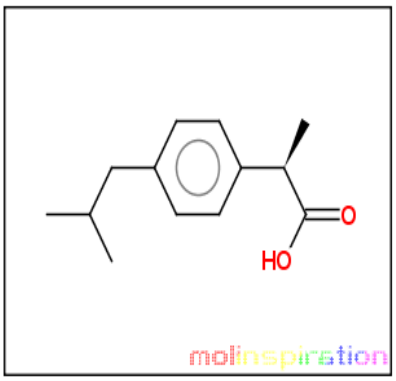


Figure 3: The visualization of the binding conformations of these analogues in the active site of 4COX protein.

3261& 3111(NH stretching vibration of 1º sulfonamide), 2953 & 2868 (CH stretching vibration of CH&CH3), 1705 (C=O stretching vibration of ester), 1589,1548 &1512 (C=C stretching vibration of Aromatic)1365 & 1157 O = S = O (stretching vibration of sulfone), 1259(Ar-O-C stretching of naproxen 1HNMR (500 MHz, DMSO) (δ ppm): 1.62(d,3H, CH3 protons of naproxen) ;3.78(s,3H, OCH3 protons of naproxen) ;3.83 (q, 1H, CH protons of naproxen); 5.39(s,1H, NH2) 7.22(d,2H, CH protons ortho to methoxy);7.67-7.90 (m, 4H, CH protons of 2 -naphthalene). Anal. calcd. For C20H19NO5S: C,62.32; H, 4.97; N,3.63; O, 20.76; S, 8.32, found, C, 63.29; H, 5.05; N, 3.84; O, 20.98; S, 8.33.

Pharmacology (anti-inflammatory activity)

Evaluations of the anti-inflammatory activities of synthesized compounds and determine their ability to reduce local edema induced in the rat paw due to the injection of an irritant agent[19-20] such as egg-white, dextran and solution of carrageenan. paw edema was induced by carrageenan and studied from the side of anti-inflammatory activity of non-steroidal agents contain some chemical mediators such as histamine the irritant agent was subcutaneous(Sc)injected into the rat paw



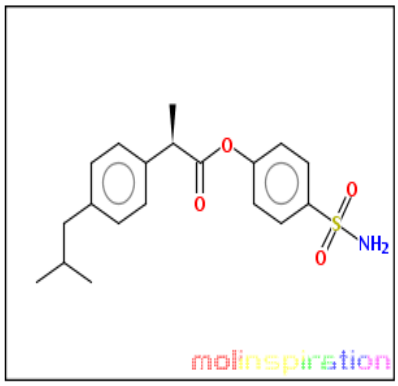
Molinspiration bioactivity score v2016.03

GPCR ligand	-0.17
Ion channel modulator	-0.01
Kinase inhibitor	-0.72
Nuclear receptor ligand	0.05
Protease inhibitor	-0.21
Enzyme inhibitor	0.12

Get data as text (for copy / paste).

Get 3D geometry BETA

Ibuprofen



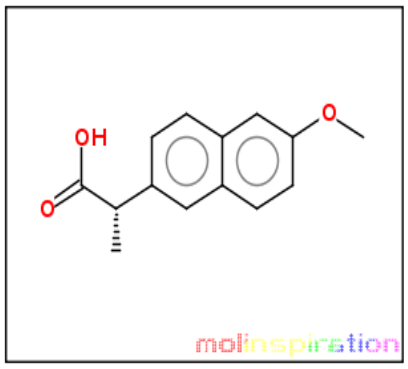
Molinspiration bioactivity score v2016.03

GPCR ligand	-0.06
Ion channel modulator	-0.18
Kinase inhibitor	-0.26
Nuclear receptor ligand	-0.05
Protease inhibitor	0.21
Enzyme inhibitor	0.20

Get data as text (for copy / paste).

Get 3D geometry BETA

Ibuprofen Sulphonamide



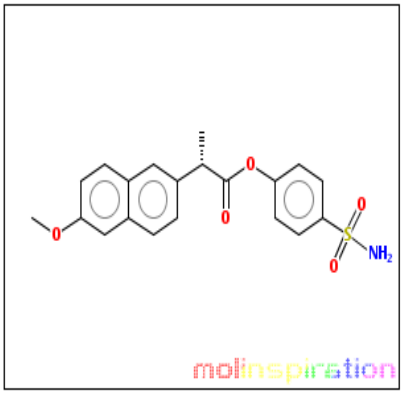
Molinspiration bioactivity score v2016.03

GPCR ligand	-0.11
Ion channel modulator	-0.06
Kinase inhibitor	-0.38
Nuclear receptor ligand	0.14
Protease inhibitor	-0.26
Enzyme inhibitor	0.15

Get data as text (for copy / paste).

Get 3D geometry BETA

Naproxen



Molinspiration bioactivity score v2016.03

GPCR ligand	-0.09
Ion channel modulator	-0.20
Kinase inhibitor	-0.14
Nuclear receptor ligand	-0.10
Protease inhibitor	0.09
Enzyme inhibitor	0.18

Get data as text (for copy / paste).

Get 3D geometry BETA

Naproxen Sulphonamide

cause plasma extravasations, increased tissue water and plasma protein exudation[21-22]. This method has been used as an experimental animal model for acute inflammation and is believed to be biphasic.Carrageenan model as early phase 1–2 hr of the is mediated by histamine, serotonin and increased the damaged prostaglandins synthesis of tissue depot[23], as shown withen table -2 and figure 2.

Thickness as mean ± SEM. n= number of animals. Time (0) is the time of i.p. injection of naproxen, tested compounds and propylene glycol. Time (30) is the time of injection of egg white(induction of paw edema).

Molecular modeling approach

The successful docking has been performed for all newly synthesized target compounds (III a–b) using genetic

optimization for ligand docking (1-click docking). This program uses a genetic algorithm (GA) to explore the full range of the rotational flexibility of selected receptor hydrogen's and ligand flexibility. The 3D crystallographic structure of COX-2 (PDB code 4COX) was used as template selected from RCSB protein data bank (PDB) for anti-inflammatory activity[24-25]. The interactions between ligand (III a–b) and receptor in the modeled complexes were investigated and observed the fitness function ability of COX-2 by all newly synthesized inhibitors. The observed docking score have been produced in Table 3. The visualization of the binding conformations of these analogues in the active site of 4COX protein show good binding orientation poses in Figs. 3[26].

CONCLUSIONS

The synthesis of the designed compounds has been successfully achieved. Characterization and identification of the synthesized compounds were confirmed by determination of physical properties& FT-IR spectroscopy. Anti-inflammatory study using egg white induced edema model of inflammation revealed that the incorporation of final ester compounds of Ibuprofen IIIa and Naproxen IIIb maintained it is anti-inflammatory activity. Interestingly, the docking results were in agreement with that of the anti-inflammatory activity and against cyclooxygenase enzyme where the important structural features, spatial arrangement and binding interaction required for activity were determined.

ACKNOWLEDGMENTS

We are grateful to dr. Sabah Jawad Salih from national center for drug control and research, Baghdad, Iraq for providing complete the docking study.

REFERENCES

1. Antonietta, M.A.C.; Bernardo, A.; Greco, A. and Minghetti, L.: Non- Steroidal Anti-Inflammatory Drugs and Brain Inflammation: Effects on Microglial Functions. Pharmaceuticals. 2010; 3: 1949-1964.
2. James, M. S. and Clemence, E. H.: Strategies to Optimize Treatment with NSAIDs in Patients at Risk for Gastrointestinal and Cardiovascular Adverse Events. Clinical Therapeutics. 2010; 32 (4): 667-677.
3. Johan, M.B. and Joham, H.B.: Wilson and Gisvolds textbook of Organic Medicinal and Pharmaceutical Chemistry (12th. ed.). Lippincott Williams and Wilkins. 2011; pp.796.
4. Ahmed, S.P.and Rasheed, S.: Studies on the mode of action of non- steroidal anti-inflammatory drugs. Pakistan J. Pharm. Sci. 1989; 2(2):1-11.
5. Dey,I.; Lejeune, M. and Chadee, K.: Prostaglandin E2 receptor distribution and function in the gastrointestinal tract. British J. of Pharmacology. 2006;149: 611-623.
6. Harizi, H.: Corcuf.: Aracchidonic acid derived eicosanoids: roles in biology and immunopathology. Trends in Molecular Medicine. 2009; 14 (10): 461-469.
7. Hayashi, S.;Ueno,N.;Murase,A.and Nakagawa,: Novel acid-type cyclooxygenase -2 inhibitors: Design, Synthesis, and Structure -activity relationship for anti-inflammatory drug. Eur. J. of Med. Chem. 2012;50:179-195.
8. Hayashi, S.; Sumi, Y.; Ueno, N.; Murase, A. and Takada, J.: Discovery of a novel COX-2 inhibitor as an orally potent anti-pyretic and anti- inflammatory drug: Design, synthesis, and structure–activity relationship. Biochemical Pharmacology. 2011; 82: 755–768.
9. Hegazy, G.H. and Ali, H.I.: Design, synthesis, biological evaluation, and Comp-arative Cox1 and Cox2 Docking of p- substituted benzylidenamino-phenyl esters of ibuprofenic and mefenamic acids Bioorganic & Medicinal Chemistry. 2012; 20: 1259 –1270.
10. Rabia Bushra.et al. An Overview of Clinical Pharmacology of Ibuprofen.omj.2010;4 (9):p 155-160.
11. Tagreed N – A. Omar. Synthesis and Preliminary Pharmacological Evaluation of Esters and Amides Derivatives of Naproxen as Potential Anti-Inflammatory Agents. Iraqi J Pharm Sci.2013; Vol.22 (1):p120 -27.
12. Arfaie, S. and Zarghi, A.: Design, synthesis and biological evaluation of new (E) and (Z)-1, 2, 3-triaryl-2-propen -1- ones as selective COX -2 inhibitors. Eur.
13. Cronstein BN."Cyclooxygenase-2-selective inhibitors: translating pharmacology into clinical utility". Cleve Clin J Med. 2002;69:13-19.
14. L. S. Varandas, C. A. M. Fraga, A. L. P. Miranda and E. J. Barreiro: Design, Synthesis and Pharmacological Evaluation of New Nonsteroidal Anti-inflammatory 1,3,4-Thiadiazole Derivatives. Letters in Drug Design and Discovery 2005;2: 62-67.
15. Hae-Sun Prk, Hee-Jeon Choi, Hea-Soon Shin, Sang Kook Lee and Myung-Sook Park: Synthesis and Characterization of Novel Hydantoins as Potential COX-2 Inhibitors:1,5-Diarylhydantoins. Bull. Korean Chem. Soc. 2007; 28(5): 751-757.
16. Rang,H.P.;Dale, M.M. and Ritter,J.M. In: Pharmacology(4th ed.), Churchill Livingstone, London, 2003; 244.
17. Matthias, P. W. and Roger, S.: lipid signaling in disease. Natural reviews molecular cell biology. 2008; 9: 162-176.
18. Shriner, R.L.; Hermann, C.K.F.; Morrill, T.C.; Curtin, D.Y.and Fuson, R.C.: The Identification of Organic Compounds (8th ed.). John Wiley and Sons, Inc. U.S.A. 2004; pp. 247-350.
19. Leblanc, Y.; Black, W.C.; Chan, C.C.; et al.: synthesis and biological evaluation of both enantiomers of L-761,066 as inhibitors of COX-1 andBioorg. Med. Chem. Lett.1996; 6:731 -736.
20. Zarghi, A.; Rao, P.N.P.; and Knaus, E.E.: Design and synthesis of new rofecoxib analogs as selective cyclooxygenase-2 (COX-2) inhibitors: replacement of the methanesulfonyl pharmacophore by a N-

acetylsulfonamidobioisostere. Pharm. Pharm. Sci. J. 2007; 10: 159-67.
21. Mahdi, M.F.; Mohammed, M.H. and Jassim, A.A.: Design, Synthesis and Preliminary Pharmacological Evaluation of New Non-Steroidal Anti- Inflammatory Agents Having a 4- (Methylsulfonyl) Aniline Pharmacophore. Molecules. 2012; 17: 1751-1763.
22. DannhardtG,Laufer, Structural Approaches to Explain the Selectivity of COX - 2 Inhibitors: Is There a Common Pharmacophore Current Medicinal Chemistry. 2000; 7(11): 1101-12.
23. Rajiv K. Tonk, Sandhya Bawa, Gita Chawla. Pyrazole incorporated 1,2- diazanaphthalene derivatives: Synthesis and in-vivo pharmacological screening as anti-inflammatory and analgesic agents. African Journal of Pharmacy and Pharmacology. 15 February, 2012;Vol. 6:(6): pp. 425-433.
24. Zhang HJ1, Wang XZ2, Cao Q3, Gong GH4, Quan ZS5.Bioorg Med Chem Lett. 2017 Sep 15;27(18):4409-4414.
25. Orlando BJ, Lucido MJ, Malkowski MG. The structure of ibuprofen bound to cyclooxygenase-2. J Struct Biol. 2015;189:62–66.
26. Raghavendra N.M., Ramakrishna K., Sirisha V., Divya P., Venkateswara Rao A. Computer aided discovery of potential anti-inflammatory (s)-naproxen analogs as COX-2 inhibitors. Med. Chem. 2013;9:553–559.