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An *In Vitro* Evaluation of Anti-Inflammatory Activity of Newly Synthesized 1,3,4 Oxadiazole Derivatives

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Abstract: In the area of heterocyclic chemistry, oxadiazole has made major contributions. An enormous number of oxadiazoles have been synthesized and exposed to biological screening; the screening results improved their status due to its potential activities and their efficacy in diverse fields of daily life. Due to its wide range of pharmacological and therapeutic effects, the 1,3,4-oxadiazole moiety is the most important oxadiazole. In this study, we discuss a new family of 2,5-disubstituted 1,3,4-oxadiazole compounds' anti-inflammatory characteristics (4a-4h).The anti-inflammatory efficacy of the oxadiazole derivative was studied by utilizing Human Red Blood Cell membrane stabilization (HRBCs) method. Many synthesized compounds displayed remarkable anti-inflammatory activity in HRBCs test. In the novel synthesized derivatives, compounds 2-(5-bromo-2-(trifluoromethoxy)phenyl)-5-p-tolyl-1,3,4-oxadiazole (4h) and 2-(5-bromo-2-(trifluoromethoxy) phenyl)-5-phenyl-1,3,4-oxadiazole (4a) exhibited the maximum activity of 90.76 % and 88.35 % protection, respectively at concentration 500 µg/ml, compared with DFS that showed 91.86 % inhibition of RBC haemolysis at the same concentration.

Keywords: Anti-inflammatory, Oxadiazole, Human Red Blood Cell membrane stabilization Test, Molecular docking

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Introduction

Inflammation is defined as a defensive tissue reaction to infection, irritation or foreign substances (Robb *et al.,* 2016). It is a part of the host defense mechanism but when it becomes great it is hopeless condition (Farges *et al.*, 2015). There are several tissue factors or mechanisms that are known to be involved in the inflammatory reaction such as release of histamine, bradykinins and prostaglandins. Inflammation is the local response of living mammalian tissue to injury due to any agents (Stefani *et al.*, 2012). It is a body defense reaction in order to eliminate or limit the

spread of injurious agent as well as to remove the consequent necrosed cells and tissues (Sasikumar *et al.*, 2016). These are the agents used to suppress the inflammation and pain sensation. The drugs used as anti-inflammatory come under the class of non-steroidal anti-inflammatory drugs (NSAIDs) (Samik Bindu *et al.,* 2020). NSAIDs are the backbone for the management of pain which arises due to inflammatory diseases (Barbagallo *et al.,* 2018). These drugs suppress natural processes that are responsible for inflammation (Shanmuganathan *et al.*, 2017). A number of non-selective non-steroidal anti-inflammatory drugs (NSNS-AIDs) such as indomethacin, ibuprofen, phenylbutazone, oxyphenylbutazone, diclofenac, fenoprofen, caprofen, benoxaprofen, sulindac and aspirin etc. are available in the market (Al-wabli *et al.*, 2018). NSNS-AIDs are nonselective inhibitors of the enzymes which are responsible for the conversion of arachidonic acid to prostaglandins (Waghmare *et al.,* 2017). These medications have unfavourable effects on the digestive system, including dyspepsia, gastroduodenal ulcers, gastritis and bleeding (Khan *et al.*, 2003). During past decades, compounds bearing heterocyclic nuclei have received much attention due to their chemotherapeutic value in the development of novel anti-inflammatory activities (Manjunatha *et al*., 2015). The oxadiazole chemistry has been developed extensively and is still developing (Sears *et al.,* 2015). Presently there are a number of drugs used clinically which comprise oxadiazole moiety in association with various heterocyclic rings (Chaudhary e*t al.*, 2017). The pharmaceutical chemistry of heterocyclic compounds promoted the researchers to synthesize different derivatives of 1,3,4-oxadiazole with diverse substituent at 2 and 5-positions (Singh e*t al*., 2018; Santhanalakshmi *et al.*, 2021) . These derivatives have been also examined for their anti-inflammatory activity. Mostly, five-membered ring aromatic systems having three hetero atoms at symmetrical position have been studied because of their physiological properties (Baptista *et al.*, 2015).

Wasim Akhter *et al*. (2015) have reported a series of 1,3,4-oxadiazole derivatives of phenoxy-acetic acid with capable anti-inflammatory potential. Singh *et al.* (2013) have designed several oxadiazole derivatives and performed anti-inflammatory activity with indometacin as a standard drug which revealed that the newly synthesized oxadiazole compounds have enhanced anti-inflammatory activities (Xian-Jing *et al*., 2020).

Therefore, it was thought that by employing fluorine substituted carboxylic acid to synthesize some new 2,5-disubstituted-1,3,4-oxadiazole derivatives and concentrating on reporting products with improved anti-inflammatory activity. It is intended in the present study to investigate the drug design as well as in the mechanistic study by placing a molecule into the binding site of the target macromolecule in a non-covalent fashion.

Materials and Methods

A novel series of 2-(5-bromo-2-(trifluoromethoxy) phenyl) – 5 – aryl - 1, 3, 4- oxadiazole (4a-4h) compounds (aryl = C_6H_5, p-ClC_6H_4, p-$NO_2C_6H_4$, C_5H_4N, p-$OCH_3C_6H_4$, p-BrC_6H_4, p-OHC_6H_4, p-$CH_3OC_6H_4$) were produced by treating acid hydrazide with 5-bromo-2-(trifluoromethoxy) benzoic acid in phosphoryl chloride (Santhanalakshmi *et al.*, 2022). The principle concerned in this method is of human red blood cell membrane by hypotonicity induced membrane lysis. Blood was collected (2 ml) from healthy volunteers and was mixed with equal volume of sterilized Alsevers solution (2% dextrose, 0.8% sodium citrate, 0.5% citric acid, and 0.42% NaCl in distilled water) and centrifuged at 3000 rpm. The packed cells were washed with isosaline solution and a 10% v/v suspension was prepared with normal saline.

Different concentrations of synthesized coumarin derivatives (25 µg/ml, 50 µg/ml, 100 µg/ml) Diclofenac sodium (25 µg/ml, 50 µg/ml, 100 µg/ml) as standard and control (distilled water instead of hyposaline to produce 100%

haemolysis) were separately mixed with 1 ml of phosphate buffer, 2 ml hyposaline solution and 0.5 ml of 10% HRBC suspension was added to prepare reaction mixture.

All the assay mixtures were incubated at 37°C nearly for 30 min and centrifuged at 3000 rpm for 20 min and hemoglobin content of the supernatant solution was estimated spectrophotometrically at 560 nm. The percentage of HRBC membrane stabilization or protection was calculated by using the formula:

%Membrane Stabilization = {(Absorbance of control-Absorbance of test)/Absorbance of control} × 100

Anti-inflammatory agents inhibit the cyclooxygenase enzymes (Kurumbail *et al*., 1996) which are accountable for the transformation of arachidonic acid to prostaglandins and human red blood cell (HRBC) membranes are similar to these lysosomal membrane components which prevent hypotonicity induced HRBC membrane lysis and it was taken as a measure in estimating anti-inflammatory activity (Kiruthiga *et al*., 2021). Anti-inflammatory activity was done by Human Red Blood Cell membrane lysis and the reference drug DFS stabilizes the Human Red Blood Cell membrane, thereby reducing the hemolysis (Kumari *et al*., 2015). The result of the *in vitro* membrane stabilization activity of the synthesized 1,3,4-oxadiazole 4(a-h) is presented in Table 1 and Figure 1.

According to these results, all the compounds showed dose dependent inhibition of hemolysis. The activity of compounds 4(a-h) along with reference diclofenac sodium was examined at concentrations of 100, 250, 500 µg/ml. Among the new derivatives, compounds 4h and 4a showed the maximum activity of 90.76 % and 88.35 % protection, respectively at concentration 500 µg/ml, compared with DFS that showed 91.86 % inhibition of RBC haemolysis at the same concentration.

The most significant class of widely prescribed therapies for the treatment of pain and inflammation is non-steroidal anti-inflammatory medications (NSAIDs) (Wehling *et al*., 2014). The principal pharmacological effects of NSAIDs increase from their inhibition of cyclooxygenases (COXs) (Khan *et al*., 2002).

Cyclooxygenases control the complex conversion of arachidonic acid to prostaglandins and thromboxanes, which trigger as autocrine and paracrine chemical messengers for many physiological and pathophysiological responses (Khan *et al*., 2022). The discovery of a second isoform of cyclooxygenase namely COX-II has opened a new line of research based on the assumption that pathological prostaglandins (PGs) are produced by the inducible isoform COX-II while physiological prostaglandins are produced by constitutive isoform COX-I (Hegazy *et al*., 2011). These physiological protective PGs preserve the integrity of the stomach lining and maintain normal renal function in compromised kidney (Coruzzi *et al*., 2007). The separation of therapeutic effects from the side effects has been a major challenge in the design and synthesis of these drugs (Kudr *et al*., 2017).

A common structural feature of many selective COX-II inhibitors is the presence of two vicinal aryl rings attached to a central five member heterocyclic moieties (Abeer *et al*., 2016). Also, most of the side effects of NSAIDs are mainly due to inhibition of both isomers COX-I and COX-II (Baptista *et al*., 2015), yet they may also relate to their acidic characters due to the presence of free carboxylic acid moiety. This issue can be partially resolved by reducing acidity or by creating derivatives that are not acidic. Additionally, 1,3,4-oxadiazole derivatives have been shown to have a variety of pharmacological effects, including antibacterial and anti-inflammatory effects (Hassanzadeh *et al*., 2019).

Docking Study of 1,3,4-oxadiazoles against Aspirin Acetylated Cyclooxygenase-1:

The crystallographic enzyme ligand was obtained from the RCSB Protein Data Bank (PDB: 3N8Y) is shown in Figure 2. In order to compare the binding affinity of the newly synthesized

Table 1: *In vitro* anti-inflammatory activity of the synthesized compounds and reference drug (DFS) using HRBCs membrane stabilization method

Compds.	**Conc. mg/ml**	**Absorbance**	**% Inhibition**
4a	100	0.613 ± 0.0120	23.27
	250	0.414 ± 0.0111	74.49
	500	0.189 ± 0.0886	88.35
4b	100	0.707 ± 0.0280	56.43
	250	0.600± 0.0100	63.03
	500	0.300 ± 0.0101	81.52
4c	100	0.800 ± 0.0342	50.7
	250	0.657 ± 0.0185	59.52
	500	0.302 ± 0.0100	81.39
4d	100	0.782± 0.0322	51.82
	250	0.478 ± 0.0157	70.55
	500	0.250 ± 0.0100	84.6
4e	100	0.680 ± 0.0171	58.1
	250	0.414 ± 0.0101	74.49
	500	0.220 ± 0.0681	86.44
4f	100	0.400 ± 0.0187	75.35
	250	0.358 ± 0.0142	78.1
	500	0.232 ± 0.0102	85.7
4g	100	0.613 ± 0.0320	62.23
	250	0.514 ± 0.0201	68.33
	500	0.239 ± 0.1560	85.27
4h	100	0.682 ± 0.0372	57.98
	250	0.378 ± 0.0147	76.7
	500	0.150 ± 0.0101	90.76
DFS	100	0.578± 0.1465	64.38
	250	0.301 ± 0.0588	81.45
	500	0.132 ± 0.0524	91.86

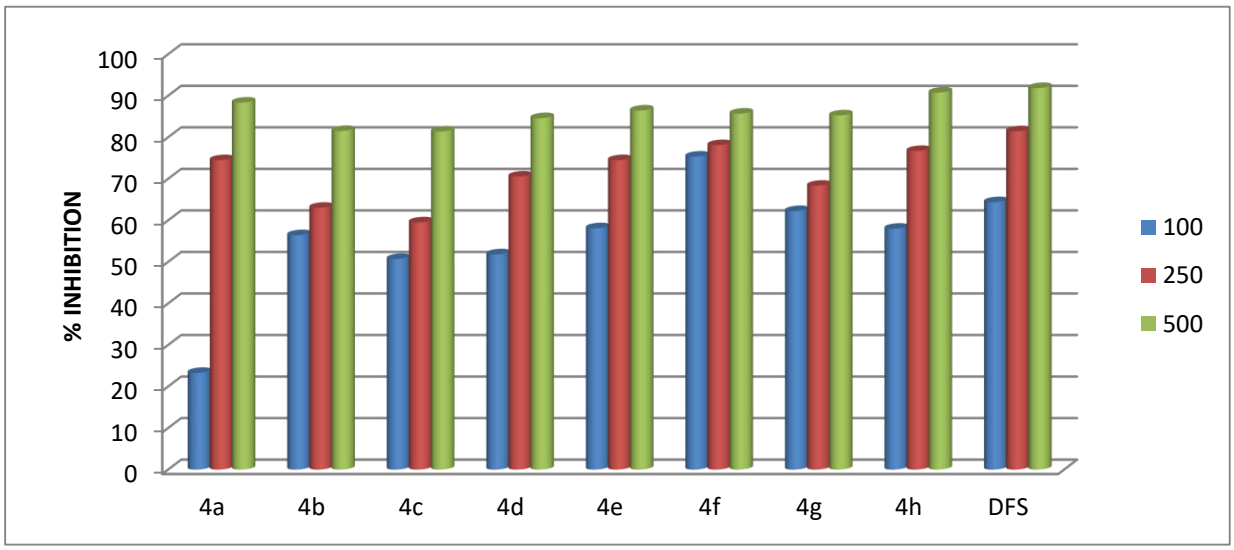

Fig. 1: *In vitro* anti-inflammatory activity of the synthesized compounds and reference drug (DFS) using HRBCs membrane stabilization method.

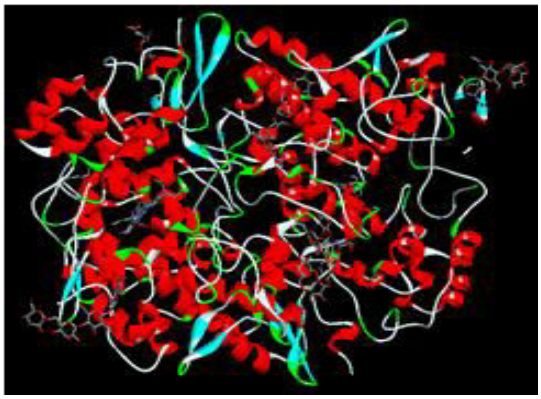

Fig. 2: 3D image of protein 3N8Y.

Table 2: Binding scores of 1,3,4- oxadiazole compounds with Aspirin Acetylate Cyclooxygenase-1 protein 3N8Y

Compounds	Binding scores (kcal/mol)
4a	-10.1
4b	-10.1
4c	-10.3
4d	-9.9
4e	-9.7
4f	-10.1
4g	-10.1
4h	-10.0
DFS	-7.92

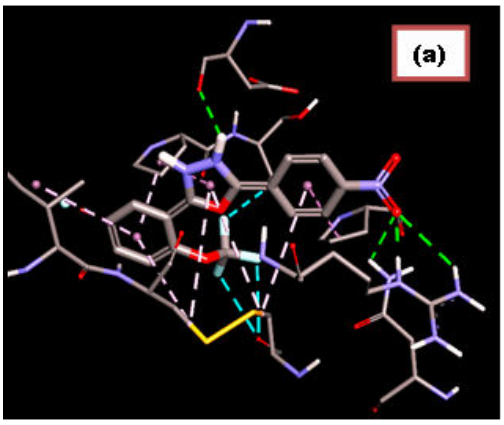

Fig. 3(a): 2D-Docked conformation of compound 4c with 3N8.

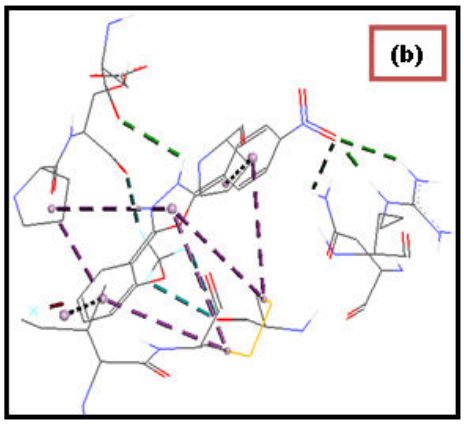

Fig. 3(b): Docking confirmation of most active compound 4c.

Table 3: Interaction pattern of 1,3,4-oxadiazole derivatives with 3N8Y proteins

Compd.	Hydrogen bond	Other interaction
4a	GLU465, GLN461	ARG469,LYS468, GLN44,LUE152, GLY45, PRO153,CYS47, CYS36
4b	ARG376, ARG374	VAL145, PHE142,PRO538,LEU224,VAL145,
4c	ASN34, ARG49, ASP135	PRO156,PRO153,CYS36,CYS47
4d	UNK1, GLU465, GLN461	LYS468,ARG469,LEN152,PRO153,CYS36,CYS47, GLY45,GLN44
4e	ASP135,	PRO153,SER154,PRO156,ASP158, CYS36,CYS47,ILE46
4f	ARG376, ARG374	PRO538,VAL145 ,PHE142,VAL145
4g	GLU465, GLN461	CYS47, CYS36,GLY45,PRO153,GLN44,ARG469,LYS468, LEU152
4h	ASP135	PRO156,SER154,CYS36,CYS47 ,ILE46,PRO153

oxadiazole derivatives, we docked all the biologically active compounds to evaluate their molecular docking. Binding scores of synthesized 1,3,4- oxadiazole compounds with Aspirin Acetylate Cyclooxygenase-1 protein 3N8Y is shown in Table 2. 2D-Docked conformation of most active compound 4(c) is shown in Figure 3. Docking confirmation of compounds 4(c) with 3N8Y is shown in Figure 3.

Docking Study of 1,3,4-oxadiazoles against Cyclooxygenase-2:

The crystallographic enzyme ligand was obtained from the RCSB Protein Data Bank (PDB: 3LN1) is shown in Figure 4.

In order to compare the binding affinity of the newly synthesized oxadiazole analogues, we docked all biologically active compounds to evaluate their molecular docking. 2D-Docked conformation of most active compound 4(h) is shown in Figure 5.

Binding scores of the 1,3,4-oxadiazole derivatives with Cyclooxygenase-2 protein is presented in Table 4. As seen from docking results, it revealed that the more active compound 4h shows nice docking score -10.8 kcal/mol.

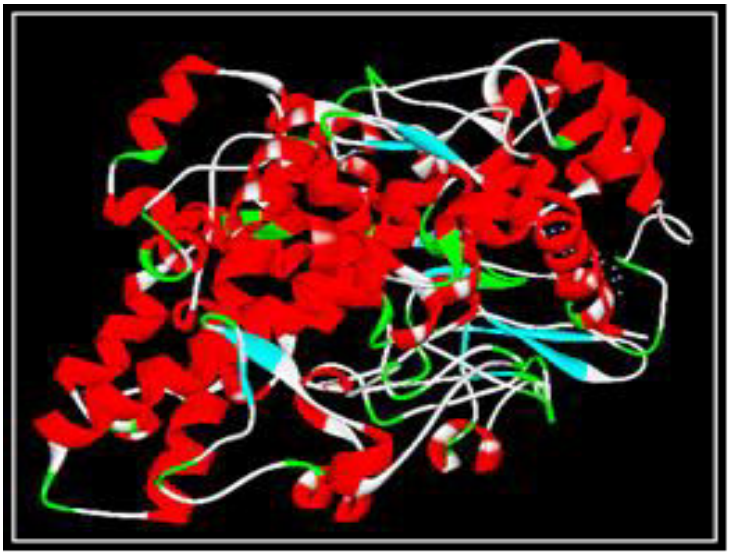

Fig. 4: 3D image of protein 3LN1.

Table 4: Binding scores of the 1,3,4oxadiazole derivatives with Cyclooxygenase-2 proteins

Compounds	Binding scores (kcal/mol)
4a	-10.6
4b	-10.6
4c	-10.5
4d	-10.6
4e	-10.5
4f	-10.7
4g	-10.7
4h	-10.8
Celecoxib	-10.9

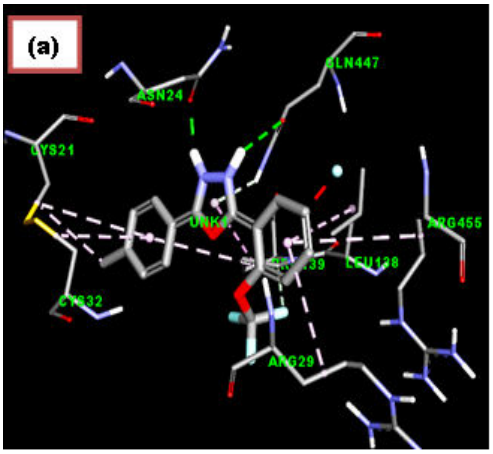

Fig. 5 (a): 2D-Docked conformation of most active compound 4h.

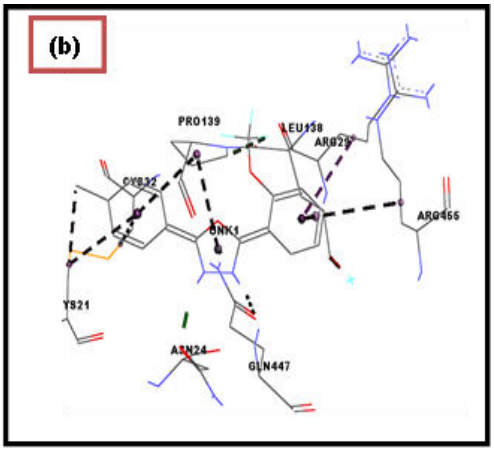

Fig. 5(b): Docking confirmation of 4h with 3LN1.

Table 5: Interaction pattern of 1,3,4-oxadiazole derivatives with 3LN1 proteins

Compound	Hydrogen bond	Other interaction
4a	ASN24,GLN447	PRO139,LEU138,UNK1,ARG455,CYS32,TYS454
4b	GLN447,ASN24	UNK1,CYS21,CYS32,ARG29,PRO139,LEU138,ARG455
4c	ALA142	PRO139,UNK1,ARG29,CYS32,CYS21,LYS532,ASN24 CYS21,CYS26,TYR116
4d	CYS21,CYS32,ASN24	PRO139,ARG29,LEU138,ARG445,UNK1,GLN447
4e	ASN24,GLN447	CYS21,CYS32,UNK1,PRO139,ARG29,ARG455,LEU138
4f	GLN447,ASN24	CYS21,CYS32,PRO139,LEU138,UNK1,ARG29,ARG455
4g	CYS21,CYS32,AS24	PRO139,LEU138,ARG455,ARG29,GLN447,UNK1
4h	ASN24	CYS21,CYS32,PRO139,LEU138,ARG29,UNK1, ARG455, GLN477

Interaction pattern of 1,3,4-oxadiazole derivatives with 3LN1 protein is displayed in Table 5. It has one hydrogen bonding with ASN24. The residues CYS21, CYS32, PRO139, LEU138, ARG29, UNK1, ARG455 and GLN477 were common in VdW and polar/electrostatic interactions. On the other hand, to investigate pyridine incorporated oxadiazole (compound 4d) show same binding energy with compound 4a and 4b.

Results and Discussion

This study deals about the anti-inflammatory activity of all the newly synthesized oxadiazole compounds (4a-4h) and its docking efficiency with Cyclooxygenase-1 and Cyclooxygenase-2. According to *in vitro* anti-inflammatory results, all the compounds displayed dose dependent inhibition of hemolysis. The activity of compounds (4a-4h) along with reference diclofenac sodium was studied at concentrations of 100, 250, 500 µg/ml. Among the synthesized derivatives, compounds 4h and 4a exhibited the maximum activity of 90.76 % and 88.35 % protection, respectively at the concentration 500 µg/ml, compared with DFS that showed 91.86 % inhibition of RBC haemolysis at the same concentration. The results of docking studies infer that the compounds 4c, 4a, 4b, 4f and 4g in COX-I and 4f, 4g, 4a, 4b and 4d in COX-II possess better binding energy and show more number of hydrogen bonding. In addition to that it forms diverse types of interactions like Pi-alkyl, Pi-Pi stacked and alkyl interactions with surrounding amino acids.

Conclusion

Pharmacological screening has confirmed that the results of experimental *in vitro* anti-inflammatory activities are in good accord with the predicted binding affinities, discovered by molecular docking investigations.The designed compounds displayed docking score values, almost equal when compared to the standard drug Diclofenac sodium (-7.92 kcal/mol) and Celecoxib (-10.9 kcal/mol) which exposes higher binding affinity with the enzyme. This study revealed that the oxadiazole as effective lead for the development of innovative anti-inflammatory agent with good efficiency and slighter side effects.

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References

Abeer AA. (2016) Drug design and synthesis of cox-2 selective inhibitors as potential NSAIDs/ Abeer Abdulhadi Abdulqader. Doctoral Dissertastion, University of Malaya.

Akhter W and Amir M. (2014) Synthesis of some new 1,2,4-triazoles and 1,3,4-oxadiazoles as a safer anti-

inflammatory and analgesic agents. J Pharm Res. 8: 1239-1247.

Al-wabli R, Fouad M and El-haggar R. (2018) Synthesis, *in vivo* and *in vitro* anti-inflammatory evaluation of some novel coumarin derivatives. Antiinflamm Antiallergy Agents Med Chem. 17(2): 115-124.

Babaheydari AK. (2015) In silico drug design on aspirin for Cyclooxygenase I and II, target for reduce the effects of inflammatory. Biosci Biotechnol Res Asia 12(1): 433-444.

Baptista PV and Fernandes AR. (2015) Heterocyclic anticancer compounds: Recent advances and the paradigm shift towards the use of nanomedicine's tool box. Molecules 20: 16852-16891.

Barbagallo M and Sacerdote P. (2018) Ibuprofen in the treatment of children's inflammatory pain: a clinical and pharmacological overview. Minerva Pediatrica 71(1): 82-99.

Chaudhary T, Singh A and Verma R. (2017) An updated review on synthesis and biological activities of 1,3,4-oxadiazole derivatives. Int J Sci Res. 7(8):1536-1544.

Coruzzi, G, Nicola V and Silvana S. (2007) Gastrointestinal safety of novel nonsteroidal antiinflammatory drugs: selective COX-2 inhibitors and beyond. Acta Biomedica-Ateneo Parmense 78(2): 96-110.

Hassanzadeh F, Sadeghi-Aliabadi H, Jafari E, Sharifzadeh A and Dana N. (2019) Synthesis and cytotoxic evaluation of some quinazolinone- 5-(4-chlorophenyl) 1, 3, 4-oxadiazole conjugates. Res Pharm Sci. 14(5): 408-413.

Hegazy GH, Ghaneya SH, Nahla AF and Ama Y. (2011) Design, synthesis and docking studies of novel diarylpyrazoline and diarylisoxazoline derivatives of expected anti inflammatory, and analgesic activities. Life Sci J. 8(1): 387-396.

Farges JC, Alliot-Licht B, Renard E, Ducret M, Gaudin A, Smith AJ and Cooper PR. (2015) Dental pulp defence and repair mechanisms in dental caries. Mediators Inflamm. 2015: 230251.

Khan H, Sharma K, Kumar A, Kaur A and Singh TG. (2022) Therapeutic implications of cyclooxygenase (COX) inhibitors in ischemic injury. Inflamm Res.71(3): 277-292.

Khan KN, Paulson SK, Verburg KM, Lefkowith JB and Maziasz TJ. (2002) Pharmacology of cyclooxygenase-2 inhibition in the kidney. Kidney Int. 61(4): 1210-1219.

Kiruthiga N, Alagumuthu M, Selvinthanuja C, Srinivasan K and Sivakumar T. (2021) Molecular modelling, synthesis and evaluation of flavone and flavanone scaffolds as anti-inflammatory agents. Antiinflamm Antiallergy Agents Med Chem. 20(1): 20-38.

Kudr J, Haddad Y, Richtera L, Heger Z, Cernak M, Adam V and Zitka O. (2017) Magnetic nanoparticles: from design and synthesis to real world applications. Nanomaterials (Basel) 7(9): 243.

Kumar A, Lohani M and Parthsarthy R. (2013) Synthesis, characterization and anti-inflammatory activity of some 1,3,4 -oxadiazole derivatives. Iran J Pharm Res.12: 319-323.

Kumari CS, Yasmin N, Hussain MR and Babuselvam M. (2015*) In vitro* anti-inflammatory and anti-artheritic property of *Rhizopora mucronata* leaves. Int J Pharma Sci Res. 6(3): 482-485.

Kurumbail RG, Stevens AM, Gierse JK, McDonald JJ, Stegeman RA, Pak JY, Gildehaus D, Miyashiro JM, Penning TD, Seibert K, Isakson PC and Stallings WC. (1996) Structural basis for selective inhibition of cyclooxygenase-2 by anti-inflammatory agents. Nature 384(6610): 644-648.

Manjunatha E, Divekar K, Palaksha MN and Sanglikar G. (2015) Synthesis, characterization and evaluation of in-vivo anti-inflammatory activity of some synthesized n-[(3, 5-sub - 4, 5- dihydroisoxazol-4-yl)methyl]aniline derivatives. World J Pharm Pharmaceut Sci. 4(2): 567-578.

Khan MSY and Akhtar M. (2003) Synthesis of some new 2,5-disubstituted 1,3,4-oxadiazole derivatives and their biological activity. Indian J Chem. 42B: 900-904.

Robb CT, Regan KH, Dorward DA and Rossi AG. (2016) Key mechanisms governing resolution of lung inflammation. Semin Immunopathol. 38(4): 425-448.

Samik B, Somnath M and Bandyopadhyay U. (2020) Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. Biochem Pharmacol. 180: 114147.

Santhanalakshmi K, Gomathi T, Margandan K and Neelakandeswari N. (2022) Larvicidal activity of 1,3,4- oxadiazole analogues and their Molecular Docking studies. International Conference on Smart Technologies and Systems for Next Generation Computing (ICSTSN) . 978-1-6654-2111-9/22, IEEE.

Santhanalakshmi K, Margandan K, Manivannan P and Jacquline Rosy P. (2021) Pharmacological significance of Oxadiazole scaffold. Res J Chem Environ. 25 (8): 177-188.

Sasikumar S, Haripriya M and Anjali T. (2016) Synthesis and evaluation of anti-inflammatory and antibacterial activities of some 1,2-benzisoxazole derivatives. Int J Curr Pharm Res. 8(4): 64-67.

Sears JE and Boger DL. (2015) Total synthesis of vinblastine, related natural products, and key analogues and development of inspired methodology suitable for the systematic study of their structure–function properties. Acc Chemical Res. 48(3): 653-662.

Shanmuganathan T. (2017) Synthesis, in vitro anti-inflammatory activity and molecular docking studies of novel 4, 5-diarylthiophene-2-carboxamide derivatives. J Chem Sci. 129: 117-130.

Singh AK, Parthsarthy R and Lohani M. (2012) Synthesis, characterization and anti-inflammatory activity of some 1, 3,4 -oxadiazole derivatives. J Chem Pharmaceut Res. 4: 779-782.

Stefani HA, Botteselle GV, Zukerman-Schpector J, Caracelli I, da Silva Corrêa D, Farsky SH, Machado ID, Santin JR and Hebeda CB. (2012) Synthesis, anti-inflammatory activity and molecular docking studies of 2,5-diarylfuran amino acid derivatives. Eur J Med Chem. 47(1): 52-58.

Waghmare RA, Lingampalle DL, Patil V and Asrondkar A. (2017) Synthesis and *in-vitro* anti-inflammatory activity of some 1-(4-methylsulphonyl amino methyl) phenyl-3,5diarylpyrazolines. Int J Chem Res. 10: 201-206.

Wehling M. (2014) Non-steroidal anti-inflammatory drug use in chronic pain conditions with special emphasis on the elderly and patients with relevant comorbidities: management and mitigation of risks and adverse effects. European J Clin Pharmacol. 70(10): 1159-1172.

Xian-Jing Zheng, Chun-Shi Li, Ming-Yue Cui, Ze-Wen Song, Xue-Qian Bai, Cheng-Wu Liang, Hui-Yan Wang and Tian-Yi Z. (2020) Synthesis, biological evaluation of benzothiazole derivatives bearing a 1,3,4-oxadiazole moiety as potential anti-oxidant and anti-inflammatory agents. Bioorg Med Chem Lett. 30(13): 127237.