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Letter to editor

Discovery of a Series of 5-benzylidene-1, 3-thiazolidine-2, 4-dione-linked Chalcone Hybrids as a Novel Class of 5-Lipoxygenase (5-LO) Inhibitors

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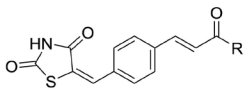
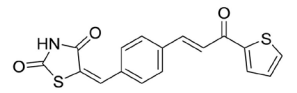
In mammals, lipoxygenases (LOXs) are enzymes containing iron that are biological targets for essential fatty acids. These fatty acids are eicosanoids, derived from arachidonic acid, play important roles in implication and development of multifactorial inflammatory diseases.[1] The 5-Lipoxygenase (5-LO) catalyses two-step reaction that is from arachidonic acid to leukotriene A4 (LTA4). In the first step, oxidation of arachidonic acid to an unstable reactive intermediate 5-hydroperoxyeicosatetraenoic acid (5-HPETE), followed by in the second step, dehydration of 5-HPETE to form LTA4. These reactions are initially leading to the biosynthesis of various classes of leukotrienes and plays a significant role in regulating leukotriene production. 5-LO has progressed its role through multiple mechanisms by its function, structure, cofactors, and the other regulatory mechanisms controlling its expression.[2] Based on these functions, lipoxygenases were identified as potential drug-target associated with pathogenesis of inflammatory diseases.[3] Zileuton is the only reversible direct inhibitor of 5-lipoxygenase that was marketed, due to its hepatotoxic effects the 300 mg immediate release tablet was withdrawn from the U.S. market on February 12, 2008.[4] Since there is an enormous demand for new 5-LO inhibitors, a series of 5-benzylidene-1,3-thiazolidine-2,4-dione-chalcone hybrids (1-24) which earlier synthesized and characterized in our study [5] were subjected to High-throughput Screening (HTS) by 5-LO inhibition assay (UV-Kinetic method) as described by.[6] The exploration of *in vitro* 5-LO inhibitory activity screening data (Figure 1) revealed that the compounds **20** and **18** were appeared to be demonstrated the most potent inhibitory activity, with IC_{50} values of 7.88 ± 0.14 and 11.77 ± 0.21 µg/mL. It is remarkable to note that the compounds **16, 17 and 12** also showed considerable inhibitory activity with IC_{50} values of 15.32 ± 0.16, 18.12 ± 0.42 and 18.12 ± 0.32 µg/mL respectively. The other compounds such as **2-4, 9-11, 13-15, 21** and **24** showed modest level of activity at concentrations (IC_{50}) ranging from 22.18 ± 0.11 to 33.31 ± 0.22 µg/mL. The compounds **1, 5-8, 19, 22** and **23** showed relatively less activity with IC_{50} values ranging from 35.11 ± 0.23 to 46.22 ± 0.12 µg/mL in comparison with the standard (abietic acid (LI01020), IC_{50}: 4.34 ± 0.37 µg/mL).

A closer investigation at the Structure-Activity Relationship (SAR) of these compounds openly showed the inherent mechanism of 5-LO inhibitory potential related with the basic scaffold comprising of 1,3-thiazolidine-2,4-dione and α,β- unsaturated ketone moieties as observed in case of the compound **1** which is an unsubstituted compound, with IC_{50} value of 38.66 ± 0.25 µg/mL, which in some compounds, improved by the influence of some functional group substituents and decreased by some other functional group substituents. For instance, the compounds **18** (*p*-F, IC_{50}: 11.77 ± 0.21 µg/mL) > **16** (*p*-Cl, IC_{50}: 15.32 ± 0.16 µg/mL) > **17** (*m*-F, IC_{50}: 18.12 ± 0.42 µg/mL) > **15** (*m*-Cl, IC_{50}: 24.81 ± 0.51 µg/mL) having halogen substituents either at *para* or *meta* positions relatively enhanced the activity. A decrease in the activity was seen when the substituted phenyl ring was changed by a naphthalene ring, as observed in the case of compound **23** with IC_{50} value 44.38 ± 0.13 µg/mL. The existence of a 3-pyridyl ring in compound **22** in the place of substituted phenyl ring of α,β- unsaturated carbonyl moiety improved the activity compared to the compound that possessing naphthalene ring as substituent, but less than that of the compound having phenyl ring substituted with functional groups. Likewise, it is also remarkable to understand that the presence of 2-pyridyl ring in the place of substituted phenyl ring contributed to an increase in activity compared to the one possessing pyridin-3-yl ring, respectively as observed in the case of compounds **21** and **22** with IC_{50} values 33.31 ± 0.22 and 41.22 ± 0.49 µg/mL, respectively. It was observed that the replacement of substituted phenyl ring with thiophene (**20**, IC_{50}: 7.88 ± 0.14 µg/mL) and fluorene (**24**, IC_{50}: 29.13 ± 0.23 µg/mL) rings improved 5-LO inhibitory activity. Conversely, it was revealed that various aromatic/heteroaromatic rings substituted at position 3 of α, β- unsaturated carbonyl system followed its activity order as thiophen-2-yl > fluoren-2-yl > pyridin-2-yl > phenyl > pyridin-3-yl > naphthalen-2-yl moieties, respectively. It is also reported that the compounds substituted with electron releasing groups were found to be biologically more significant and the order of inhibitory potential was (**12** (4-NH_2, IC_{50}: 18.12 ± 0.32 µg/mL) > **4** (4-OCH_3, IC_{50}: 22.18 ± 0.11 µg/mL) > **3** (3-OCH_3, IC_{50}: 23.11 ± 0.32 ± 0.23 µg/mL) > **2** (4-CH_3, IC_{50}: 25.24 ± 0.45 µg/mL) > **11** (3-NH_2, IC_{50}: 29.41 ± 0.27 µg/mL)), respectively. It is essential that relatively less activity was seen when the hydroxyl groups are substituted at different positions on the phenyl ring as observed in the case of compounds **5**-**8** and the order of activity was **5** (2-OH, IC_{50}: 35.13 ± 0.45 µg/mL) > **6** (4-OH, IC_{50}: 39.24 ± 0.34 µg/mL) > **8** (2,4-diOH, IC_{50}: 44.18 ± 0.53 µg/mL) > **7** (2,5-diOH, IC_{50}: 46.22 ± 0.12 µg/mL), respectively. The compounds **10** (IC_{50}: 22.18 ± 0.17 µg/mL) and **9** (IC_{50}: 26.31 ± 0.52 µg/mL) having substituted with the methyl group on the phenyl ring at position 5 along with the hydroxyl group substitution at 6 (**10**) and 2 (**9**) positions, respectively showed enhanced level of 5-LO inhibitory potential when compared with that of the compounds (**5-8**) possessing only hydroxyl group substitution. It is unexpected that improved level of activity was observed when the nitro group hosted on to the phenyl ring of α, β- unsaturated ketone system at 3 and 4 positions as observed in case of compounds **14** and **13** with IC_{50} values 24.28 ± 0.13 and 33.66 ± 0.6 µg/mL, respectively. The compound **19** (IC_{50}: 35.11 ± 0.23 µg/mL) having substituted with dibenzyloxy group on the phenyl ring at



(1-24)

Compound	R	IC_{50} (µg/mL) (mean ± SEM)	Compound	R	IC_{50} (µg/mL) (mean ± SEM)
1	C_6H_5	38.66 ± 0.25	14	4-$NO_2C_6H_4$	24.28 ± 0.13
2	4-MeC_6H_4	25.24 ± 0.45	15	3-ClC_6H_4	24.81 ± 0.51
3	3-$OMeC_6H_4$	23.11 ± 0.32	16	4-ClC_6H_4	15.32 ± 0.16
4	4-$OMeC_6H_4$	22.18 ± 0.11	17	3-FC_6H_4	18.12 ± 0.42
5	2-OHC_6H_4	35.13 ± 0.45	18	4-FC_6H_4	11.77 ± 0.21
6	4-OHC_6H_4	39.24 ± 0.34	19	3,5-di$C_7H_7OC_6H_3$	35.11 ± 0.23
7	2,4-diOHC_6H_3	46.22 ± 0.12	20	Thiophen-2-yl	7.88 ± 0.14
8	2,5-diOHC_6H_3	44.18 ± 0.53	21	Pyridin-2-yl	33.31 ± 0.22
9	2-OH,5-MeC_6H_3	26.31 ± 0.52	22	Pyridin-3-yl	41.22 ± 0.49
10	6-OH,5-MeC_6H_3	22.18 ± 0.17	23	Naphthalen-2-yl	44.38 ± 0.13
11	3-$NH_2C_6H_4$	29.41 ± 0.27	24	Fluoren-2-yl	29.13 ± 0.23
12	4-$NH_2C_6H_4$	18.12 ± 0.32	Abietic acid (LI01020)	-	4.34 ± 0.37
13	3-$NO_2C_6H_4$	33.66 ± 0.61			



Compound 20: IC_{50} (7.88 ± 0.14 µg/mL)

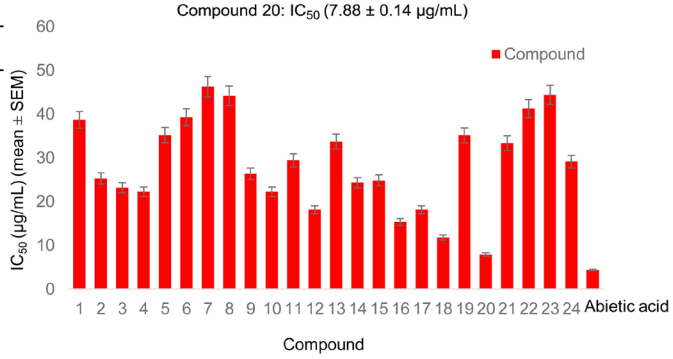


Figure 1: 5-LO inhibitory activity data of 5-benzylidene-1,3-thiazolidine-2,4-dione-chalcone hybrids 1-24.

positions 3 and 5 displayed lower level of 5-LO inhibitory activity. In summary, the SAR revealed the positive contribution of α, β-unsaturated ketone and 5-benzylidene-1, 3-thiazolidine-2, 4-dione moieties towards the observed activity. The results indicated that further development of thiophene ring substitution could be of biological interest.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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