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Myxochelin-Inspired 5-Lipoxygenase Inhibitors – Synthesis and Biological Evaluation

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Abstract: A total of 48 analogues of the natural product myxochelin A were prepared and evaluated for their inhibitory effects on human 5-lipoxygenase in both cell-free and cell-based assays. Structure-activity relationship analysis revealed that the secondary alcohol function and only chiral center of myxochelin A is not required for the biological activity. By expanding the diaminoalkane linker of the two aromatic residues it was possible to generate a myxochelin derivative with superior activity against 5-lipoxygenase in intact cells.

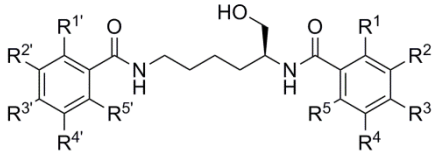
The enzyme human 5-lipoxygenase (5-LO) is responsible for the catalysis of the two initial steps in the biosynthesis of leukotrienes starting from arachidonic acid. Leukotrienes are well-known mediators of a variety of inflammatory and allergic reactions, which include bronchial asthma, rheumatic arthritis, allergic rhinitis, and cardiovascular diseases.[1,2] The 5-LO pathway was also associated with cancer including brain, breast, colon, esophageal mucosa, lung, kidney, mesothelium, pancreas, prostate and leukemia, and in most of these studies an increased formation of 5-LO products was observed.[2] This was confirmed for tissue isolated from patients suffering from breast and pancreatic cancer.[3,4] The therapeutic value of inhibitors of the 5-LO pathway is supported by various animal studies and clinical trials of inflammation and cancer.[4-6] Thus, human 5-LO is a promising pharmacological target, because its inhibition blocks the biosynthesis of all leukotrienes and the bioactive 5-hydroxyeicosatetraenoic acid.

We recently described the isolation of the catechol siderophore myxochelin A from the predatory bacterium *Pyxidicoccus fallax* HKI727.[7] The natural product strongly suppressed the growth of K-562 leukemia cells and pharmacological characterization revealed human 5-LO as the molecular target, which was inhibited with an IC_{50} of 1.9 ± 0.2 µM in a cell-free assay.[7] The active site of human 5-LO contains a non-heme iron, which serves as an electron donor (Fe^{2+}) or acceptor (Fe^{3+}) during catalysis.[8-10] Our original assumption that the inhibition of human 5-LO was solely due to the complexation of this active site iron by myxochelin A could be disproven by structure activity relationship (SAR) studies of myxochelin derivatives which were generated by precursor-directed biosynthesis.[11] In this study, two engineered analogues showed much less affinity for the coordination of ferric iron than myxochelin A, but still maintained significant activity against human 5-LO.[11] To further explore the SAR, we now tested 48 additional derivatives, which were prepared using a recently developed synthetic strategy.[12] In particular, we set out to evaluate the effects of different aromatic substitution patterns on 5-LO inhibition. Furthermore, the importance of the lysinol moiety in myxochelin A was investigated by replacing it with lysine esters or diaminoalkanes, respectively.

The first set of analogues consisted of 17 compounds which all contained the lysinol partial structure (Table 1). Myxochelin S1, in which the two 2,3-dihydroxybenzamide residues of myxochelin A had been replaced by 3,4-dihydroxybenzamides inhibited 5-LO activity in cell-free assays at 10 µM by 41.6%, which indicates a significant loss of bioactivity in comparison to the natural product. While a 2,4-dihydroxy substitution pattern at the aromatic residues almost abolished 5-LO inhibition, 2,5-dihydroxy substitution was surprisingly well tolerated. The corresponding compound, myxochelin S3, inhibited 5-LO in a concentration-dependent manner with an IC_{50} of 2.3 µM. Derivatives featuring two dimethoxybenzamides were fully inactive (see data for myxochelins S4-S8 in Table 1), and even single methoxy substituents at the aromatic rings negatively affected 5-LO inhibition. Only few compounds of this series, namely myxochelins S9 and S10, retained some modest 5-LO inhibitory activity. We also tested a synthetic analogue with 4-hydroxybenzamide rings. In contrast to related myxochelins with 2- or 3-hydroxybenzamide moieties, which had previously been shown to sustain 5-LO inhibitory properties,[11] the exclusive *para*-hydroxylation pattern in myxochelin S15 turned out to be disadvantageous for the biological activity.

Since modification of the ring substitution pattern apparently was not very permissive in terms of 5-LO inhibition, we then turned our attention to the lysinol motive, which linked the two aromatic moieties. Here, we explored the importance of the secondary alcohol by replacing it by a carboxylic acid group and by ester functions, respectively (Table 2). The most active derivative hitherto (*i.e.*, myxochelin S3) served as a lead

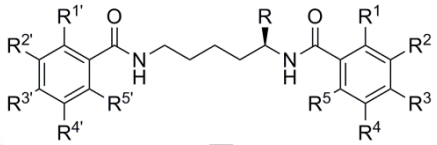
Table 1. Chemical structures of lysinol-derived myxochelin analogues and their 5-LO inhibitory effects in a cell-free assay. The known 5-LO inhibitor zileuton[1] was used as a control.



	R^1	$R^{1'}$	R^2	$R^{2'}$	R^3	$R^{3'}$	R^4	$R^{4'}$	R^5	$R^{5'}$	5-LO activity[a] [%]	IC_{50}[a] [μM]
A	OH	OH	OH	OH	H	H	H	H	H	H	9.5 ± 3.1	1.9 ± 0.2
S1	H	H	OH	OH	OH	OH	H	H	H	H	58.4 ± 5.9	n.d.
S2	OH	OH	H	H	OH	OH	H	H	H	H	87.8 ± 7.0	n.d.
S3	OH	OH	H	H	H	H	OH	OH	H	H	30.8 ± 6.5	2.3 ± 0.3
S4	H	H	OMe	OMe	OMe	OMe	H	H	H	H	89.5 ± 1.9	n.d.
S5	OMe	OMe	H	H	H	H	OMe	OMe	H	H	85.0 ± 3.0	n.d.
S6	OMe	OMe	OMe	OMe	H	H	H	H	H	H	81.1 ± 7.8	n.d.
S7	OMe	OMe	H	H	OMe	OMe	H	H	H	H	91.5 ± 11.0	n.d.
S8	OMe	OMe	H	H	H	H	H	H	OMe	OMe	91.3 ± 11.1	n.d.
S9	OMe	OMe	H	H	H	H	H	H	OH	OH	61.7 ± 6.6	n.d.
S10	OMe	OH	H	H	H	H	H	H	OH	OH	44.7 ± 2.0	n.d.
S11	OH	OH	H	H	OMe	OH	H	H	H	H	84.5 ± 8.1	n.d.
S12	OH	OH	H	H	OMe	OMe	H	H	H	H	82.5 ± 3.0	n.d.
S13	H	H	H	H	OMe	OMe	H	H	H	H	94.9 ± 0.9	n.d.
S14	H	H	H	H	OMe	OH	H	H	H	H	106.6 ± 12.6	n.d.
S15	H	H	H	H	OH	OH	H	H	H	H	98.4 ± 9.8	n.d.
S16	OMe	OMe	H	H	H	H	F	F	H	H	96.4 ± 6.4	n.d.
S17	OH	OH	H	H	H	H	F	F	H	H	78.4 ± 10.0	n.d.
zileuton	-	-	-	-	-	-	-	-	-	-	7.2 ± 2.4	0.5 ± 0.1

[a] Data are expressed as means ± S.E. of single determinations obtained in three independent experiments; n.d. = not determined

Table 2. Chemical structures of myxochelin analogues with an ester motif and their 5-LO inhibitory effects in a cell-free assay.



	R^1	$R^{1'}$	R^2	$R^{2'}$	R^3	$R^{3'}$	R^4	$R^{4'}$	R^5	$R^{5'}$	R	5-LO activity[a] [%]	IC_{50}[a] [μM]
S18	OH	OH	H	H	H	H	OH	OH	H	H	CO_2Me	16.4 ± 1.1	0.7 ± 0.1
S19	OH	OH	H	H	H	H	OH	OH	H	H	CO_2Et	12.3 ± 1.0	0.5 ± 0.1
S20	OMe	OMe	H	H	H	H	OMe	OMe	H	H	CO_2Et	102.9 ± 5.5	n.d.
S21	OH	OH	H	H	H	H	OH	OH	H	H	CO_2H	84.4 ± 1.3	n.d.
S22	OMe	OH	H	H	H	H	F	F	H	H	CO_2H	77.1 ± 4.6	n.d.
S23	OMe	OH	H	H	H	H	F	F	H	H	CO_2Et	67.4 ± 3.1	n.d.
S24	OMe	OMe	H	H	H	H	F	F	H	H	CO_2Et	101.2 ± 4.5	n.d.
S25	OH	OH	H	H	H	H	H	H	OMe	OMe	CO_2Et	62.7 ± 5.5	n.d.
S26	OH	OH	H	H	H	H	H	H	F	F	CO_2Et	75.0 ± 8.0	n.d.
S27	OMe	OMe	H	H	H	H	H	H	F	F	CO_2Et	101.8 ± 12.1	n.d.

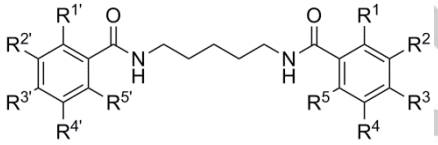
[a] Data are expressed as means ± S.E. of single determinations obtained in three independent experiments; n.d. = not determined

compound for this evaluation. The carboxylic acid analogue of myxochelin S3 was barely active, but the corresponding methyl and ethyl esters efficiently suppressed 5-LO activity. Myxochelin S18 and S19 were even more active than their ancestor with IC_{50} values of 0.7 μM and 0.5 μM, respectively. Again, this outcome could be completely reversed through methoxylation of

the aromatic hydroxyl groups (see data for myxochelin S20 in Table 1). Further attempts to exploit the activity-enhancing effect of the carboxylic acid ester function for altering the aromatic substitution pattern were largely unsuccessful, albeit some derivatives, such as myxochelins S23 and S25, exhibited weak activities against 5-LO.

To clarify whether the ester function is truly beneficial for 5-LO inhibition or whether the observed effect could be ascribed to increasing lipophilicity, a series of myxochelins lacking functional groups in the linker region was synthesized (Table 3). Myxochelin S28, which featured a cadaverine (*i.e.*, 1,5-diaminopentane) core, but was otherwise identical to myxochelin A, turned out as a potent 5-LO inhibitor with an IC_{50} of 0.6 µM. It hence became evident that functionalization of the region linking the two aromatic residues is not necessary for 5-LO inhibition. Similar to our previous observations, methoxylation of the phenolic groups gradually reduced the biological activity. While the monomethoxylated myxochelin S30 was still capable to suppress 5-LO-catalyzed product formation (IC_{50} = 0.8 µM), the introduction of another methoxy group abolished the activity, as exemplified by myxochelin S31. Surprisingly, coupling of 2,4-dihydroxybenzoates with 1,5-diaminopentane led to a derivative with modest activity, which even tolerated a single methoxylation (see data for myxochelins S33 and S34 in Table 3). Attempts to further increase the bioactivity of myxochelin S34 resulted in myxochelin S41, which contained 2,3,4-trihydroxybenzamide residues. Structurally, this compound was related to myxochelin S28 and also showed comparable activity (IC_{50} = 0.8 µM).

Table 3. Chemical structures of 1,5-diaminopentane-derived myxochelin analogues and their 5-LO inhibitory effects in a cell-free assay.



	R^1	$R^{1'}$	R^2	$R^{2'}$	R^3	$R^{3'}$	R^4	$R^{4'}$	R^5	$R^{5'}$	5-LO activity[a] [%]	IC_{50}[a] [µM]
S28	OH	OH	OH	OH	H	H	H	H	H	H	4.8 ± 0.6	0.6 ± 0.1
S29	OMe	OMe	OMe	OMe	H	H	H	H	H	H	109.4 ± 8.1	n.d.
S30	OH	OH	OMe	OH	H	H	H	H	H	H	11.9 ± 1.4	0.8 ± 0.3
S31	OH	OH	OMe	OMe	H	H	H	H	H	H	82.0 ± 13.1	n.d.
S32	OMe	OMe	H	H	OMe	OMe	H	H	H	H	97.7 ± 7.3	n.d.
S33	OH	OH	H	H	OMe	OH	H	H	H	H	66.4 ± 2.0	n.d.
S34	OH	OH	H	H	OH	OH	H	H	H	H	65.7 ± 3.5	n.d.
S35	OH	OH	OMe	OMe	H	H	H	H	F	F	97.3 ± 6.4	n.d.
S36	OMe	OMe	H	H	H	H	H	H	H	H	102.2 ± 0.4	n.d.
S37	H	H	OMe	OMe	H	H	H	H	H	H	96.9 ± 7.7	n.d.
S38	OH	OH	H	H	H	H	H	H	H	H	68.8 ± 7.2	n.d.
S39	H	H	OH	OH	H	H	H	H	H	H	90.6 ± 18.7	n.d.
S40	H	H	OMe	OH	H	H	H	H	H	H	100.1 ± 6.7	n.d.
S41	OH	OH	OH	OH	OH	OH	H	H	H	H	3.8 ± 0.1	0.8 ± 0.2
S42	OMe	OMe	OMe	OMe	OMe	OMe	H	H	H	H	85.2 ± 22.3	n.d.

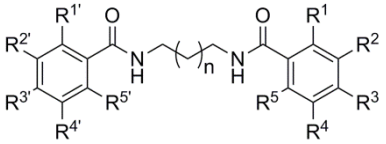
[a] Data are expressed as means ± S.E. of single determinations obtained in three independent experiments; n.d. = not determined

Next, we evaluated the activities of myxochelins possessing 1,6-diaminohexane and 1,4-diaminobutane moieties (Table 4). While the former were slightly more active than the cadaverine-derived analogues, the latter showed somewhat impaired 5-LO inhibition. Even though myxochelin S43, which was prepared from 1,6-diaminohexane, had an excellent IC_{50} value of 0.1 µM, the 1,4-diaminobutane-derived myxochelin S45 was also a highly potent inhibitor (IC_{50} = 0.5 µM). Derivatization of the free phenolic groups in these compounds again led to a significant activity loss.

The most active myxochelin analogues (*i.e.*, S3, S18, S19, S28, S30, S41, S43, S45, and S46) were eventually tested in a cell-based assay using human polymorphonuclear leukocytes (PMNL) stimulated with Ca^{2+}-ionophore A23187. While the derivatives S3 and S41 completely failed to inhibit 5-LO product formation in PMNL, myxochelins S18, S19, S28, S30, S45, and S46 showed partial inhibition (Table 5). The only potent cellular 5-LO inhibitor was myxochelin S43, which reduced 5-LO product formation by 88.7% at 10 µM, corresponding to an IC_{50} value of 1.1 ± 0.3 µM. In comparison, myxochelin A was found to be much less efficient in the PMNL assay (inhibition of 5-LO product formation at 10 µM by only 26.5%).

From the obtained data, some general conclusions concerning the SAR can be drawn. Thus, the secondary alcohol of myxochelin A is not important for the 5-LO inhibitory activity and can be omitted. To further improve cellular inhibition of 5-LO, it might be advisable to extend the length of the carbon chain linking the two aromatic residues. The latter appear not to be very permissive for variations of their substitution patterns. Free phenolic groups in *ortho*-position to the amide substituent turned out to be crucial for 5-LO inhibition, which is also consistent with our previous study.[11] Additional hydroxyl residues in *meta*-position further improve the bioactivity, whereas *para*-oriented hydroxyl groups are in general detrimental. By applying these

Table 4. Chemical structures of diaminoalkyl-derived myxochelin analogues and their 5-LO inhibitory effects in a cell-free assay.



	R^1	$R^{1'}$	R^2	$R^{2'}$	R^3	$R^{3'}$	R^4	$R^{4'}$	R^5	$R^{5'}$	n	5-LO activity[a] [%]	IC50[a] [μM]
S43	OH	OH	OH	OH	H	H	H	H	H	H	4	2.3 ± 0.4	0.1 ± 0.04
S44	OMe	OMe	OMe	OMe	H	H	H	H	H	H	4	102.6 ± 7.1	n.d.
S45	OH	OH	OH	OH	H	H	H	H	H	H	2	8.0 ± 0.3	0.5 ± 0.1
S46	OH	OH	OMe	OH	H	H	H	H	H	H	2	16.7 ± 0.8	1.8 ± 0.5
S47	OH	OH	OMe	OMe	H	H	H	H	H	H	2	59.2 ± 1.8	n.d.
S48	OMe	OMe	OMe	OMe	H	H	H	H	H	H	2	107.2 ± 12.5	n.d.

[a] Data are expressed as means ± S.E. of single determinations obtained in three independent experiments; n.d. = not determined

few guidelines, a new potent 5-LO inhibitor, myxochelin S43, was designed, which is superior to the natural product myxochelin A, especially concerning 5-LO inhibition in intact cells.

Table 5. 5-LO activity in PMNL cells after treatment with selected myxochelin analogues and zileuton, respectively (10 μM).

	5-LO activity PMNL [%][a]
S3	92.9 ± 4.9
S18	61.4 ± 6.3
S19	50.3 ± 1.6
S28	36.4 ± 1.4
S30	50.5 ± 3.5
S41	90.3 ± 4.5
S43	11.3 ± 2.6
S45	68.7 ± 11.4
S46	59.3 ± 4.1
zileuton	10.1 ± 4.1

[a] Data are expressed as means ± S.E. of single determinations obtained in three independent experiments

Experimental Section

Preparation of methoxymethyl acetal protective groups

To a solution of 10 mmol of phenolic compound in 10 mL dry DMF under an argon atmosphere 20 mmol of N,N-diisopropylethylamine was added and the mixture was cooled in an ice water bath. Chloro(methoxy)methane (15 mmol) was slowly added and the solution was stirred for one hour at 0 °C. After warming up to room temperature, the solution was stirred for further three hours. Water (10 mL) was added and the mixture was extracted three times with dichloromethane. The organic fractions were combined and the solvent was evaporated under reduced pressure. Purification of the crude product was achieved by normal phase flash chromatography using a mixture of dichloromethane and ethyl acetate (9.5 : 0.5) or a mixture of ethyl acetate and methanol (9 : 1) as eluent.

Preparation of 2-fluoro-6-(methoxymethoxy)benzoic acid

A stirred solution of 1-fluoro-3-(methoxymethoxy)benzene (5.3 mmol) in 5 mL of dry THF and 2 mL of dry n-hexane under an argon atmosphere was cooled to -78 °C. Subsequently, 2 mL of n-butyl lithium (2.5 M) dissolved in THF were added and the mixture was stirred for two hours. Carbon dioxide was bubbled through the solution for 15 min, which induced the formation of a white precipitate. The solution was allowed to warm up to room temperature slowly, and then 20 mL of water were added. The aqueous phase was washed three times with ethyl acetate and the crude product was purified by reverse phase HPLC.

Preparation of 6-fluoro-3-methoxy-2-(methoxymethoxy) benzoic acid

A solution of 4-fluoro-1-methoxy-2-(methoxymethoxy)benzene (7 mmol) in 10 mL dry THF was prepared under an argon atmosphere. To the cooled solution (-78 °C), 5 mL of a 2 M solution of LDA in dry THF was added and the mixture was stirred for 1 h. Afterwards, carbon dioxide was bubbled through the cooled solution for 20 min which resulted in the production of a yellow precipitate. The solution was then allowed to warm up to 0 °C and 4 mL of water were added slowly. After 10 more minutes of stirring at 0 °C, the reaction mixture was warmed to room temperature. Subsequently, the mixture was diluted by the addition of 40 mL of water and the THF was distilled off. The aqueous solution was extracted five times with ethyl acetate (50 mL each), the organic phases were combined, residual water was removed by the addition of Na_2SO_4 and afterwards evaporated to dryness. The crude product was purified by reverse phase HPLC.

Peptide synthesis

To a stirred solution of 1 mmol of aryl carboxylic acid in 5 mL dry DMF under an argon atmosphere, 1.5 mmol benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate, 1.5 mmol N,N-diisopropylethylamine and 0.5 mmol of L-lysine ethyl ester hydrochloride, hexamethylenediamine, cadaverine or putrescine were added and the solution was stirred overnight. Afterwards the mixture was poured into 20 mL water which was extracted five times with ethyl acetate. If a MOM protective group was present, 0.5 N HCl was used instead of water and the mixture

was stirred for one hour prior to the extraction with ethyl acetate. The organic layers were combined, residual water removed by the addition of Na_2SO_4 and the solvent removed under reduced pressure. Crude products were purified by reverse phase HPLC.

Dealkylation of methoxy groups

For the dealkylation, 0.5 mmol of educt were dissolved in 5 mL dry dichloromethane under an argon atmosphere in an ice water bath. To this solution, 3 mmol of boron tribromide was slowly added and the solution was stirred for 4 hours at 0 °C. Afterwards, it was allowed to warm up to room temperature and the stirring was continued for two hours. The solvent was removed under reduced pressure and crude products were purified by reverse phase HPLC.

Reduction of ethyl ester

For the reduction of the ethyl ester side chains, 0.7 mmol of ester and 1.4 mmol of $LiBH_4$ were dissolved in 5 mL THF at room temperature. To this solution, 5 mL of ethanol was added slowly and the solution was stirred for 16 h. Afterwards 20 mL of saturated aqueous NH_4Cl solution was added. The organic solvents were removed under reduced pressure and the aqueous suspension was exhaustively extracted with 20 mL ethyl acetate. The organic fractions were combined, dried with Na_2SO_4 and purified by reverse phase HPLC.

Purification 5-LO from *E. coli* and cell-free 5-LO activity assay

Human recombinant 5-LO was expressed in *E. coli* BL21 (DE3) harboring plasmid pT3-5LO[13] (kindly provided by Dr. Olof Radmark, Karolinska Institute Stockholm, Sweden). Cells were lysed in 50 mM triethanolamine/HCl pH 8.0, 5 mM EDTA, soybean trypsin inhibitor (60 µg/mL), 1 mM phenylmethanesulfonyl fluoride, 1 mM dithiothreitol and 1 mg/mL lysozyme, followed by sonification (3 x 15 s). The homogenate was centrifuged (10,000 g, 15 min, 4 °C), the supernatant was centrifuged again (40,000 g, 70 min, 4 °C), and 5-LO in the resulting supernatant was purified by affinity chromatography on an ATP-agarose column. Semi-purified 5-LO was diluted in PBS containing 1 mM EDTA. Samples were pre-incubated with the test compounds for 10 min at 4 °C. 5-LO product formation was initiated by addition of $CaCl_2$ (2 mM) and arachidonic acid (20 µM) at 37 °C for 10 min. The reaction was stopped by addition of 1 mL ice-cold methanol and formed 5-LO metabolites were analyzed by RP-HPLC as previously described.[14]

Blood cell isolation and activation of 5-LO product formation in human PMNL

Human PMNL were isolated from leukocyte concentrates of healthy adult human donors, received from the Institute of Transfusion Medicine, University Hospital Jena, Germany, by dextran sedimentation and centrifugation on Nycoprep cushions.[14] PMNL were washed twice with ice-cold PBS and resuspended in PBS plus glucose 0.1% containing $CaCl_2$ (1 mM). Samples were preincubated with the test compounds for 10 min at 37 °C. 5-LO product formation was triggered by 2.5 µM A23187 and terminated after 10 min by addition of 1 mL ice-cold methanol. The production of formed 5-LO metabolites was analyzed by RP-HPLC as described.[14]

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Keywords: myxochelin • 5-lipoxygenase • leukotriene • inflammation • inhibitor

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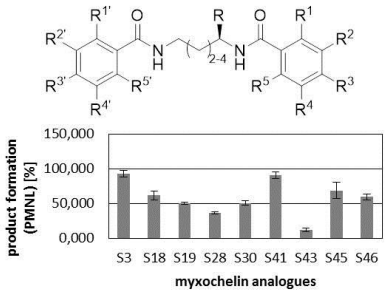

The enzyme 5-lipoxygenase (5-LO) plays a key role in the biosynthesis of leukotrienes, which are well-known mediators of allergic and inflammatory reactions. Furthermore, the 5-LO pathway is associated with tumorigenesis, which makes 5-LO a promising therapeutic target. Recently, the natural product myxochelin A was shown to be a potent 5-LO inhibitor. Here, we report the synthesis of 48 myxochelin analogues and evaluation of their inhibitory effects on 5-LO in both cell-free and cell-based assays.