PSM | Biological Research ISSN: 2517-9586 – An International Peer-reviewed Journal

Short Communication 2018 | Volume 3 | Issue 3 | 120-124

Article Info

Open Access
Citation: Rehman, T., Zeb, M.A., Liaqat, W., Xiao, W-L., 2018. Molecular Docking of 3,7-Dihydroxy-2-phenyl-4H-chromen-4-one as a LOX Inhibitory Compound. PSM Biol. Res., 3(3): 120-124.

Received: July 15, 2018

Accepted: July 31, 2018

Online first: August 7, 2018

Published: August 18, 2018

***Corresponding author:**
Muhammad Aurang Zeb;
Email:
muhammad_aurangzeb@hotmail.com

Scan QR code to see this publication on your mobile device.

Molecular Docking of 3,7-Dihydroxy-2-phenyl-4H-chromen-4-one as a LOX Inhibitory Compound

Taj Ur Rehman[1], Muhammad Aurang Zeb[2]*, Wajiha Liaqat[3], Wei-Lie Xiao[2]

[1]Department of Chemistry, Mohi-Udin Islamic University, AJ&K, Pakistan.
[2]Key Laboratory of Medicinal Chemistry for Natural Resource, Ministry of Education, School of Chemical Science and Technology, Yunnan University, Kunming, Yunnan 650091, P.R China.
[3]Institute of Chemical Sciences, University of Peshwar-25120, Pakistan.

Abstract
The present study was carried out to explore phytochemically and pharmacologically the medicinal plant botanically classified as *Millettia ovalifolia.* The structure of the isolated compound 3,7-Dihydroxy-2-phenyl-4H-chromen-4-one was confirmed by modern spectroscopic techniques besides its comparison with analytical data available in literature. The compound was further studied for lipoxygenase (LOX) inhibitory activity and docking studies. The compound was found to reveal important LOX inhibitory potential with the IC_{50} value 31.92±0.02 µM. The molecular docking study further showed the important molecular interactions between the compound and LOX displaying encouraging activity for more optimization as an approaching anti-inflammatory lead compound. The results showed that this plant is very significant and can act as a source to treat inflammation.
Keywords: *Millettia ovalifolia*, 3,7-Dihydroxy-2-phenyl-4H-chromen-4-one, Lipoxygenase, Inflammation, Docking.

INTRODUCTION

The genus *Millettia* consists of around 150 species which are distributed in the tropical and subtropical areas of the globe. Out of which only two species exist in Pakistan i.e., *M. extensa* and *M. peguensis* (Ali, 1977). Some species belonging to the genus *Millettia* showed fish poisoning activity. Flavones, flavonones, flavans, flavanoles, prenylated isoflavones, chalcones, pongamol, lancelolatin, kanjone, ovalitenone, milletenone and pongaglabol have been reported from this genus (Sritularak *et al.,* 2002). Some species of this genus contain hypotensive agents (Ngamga *et al.,* 2007).

The flavonoids of genus *Millettia* such as chalcones showed antimalarial activity (Yenesew *et al.,* 2003). Isoflavonoids such as maximaisoflavone and griffonianone are also isolated from the species of this genus (Yankep *et al.,* 2001). A new isoflavan-quinone, named, laurentiquinone along with flavonol named as laurentinol have been isolated from this genus in addition to two known isoflavones, glyricidin and calycosin (Kamnaing *et al.,* 1999). The genus *Millettia* also contains, cis-jasmone used as an activator for secondary metabolism of wheat seedlings (Moraes *et al.,* 2008). Other compounds such as maximaisoflavone-G, barbigerone, Jamaicin, isoliquiritigenin and *O*-geranylisoliquiritigenin are reported from various species (Yenesew *et al.,* 1998). Four compounds namely N-Ethylacetamide, (E)-Ethyl 13-(3,4-dimethoxyphenyl) acrylate, (E)-Methyl 3-(3,4-dimethoxyphenyl) acrylate and 3,7-Dihydroxy-2-phenyl-4H-chromen-4-one were isolated from *M. ovalifolia* which exhibited significant docking interaction with different enzymes (Rahman *et al.,* 2017).

In the present research study, a compound known as 3,7-Dihydroxy-2-phenyl-4H-chromen-4-one was isolated with capable lipoxygenase inhibitory potential along with computational insights based on molecular docking.

MATERIALS AND METHODS

Plant material

The plant material was collected in June 2008 from Pakistan. The plant was authenticated at the Botany Department of Islamia College University, Peshawar, Pakistan. The voucher specimen (SJ-33) was placed in the herbarium of the Department of Department, Islamia University, Peshawar, Pakistan.

Extraction and isolation

The shade dried and crushed (70 kg) stem bark was soaked for one week (x 3) in 5% water and methanol. The crude extract was concentrated by a vacuum rotary evaporator under reduced pressure to gained brownish residue F1 (5 kg) which was further suspended in water and partitioned with different organic solvents like *n*-hexane, chloroform, ethyl acetate and insoluble fraction. To get *n*-hexane fraction FX1 (1.2 kg), chloroform fraction FX2 (1.6 kg), ethyl acetate fraction FX3 (1.0 kg) and insoluble fraction FX4 (0.8 kg). The chloroform fraction FX2 (500 g) was further subjected to column chromatography using silica gel and eluted with n-hexane: chloroform in increasing order of polarity from which several fractions were obtained, which were further combined on the basis of TLC and yield(1-6). The fractions 3 (14.3 g), fraction 4 (25 g) and fraction 5 (19.7 g) were combined together on the basis of TLC which was re-chromatographed using silica gel and eluted with *n*-hexane and chloroform in increasing order of polarity and 56 fractions were obtained. Fractions 20-40 were combined together on the base of TLC and were purified by Preparative TLC which resulted in the isolation of a new source compound (12 mg). The structure of the isolated compound was further confirmed by different modern spectroscopic techniques and its comparison with already reported data in the literature available (Figure 1) (Ngandeu *et al.,* 2008).

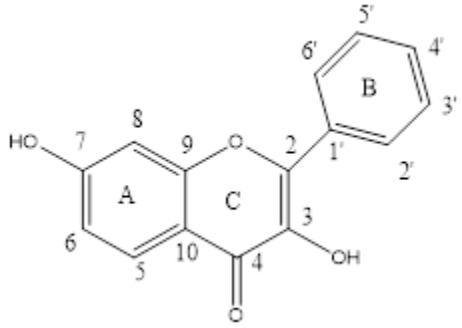

Fig. 1. Chemical structure of 3,7-Dihydroxy-2-phenyl-4H-chromen-4-one.

Molecular docking simulations

In this study, the FRED 2.1 (Mcgann *et al.,* 2003; Khan *et al.,* 2009) was used to dock the OMEGA pre-generated multi-conformer library cited above. FRED 2.1 approach is to fully dock/score all the probable sites of each ligand in the binding site. The complete exploration is based on rigid rotations and translations of each conformer within the binding site defined by a box. FRED examined the positions joint by refusing the ones that clank with the protein (LOX) or that doesn't have sufficient interactions with the protein. The final positions can then be scored or re-scored using one or more than one scoring functions. In the current study, the smooth shape-based Gaussian scoring function (shape gauss) was chosen to assess the shape complementarily between each ligand and binding

pocket. Default FRED protocol was used except for the size of the box defining the binding sites. In an effort to improve the docking-scoring performance, we made complete docking with shape gauss applying the "Optimization" mode. The "Optimization" mode involves a systematic solid body optimization of the upper ranked positions from the exhaustive docking. Three different boxes were investigated for LOX. Three dissimilar simulations were carried out with an added value of 8 Å around the reference ligand.

Lipoxygenase inhibition assay

The lipoxygenase inhibition activity was carried out by using various concentrations of the isolated compound. The lipoxygenase inhibitory potential was measured by a slight modification in the spectrometric method as earlier reported (Khan *et al.,* 2009; Khan *et al.,* 2011). Lipoxygenase (EC 1.13.11.12) type I-B and linoleic acid were got from Sigma (St. Louis, MO) and were used without additional purification. All the chemicals were of analytical grade and purchased from Sigma (St. Louis, MO). 160µl of sodium phosphate buffer, 0.1 mM (pH 7.0), 10ml of the test compound and standards and 20µL of lipoxygenase solution were mixed together and further incubated at 258 ˚C for 5 minutes. The reaction was started by adding of 10µl linoleic acid substrate solution and absorption change with the formation of (9Z, 11E)-13S)-13-hydroperoxyo-ctadeca-9,11-dienoate was followed for 10 minutes. The test sample and control were dissolved in 50% of ethanol. All the reactions were made in triplicate. Tenidap sodium and Baicalein were used as positive controls for LOX inhibition (Khan *et al.,* 2009). Using the EZFit Enzyme Kinetics (Perrella Scientific Inc., Amherst, USA) program the IC_{50} values were calculated. The results were expressed as mean±S.E.M.

RESULTS AND DISCUSSION

In vitro lipoxygenase inhibition assay

In the current study, the compound revealed significant LOX inhibitory activity with (IC_{50} value: 31.92±0.02 µM), while the standards Tenidap sodium and Baicalein exhibited the IC_{50} value 22.1±0.03µM and 41.6±0.02 µM respectively.

Molecular docking simulations

Molecular insights of the compound revealed significant molecule interactions (Figures 2-4) with the active site (catalytic triad and iron atom) of LOX. Favorable hydrogen bonding and other attractive forces between the ligand and proteins were the main causes behind its promising LOX inhibitory potential. The O (oxygen) atom at position 1 of ring B of the compound was found to be interacting with His518 at a distance of 3.17 °A through hydrogen bonding. Hydroxyl moiety at position 7 of ring A has shown its favorable molecular contacts via hydrogen bonding with Ileu857 at a distance of 3.00°A. Furthermore, π-π interactions between ring A with His523 at a distance of 3.92°A. Methoxy group of Ring A at position 6 of the compound showed charge-dipole interactions with Iue557. In order to further improve the activity of the compound, methoxy group should be replaced by a more polar and bulky group that will penetrate deeply into the adjoin pocket of the active site due to favorably enhanced steric and electrostatic interactions. Lipoxygenase (EC 1.13.11.12) constitutes a family of nonheme iron comprising enzymes, as multipurpose biocatalysts are proficient of catalyzing various reactions involved in xenobiotic metabolism. They are responsible for the metabolism of the fatty acids and their metabolites provoking inflammatory responses in the body. In cancer cell growth they also show an important role, invasiveness, metastasis, induction of tumor necrosis factor (TNF) and cell survival (Nisar *et al.,* 2011). The active or catalytic site of LOX is composed of three significant amino acid residues the so-called catalytic triad (His523, His518, Ile875) along with iron atom. Any compound can be developed as new and therapeutically effective LOX inhibitor which is proficient to display strong molecular interaction with the catalytic triad.

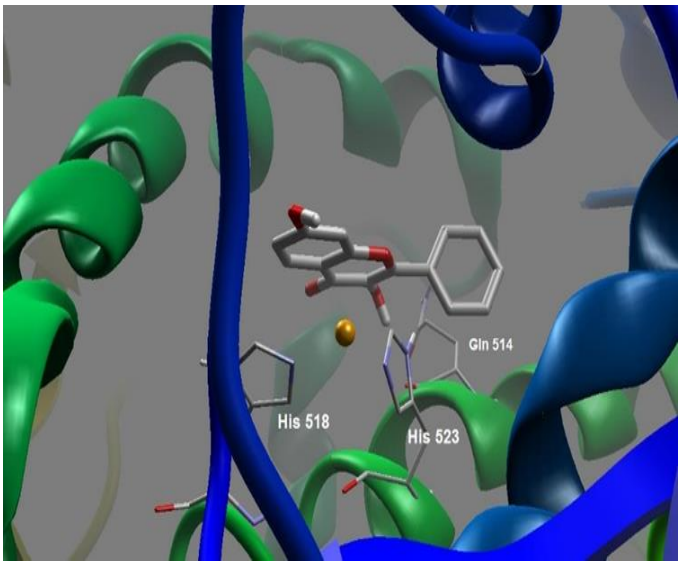

Fig. 2. Binding mode of the compound inside catalytic site of lipoxygenase. Orange colored round object is Fe atom. Hydrogen bonding (green dotted lines) are selectively (only for His523 and His519,) shown for clarity. Hydrogen atoms (except polar ones) were omitted for clarity.

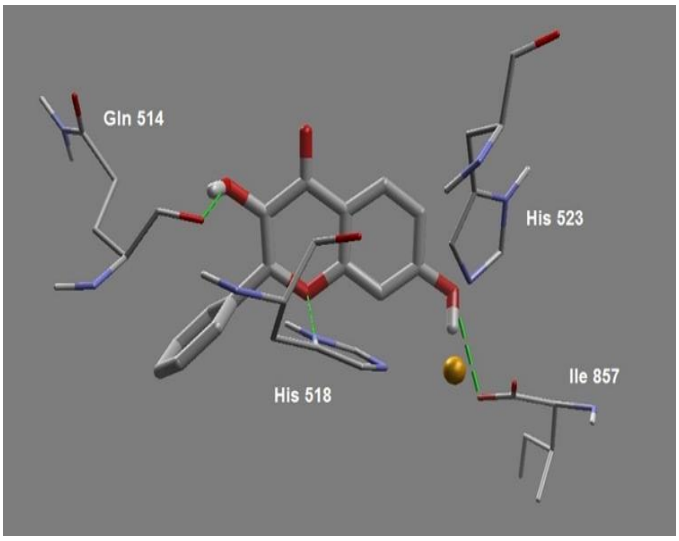

Fig 3. Closer view of molecular interactions of the compound inside catalytic site of lipoxygenase. Orange colored round object is Fe atom. Hydrogen atoms (except polar ones) were omitted for clarity.

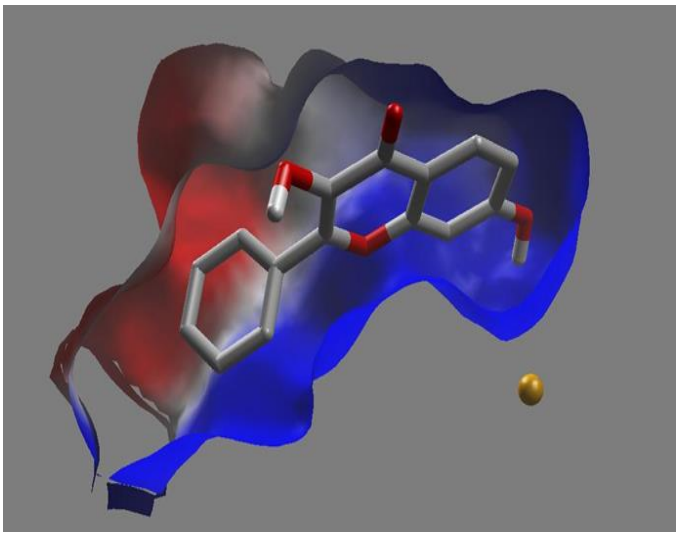

Fig. 4. Electrostatic interactions of the compound inside active site of LOX. Color encoding (White area: hydrophobic region, red area: area with aggregated negative electrostatic potential, and blue area: area with aggregated positive electrostatic potential).

CONCLUSION

In the present study, the 3,7-Dihydroxy-2-phenyl-4H-chromen-4-one isolated from *M. ovalifolia* was studied for lipoxygenase inhibitory activity and docking studies and was found to reveal important LOX inhibitory potential with the IC_{50} value 31.92±0.02 µM. The molecular docking study further exposed important molecular interactions between the compound and LOX. The test compound has a significant profile as a possible lead compound for the cure of inflammation and associated pathological conditions.

ACKNOWLEDGMENTS

We are highly thankful to the Department of Chemistry, Mohi-Udin Islamic University, AJ&K, Pakistan, for supporting this research.

CONFLICT OF INTEREST

Authors declare no competing interests.

REFERENCES

Ali, S.I., 1977. *Flora of Pakistan:* Shamim Printing Press: Karachi. 100, pp 51-52.

Kamnaing, P., Free, S.N.F., Nkengfack, A.E., Folefoc, G., Fomum, Z.T., 1999. An isoflavan-quinone and a flavonol from *Millettia laurentii*. Phytochem., 51(6): 829-832.

Khan, I., Nisar, M., Ebad, F., Nadeem, S., Saeed, M., Khan, H., Khuda, F., Karim, N., Ahmad, Z., 2009. Anti-inflammatory activities of Sieboldogenin from *Smilax china* Linn.: experimental and computational studies. J. Ethnopharmacol., 121(1): 175-177.

Khan, I., Nisar, M., Shah, M.R., Shah, H., Gilani, S.N., Gul, F., Abdullah, S.M., Ismail, M., Khan, N., Kaleem, W.A., Qayum, M., 2011. Anti-inflammatory activities of Taxusabietane A isolated from *Taxus wallichiana* Zucc. Fitoterapia, 82(7): 1003-1007.

Mcgann, M.R., Almond, H.R., Nicholls, A., Grant, J.A., Brown, F.K., 2003. Gaussian docking functions. Biopolymers, 68(1), pp.76-90.

Moraes, M.C.B., Birkett, M.A., Gordon-Weeks, R., Smart, L.E., Martin, J.L., Pye, B.J., Bromilow, R., Pickett, J.A., 2008. cis-Jasmone induces accumulation of defence compounds in wheat, *Triticum aestivum*. Phytochem., 69(1): pp.9-17.

Ngamga, D., Free, S.F., Tane, P., Fomum, Z.T., 2007. Millaurine A, a new guanidine alkaloid from seeds of *Millettia laurentii*. Fitoterapia, 78(3): 276-277.

Ngandeu, F., Bezabih, M., Ngamga, D., Tchinda, A.T., Ngadjui, B.T., Abegaz, B.M., Dufat, H., Tillequin, F., 2008. Rotenoid derivatives and other constituents of the twigs of *Millettia duchesnei*. Phytochem., 69(1): 258-263.

Nisar, M., Kaleem, W.A., Khan, I., Adhikari, A., Khan, N., Shah, M.R., Khan, I.A., Qayum, M., Ismail, M., Aman, A., 2011. Molecular simulations probing Kushecarpin A

as a new lipoxygenase inhibitor. Fitoterapia, 82(7): 1008-1011.

Rahman, T.U., Zeb, M.A., Hussain, S., Liaqat, W., 2017. Physiochemical extraction, spectroanalytical identification, antibacterial and docking studies of four new source phytochemicals from the bark of *Millettia ovalifolia*. Int. J. Biosci., 11(1): 222-231.

Sritularak, B., Likhitwitayawuid, K., Conrad, J., Kraus, W., 2002. Flavonoids from the roots of *Millettia erythrocalyx*. Phytochem., 61(8): 943-947.

Yankep, E., Mbafor, J.T., Fomum, Z.T., Steinbeck, C., Messanga, B.B., Nyasse, B., Budzikiewicz, H., Lenz, C., Schmickler, H., 2001. Further isoflavonoid metabolites from *Millettia griffoniana* (Bail). Phytochem., 56(4): 363-368.

Yenesew, A., Derese, S., Midiwo, J.O., Oketch-Rabah, H.A., Lisgarten, J., Palmer, R., Heydenreich, M., Peter, M.G., Akala, H., Wangui, J., Liyala, P., 2003. Anti-plasmodial activities and X-ray crystal structures of rotenoids from *Millettia usaramensis* subspecies usaramensis. Phytochem., 64(3): 773-779.

Yenesew, A., Midiwo, J.O., Waterman, P.G., 1998. Rotenoids, isoflavones and chalcones from the stem bark of *Millettia usaramensis* subspecies usaramensis. Phytochem., 47(2): 295-300.