Content available at: https://www.ipinnovative.com/open-access-journals

International Journal of Pharmaceutical Chemistry and Analysis

Journal homepage: https://www.ijpca.org/

Original Research Article

Anti-inflammatory activity of novel xanthone derivatives

Darakhshan Parveen[1,*], Amrita Parle[1], Rajnish Srivastava[2]

[1]*Dept. of Pharmaceutical Chemistry, Delhi Pharmaceutical Sciences and Research University, Pushp Vihar, New Delhi, India*
[2]*Dept. of Pharmacology, MET Faculty of Pharmacy, Moradabad, Uttar Pradesh, India*

ARTICLE INFO

Article history:
Received 17-12-2021
Accepted 04-01-2022
Available online 25-01-2022

Keywords:
Xanthone Derivatives
Antiinflammatory
Molecular Docking
2D&3D interactions
COX 1

ABSTRACT

As many diseases such as cancer, metabolic disorders, aging, and neurodegenerative diseases present themselves via inflammation,there is always a need to have better anti-inflammatory drugs. Xanthones, a unique scaffold with a 9H-Xanthen-9-one core structure possesses anti-inflammatory activity. This research work comprised of theoretically designing thirty 3-aminoalkoxy derivatives of xanthone, estimation of physicochemical properties and their Molecular Docking with COX-1 receptor. The best docking scores are possessed by LIG12, LIG23 and LIG30 which were halo substituted phenyl derivatives, LIG7 which had an anilino substitution and LIG27 which had ortho-nitro phenyl substituted derivative. The docking scores of LIG7, LIG12, LIG23, LIG27 and LIG30 were found to be -10.6, -10.7, -10.7, -10.8 and -10.5 kcal/mol.

1. Introduction

Inflammation is the protective response of body to external as well as internal untoward stimuli like exposure to harmful substances or internal danger signals released after trauma or cell dysfunction.[1–3] Mankind is always in desire to be healthy and fit. As many diseases such as cancer, metabolic disorders, aging, and neurodegenerative diseases present themselves via inflammation,[4–7]there is always a need to have better anti-inflammatory drugs. The current therapeutic approaches to treat the inflammation includes use of non-steroidal anti-inflammatory drugs and glucocorticoids. These classes of drugs have limitations due to associated severe side effects,[8,9] Thus, there is scope to develop novel effective anti-inflammatory therapeutic agents. Xanthones possesses a unique 9H-Xanthen-9-one scaffold, which occurs mainly in the plants of the families Gentianaceae and Hypericaceae, as well as some fungi and lichens.[10,11] The studies of xanthones are provoking not only due to structural diversity but also due to pharmacological diversity. Xanthone derivatives have shown anti-inflammatory potential[12] in previous studies. Thus, we decided to explore the anti-inflammatory potential of novel 3-aminoalkoxy derivatives of xanthone. This research work comprised of theoretically designing thirty 3-aminoalkoxy derivatives of xanthone, estimation of physicochemical properties and their Molecular Docking with COX-1 receptor.

2. Materials and Methods

2.1. Designing and novelty check

Thirty 3-aminoalkoxy derivatives of xanthone were theoretically designed with the general structure- Their novelty was established using Sci-Finder at IIT, Delhi.

* *Corresponding author*.
E-mail address: suhana.dk@gmail.com (D. Parveen).

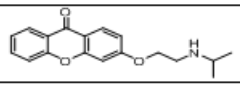
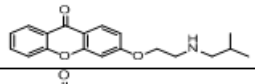
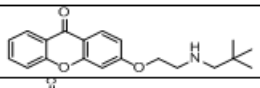
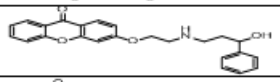
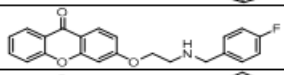
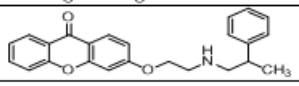
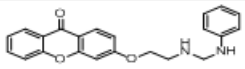
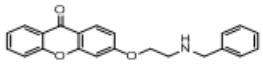
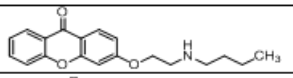
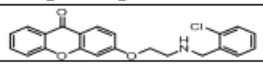
https://doi.org/10.18231/j.ijpca.2021.034

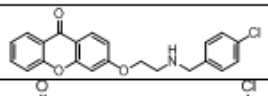
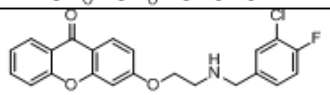
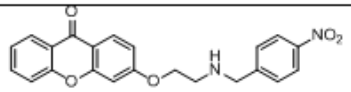
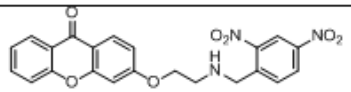
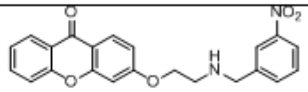
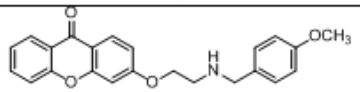
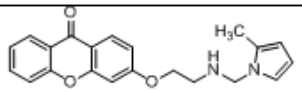
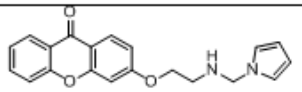
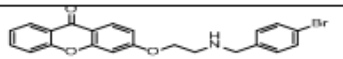
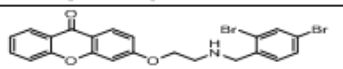
Table 1: Physicochemical properties, lipophilicity, water solubility, drug likeness through Lipinski Rule

Ligand	-R	M.W.	HBA	HBD	No. of R.B.	clogP	Sol	TPSA(Å^2)	Drug likeness (Lipinski)	DS
LIG1	Iso-propyl	297.35	4	1	5	3.32	-5.4	51.47	2.83	0.36
LIG2	Iso-butyl	311.37	4	1	6	3.62	-5.5	51.47	0.44	0.24
LIG3	tert-Butyl	325.40	4	1	6	3.92	-5.6	51.47	-2.09	0.18
LIG4	2-hydroxy-2-phenyl-ethyl	389.44	5	2	8	3.62	-5.9	71.70	3.26	0.3
LIG5	4-fluoro-phenyl	363.38	5	1	6	4.12	-6.4	51.47	0.87	0.4
LIG6	1-phenyl ethyl	373.44	4	1	7	4.38	-6.6	51.47	1.74	0.22
LIG7	Anilinyl	360.41	4	2	7	3.64	-6.6	63.50	-0.1	0.21
LIG8	Phenyl	345.39	4	1	6	3.76	-6.1	51.47	0.87	0.26
LIG9	n-propyl	311.37	4	1	7	3.70	-5.6	51.47	-0.86	0.17
LIG10	2-chloro-phenyl	379.84	4	1	6	4.35	-6.8	51.47	1.34	0.22
LIG11	4-chloro phenyl	363.38	5	1	6	4.12	-6.4	51.47	0.87	0.24
LIG12	3-chloro-4-fluoro-phenyl	397.83	5	1	6	4.64	-7.1	51.47	-1.56	0.13
LIG13	4-nitro phenyl	390.39	6	1	7	3.07	-6.5	97.29	-8.69	0.16
LIG14	2,4-dinitro phenyl	435.39	8	1	8	2.27	-7	143.11	-9.98	0.14
LIG15	3-nitro phenyl	390.39	6	1	7	3.08	-6.5	97.29	-4.28	0.16
LIG16	4-methoxy phenyl	375.42	5	1	7	3.82	-6.1	60.70	2.0	0.28
LIG17	2-methyl, 1H-pyrrol-1-yl	348.40	4	1	6	3.26	-5.3	56.40	2.48	0.34
LIG18	1H-pyrrol-1-yl	334.37	4	1	6	2.92	-4.9	56.40	1.99	0.37
LIG19	4-bromo phenyl	424.29	4	1	6	4.43	-6.9	51.47	-0.42	0.16
LIG20	2, 4-di-bromo phenyl	503.18	4	1	6	5.04	-7.7	51.47	-1.09 1 violation: MW>500	0.06
LIG21	2-bromo phenyl	424.29	4	1	6	4.43	-6.9	51.47	-2.79	0.12
LIG22	3-bromo phenyl	424.29	4	1	6	4.44	-6.9	51.47	-2.45	0.12
LIG23	3-fluoro phenyl	363.38	5	1	6	4.12	-6.4	51.47	-1.88	0.16
LIG24	n-butyl	325.40	4	1	8	4.05	-5.9	51.47	-4.31	0.15
LIG25	2, 4- difluoro phenyl	381.37	6	1	6	4.42	-6.7	51.47	-0.64	0.17
LIG26	2-fluoro phenyl	363.38	5	1	6	4.13	-6.4	51.47	-0.46	0.19
LIG27	2-nitro phenyl	390.39	6	1	7	3.07	-6.5	97.29	-6.26	0.16
LIG28	2, 4-di methoxy phenyl	405.44	6	1	8	3.81	-6.1	69.93	-0.23	0.21
LIG29	2-methoxy phenyl	375.42	5	1	7	3.81	-6.1	60.70	0.81	0.25
LIG30	3, 4-dichloro phenyl	414.28	4	1	6	4.86	-7.5	51.47	1.11	0.17

Table 2: Toxicity profile

Ligand	Mutagenic	Tumorigenic	Irritant	Reproductive effective
LIG1	Yes	No	No	No
LIG2	Yes	No	No	No
LIG3	Yes	No	No	No
LIG4	Yes	No	No	No
LIG5	Yes	No	No	No
LIG6	Yes	No	No	No
LIG7	Yes	No	No	No
LIG8	Yes	No	No	No
LIG9	Yes	No	Slight	No
LIG10	Yes	No	No	No
LIG11	Yes	No	No	No
LIG12	Yes	No	No	No
LIG13	Yes	No	No	No
LIG14	Yes	No	No	No
LIG15	Yes	No	No	No
LIG16	Yes	No	No	No
LIG17	Yes	No	No	No
LIG18	Yes	No	No	No
LIG19	Yes	No	No	No
LIG20	Yes	No	No	Yes
LIG21	Yes	No	No	No
LIG22	Yes	No	No	No
LIG23	Yes	No	No	No
LIG24	Yes	No	No	No
LIG25	Yes	No	No	No
LIG26	Yes	No	No	No
LIG27	Yes	No	No	No
LIG28	Yes	No	No	No
LIG29	Yes	No	No	No
LIG30	Yes	No	No	No

S.No.	Molecule	Docking Score (Kcal/mol)
Native		-7.9
LIG1		-9.6
LIG2		-7.0
LIG3		-7.3
LIG4		-10.2
LIG5		-10.3
LIG6		-10.2
LIG7		-10.6
LIG8		-10.4
LIG9		-9.4
LIG10		-9.2

S.No.	Molecule	Docking Score (Kcal/mol)
LIG11		-6.4
LIG12		-10.7
LIG13		-8.8
LIG14		-7.9
LIG15		-6.8
LIG16		-8.7
LIG17		-8.0
LIG18		-7.8
LIG19		-6.6
LIG20		-10.7

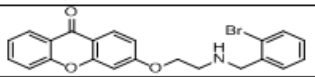
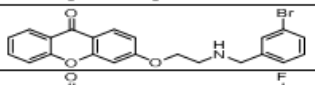
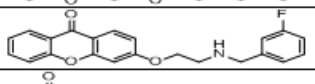
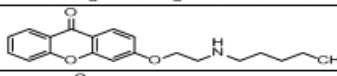
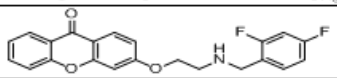
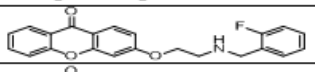
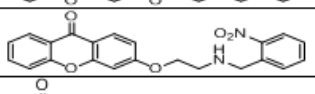
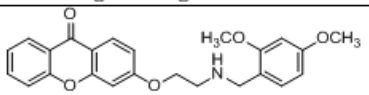
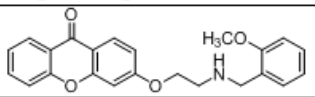
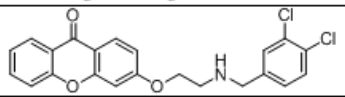
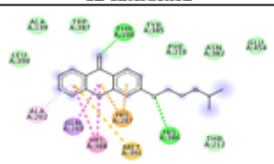
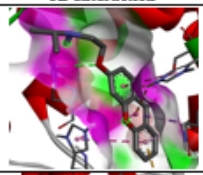
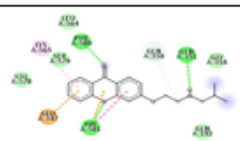
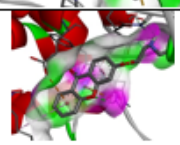
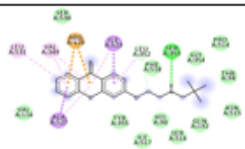
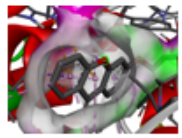
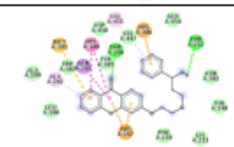
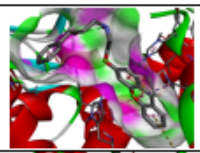
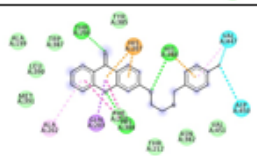
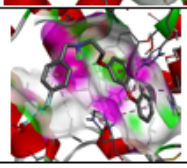
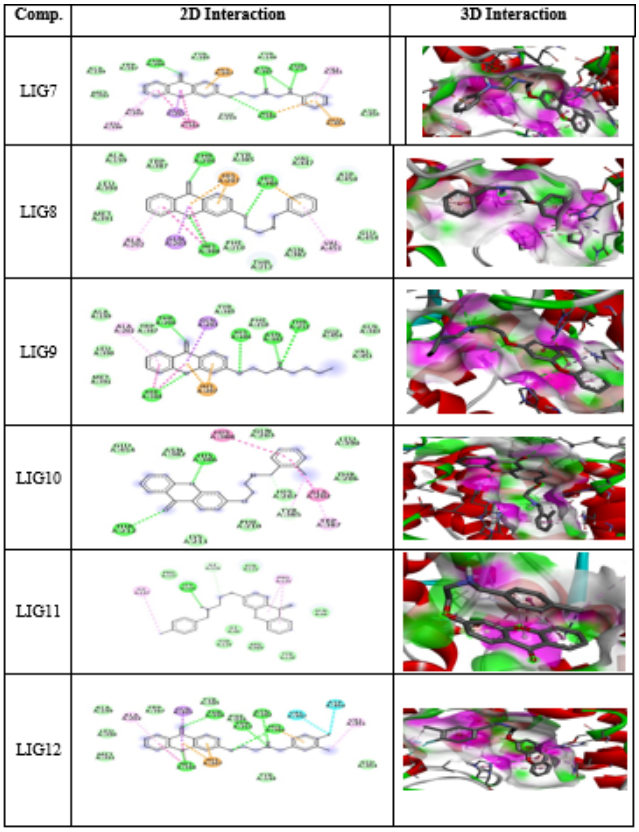
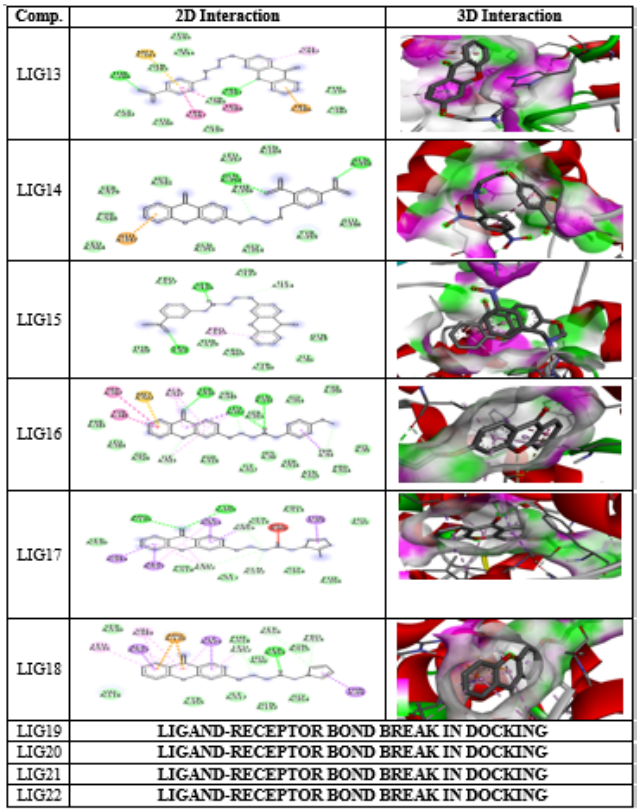
S.No.	Molecule	Docking Score (Kcal/mol)
LIG21		-10.9
LIG22		-10.6
LIG23		-10.7
LIG24		-7.8
LIG25		-8.3
LIG26		-8.0
LIG27		-10.8
LIG28		-8.5
LIG29		-7.9
LIG30		-10.5

Fig. 1: Docking scores of LIG1- LIG30 against COX-1 receptor

Comp.	2D Interaction	3D Interaction
LIG1		
LIG2		
LIG3		
LIG4		
LIG5		
LIG6		





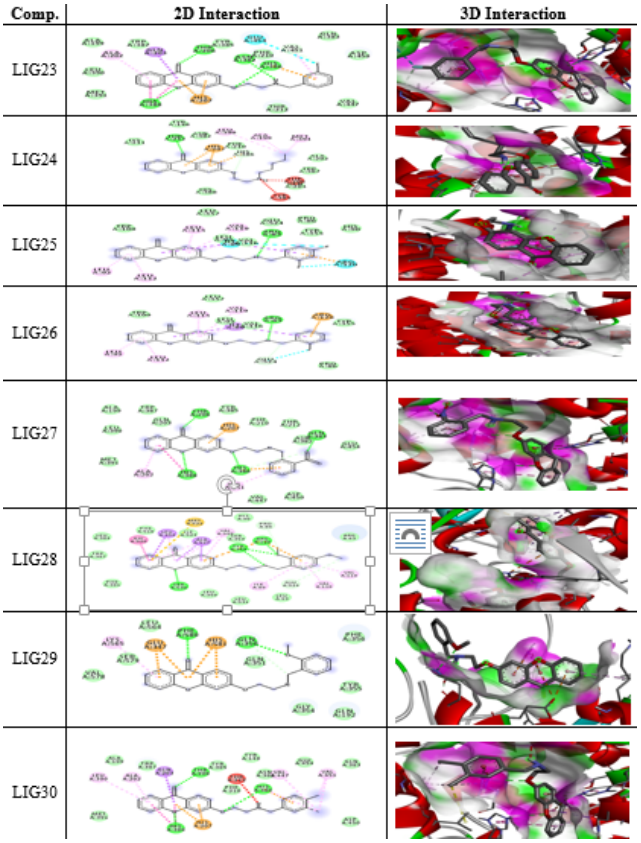


Fig. 2: 2D and 3D interaction of ligand LIG1- LIG30 with COX-1 receptor

2.2. *Estimation of physicochemical properties*

Estimation of Physicochemical Properties helps in determining the potential of the designed compounds to become useful drugs by taking into consideration their Absorption, Distribution, Metabolism and Excretion (ADME) drug score and Toxicity profile. The process is relatively fast and inexpensive and can be readily done at the initial stages for the alternatives assessment.[13]

ADME and toxicity analysis were performed using Osiris Property Explorer, Swiss ADME and Molinspiration softwares.

2.3. *Molecular docking*

The preparation of ligands and receptors were done by the software UCSF Chimera 1.13.1rc (build 41965) developed by University of California. Docking was done by Autodock 1.5.6 developed by molecular graphics laboratory, The Scripps Research Institute, NBCR. Interaction of ligands with receptor was accessed by using Biovia Discovery Studio Visualizer v 17.2.0.16349 developed by Dassault Systemes Biovia Corp.

Table 3: Bioactivity score

Ligand	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
LIG1	-0.06	-0.24	-0.10	-0.02	-0.15	0.02
LIG2	-0.03	-0.18	-0.08	0.08	-0.06	0.04
LIG3	-0.03	-0.18	0.01	0.08	-0.04	0.08
LIG4	0.21	-0.05	-0.03	0.29	0.01	0.20
LIG5	-0.04	-0.22	-0.00	0.06	-0.12	0.03
LIG6	0.03	-0.14	-0.01	0.01	-0.15	0.00
LIG7	-0.05	-0.34	-0.02	-0.14	-0.03	0.02
LIG8	-0.05	-0.22	-0.03	0.05	-0.10	0.05
LIG9	0.03	-0.19	-0.04	0.11	-0.09	0.10
LIG10	-0.07	-0.24	-0.07	0.04	-0.15	-0.03
LIG11	-0.04	-0.22	-0.00	0.06	-0.12	0.03
LIG12	-0.04	-0.22	0.03	0.06	-0.17	-0.02
LIG13	-0.18	-0.25	-0.16	-0.06	-0.22	-0.06
LIG14	-0.18	-0.23	-0.16	-0.12	-0.21	-0.07
LIG15	-0.19	-0.26	-0.15	-0.06	-0.23	-0.08
LIG16	-0.07	-0.24	-0.04	0.01	-0.13	0.02
LIG17	-0.14	-0.40	-0.11	-0.04	-0.39	0.00
LIG18	-0.11	-0.27	0.03	-0.02	-0.30	0.04
LIG19	-0.14	-0.28	-0.07	-0.06	-0.20	-0.02
LIG20	-0.23	-0.32	-0.12	-0.10	-0.28	-0.04
LIG21	-0.17	-0.28	-0.10	-0.05	-0.25	-0.03
LIG22	-0.15	-0.29	-0.10	-0.08	-0.22	-0.03
LIG23	-0.03	-0.21	0.00	0.07	-0.10	0.03
LIG24	0.04	-0.17	-0.04	0.12	-0.05	0.10
LIG25	-0.04	-0.23	-0.00	0.06	-0.10	0.00
LIG26	-0.04	-0.23	-0.03	0.05	-0.13	0.01
LIG27	-0.16	-0.22	-0.16	-0.07	-0.20	-0.05
LIG28	-0.08	-0.25	-0.06	0.03	-0.16	-0.00
LIG29	-0.08	-0.26	-0.07	0.01	-0.16	-0.01
LIG30	-0.03	-0.19	-0.06	0.02	-0.13	0.01

3. Results and Discussion

3.1. Estimation of physicochemical properties

ADME analysis of the designed compounds include:

1. *Assessing compliance with Lipinski rule and the possible violations:* According to the Lipinski rule-of-five, poor absorption or permeation is more likely when the molecular weight is greater than 500, there are more than 5 H-bond donors, 10 H-bond acceptors, and the calculated Log P (CLog P) is greater than 5.[14,15] For good absorption, TPSA value should be between 20-130 Å.[2] For good solubility, LogS should not be higher than 6. Molecule become flexible when it does not contain more than 9 rotatable bonds. The designed compound with higher value of drug score and drug likeness is considered as better molecule. As shown in Table 1, all the designed xanthone derivatives, LIG1- LIG30 have adequate number of hydrogen bond acceptors, hydrogen bond donors and rotatable bonds. Solubility, TPSA and cLogP are also in the specified range. Molecular weight of LIG20 is 503.18 which exceeds 500 and hence, a violation of Lipinski Rule of Five. LIG1, LIG4 and LIG17 showed highest values of 2.83, 3.26 and 2.48 respectively for drug likeness. LIG1, LIG5 and LIG18 showed best drug scores of 0.36, 0.4 and 0.37 respectively out of 30 designed compounds.
2. *Assessing Toxicity profile:* It includes study of compounds for mutagenicity, tumorigenicity, irritancy and reproductive effects. As shown in Table 2, all the designed xanthone derivatives were found to be mutagenic but none was tumorigenic. No compound showed reproductive system related effects. Except LIG9, all other compounds were nonirritant.
3. *Assessing Bioactivity score:* When the bioactivity score is more than 0, the complex is active; if it is in between −5 to 0, the complex is moderately active and if it is less than −5, complex is inactive. Bioactivity score of the designed compounds against various receptors is shown in Table 3. Native ligand Nimuselide showed bioactivity score of -0.15, -0.01, -0.15, -0.17, -0.11 and -0.12 against G-protein coupled receptors (GPCR), Ion channel modulator receptors,

Kinase inhibitor receptor, Nuclear receptor, Protease inhibitor receptor and Enzyme inhibitor receptor respectively. LIG4 and LIG24 showed best bioactivity score of 0.21 and 0.04 against GPCR. LIG4, LIG6 and LIG24 showed best bioactivity score of -0.05, -0.14 and -0.17 against ion channel receptor. LIG3, LIG12 and LIG18 showed best bioactivity score of 0.01, 0.03 and 0.03 against kinase inhibitor receptor. LIG4, LIG9 and LIG24 showed best bioactivity score of 0.29, 0.11 and 0.12 against nuclear receptor. LIG4, LIG3 and LIG7 showed best bioactivity score of 0.01, -0.04 and -0.03 against protease inhibitor receptor and LIG4, LIG9 and LIG24 showed best bioactivity score of 0.20, 0.10 and 0.10 against enzyme inhibitor receptor. It was observed that LIG4 showed good bioactivity score against all the six receptors.

M.W.: Molecular Weight; HBA: Hydrogen Bond Acceptor; HBD: Hydrogen Bond Donor; R.B.: Rotatable Bonds; Sol: Aqueous Solubility; TPSA: Topological Polar Surface Area; DS: Drug Score

3.2. Molecular docking

All the thirty molecules (LIG1- LIG30) were docked against the 3D structures of COX-1 (Cyclooxygenase-1) receptor (PDB: 3N8X). The Docking Scores are shown in Figure 1 while Figure 2 gives images of 2D and 3D interaction of Ligands (LIG1- LIG30) with COX-1 receptor. The docking scores of LIG21 and LIG27 were found to be -10.9 and -10.8 kcal/mol. It is observed that best docking scores are given by various bromo phenyl substituted derivatives namely LIG20, LIG21 and LIG22 but in docking studies, ligand-receptor bond breaking is shown. Thus, these derivatives are not suitable as drug candidates.

The halo substituted phenyl derivatives such as LIG12, LIG23 and LIG30 showed good docking scores indicating that the electron releasing substitution increases the COX-1 binding ability with the compound. LIG7 has anilino substitution and probably the amino group of aniline is responsible for better binding to the receptor due to its strong electron releasing action. A contradictory result was observed in case of ortho-nitro phenyl substituted derivatives as in LIG27 which shows good binding ability but all the other nitro derivatives exhibited poor binding ability.

4. Conclusion

Majority of the ssynthesized compounds showed better docking scores than the native ligand, Nimuselide. The halo substituted phenyl derivatives such as LIG12, LIG23 and LIG30 showed good docking scores indicating that the electron releasing substitution increases the COX-1 binding ability with the compound. LIG7 has anilino substitution and probably the amino group of aniline is responsible for better binding to the receptor due to its strong electron releasing action.

5. Acknowledgment

The authors are thankful to the Vice Chancellor of Delhi Pharmaceutical Sciences and Research University (DPSRU) and to the Director of Delhi Institute of Pharmaceutical Sciences and Research (DIPSAR) for their motivational support and guidance.

6. Source of Funding

None.

7. Conflict of Interest

None.

References

1. Artis D, Spits H. The biology of innate lymphoid cells. *Nature*. 2015;517(7534):293–301.
2. Rock KL, Lai JJ, Kono H. Innate and adaptive immune responses to cell death. *Immunol Rev*. 2011;243(1):191–205. doi:10.1111/j.1600-065X.2011.01040.x.
3. Alva GP, Martínez LP, Hernández LV, Sosa KFM, Kuri MA. Negative regulation of the inflammasome: keeping inflammation under control. *Immunol Rev*. 2015;265(1):231–57. doi:10.1111/imr.12294.
4. Wentworth JM, Naselli G, Brown WA, Doyle L, Phipson B, Smyth GK, et al. Pro-inflammatory CD11c+ CD206+ adipose tissue macrophages are associated with insulin resistance in human obesity. *Diabetes*. 2010;59(7):1648–56. doi:10.2337/db09-0287.
5. Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. *J Clin Invest*. 2007;117(1):175–84. doi:10.1172/JCI29881.
6. Vegeto E, Benedusi V, Maggi A. Estrogen anti-inflammatory activity in brain: a therapeutic opportunity for menopause and neurodegenerative diseases. *Front Neuroendocrinol*. 2008;29(4):507–26. doi:10.1016/j.yfrne.2008.04.001.
7. Navab M, Gharavi N, Watson AD. Inflammation and metabolic disorders. *Curr Opin Clin Nutr Metab*. 2008;11(4):459–64. doi:10.1097/MCO.0b013e32830460c2.
8. Bally M, Dendukuri N, Rich B, Nadeau L, Salmivaara AH, Garbe E, et al. Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data. *BMJ*. 2009;357:1909. doi:10.1136/bmj.j1909.
9. Sriuttha P, Sirichanchuen B, Permsuwan U. Hepatotoxicity of nonsteroidal anti-inflammatory drugs: a systematic review of randomized controlled trials. *Int J Hepatol*. 2018;2018(5253623):1–14. doi:10.1155/2018/5253623.
10. Masters KS, Bräse S. Xanthones from fungi, lichens, and bacteria: the natural products and their synthesis. *Chem Rev*. 2012;112(7):3717–76. doi:10.1021/cr100446h.
11. Cardona ML, Fernández I, Pedro JR, Serrano A. Xanthones from Hypericum reflexum. *Phytochemistry*. 1990;29(9):3003–9. doi:10.1021/np50020a004.
12. Moreira ME, Pereira RG, Silva D, Dias MJ, Gontijo DF, Paiva VSG, et al. Analgesic and anti-inflammatory activities of the 2,8-dihydroxy-1,6-dimethoxyxanthone from Haploclathra paniculata (Mart) Benth (Guttiferae). *J Med Food*. 2014;17(6):686–93. doi:10.1089/jmf.2013.0122.
13. A framework to guide selection of chemical alternatives; 2014. p. 280. doi:10.17226/18872..

14. Benet LZ, Hosey CM, Ursu O, Oprea TI. BDDCS, the Rule of 5 and drugability. *Adv Drug Deliv Rev*. 2016;101:89–98. doi:10.1016/j.addr.2016.05.007.
15. Kenakin T. Pharmacology in drug discovery and development: Understanding drug response; 2016. p. 321–6.

Author biography

Darakhshan Parveen, Research Scholar

Amrita Parle, Associate Professor

Rajnish Srivastava, Associate Professor

Cite this article: Parveen D, Parle A, Srivastava R. Anti-inflammatory activity of novel xanthone derivatives. *Int J Pharm Chem Anal* 2021;8(4):174-181.