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Activating human 15-lipoxygenase-1 beyond flatland: discovery of non-aromatic modulators†

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Modulation of enzyme activity by small molecules is a powerful therapeutic strategy. While human 15-lipoxygenase-1 inhibitors are well-studied, activators have remained elusive. Here, we have successfully identified novel modulators of 15-LOX-1 by focusing on non-aromatic, sp³-rich five-membered ring scaffolds. Through systematic SAR analysis, we found that γ -lactam derivatives act as inhibitors, while butenolide and cyclopentanone derivatives serve as enzyme activators. Structure–activity relationship analysis revealed that the identity of the atom at the β -position and the nature of the substituents at the γ -position, both relative to the ring carbonyl, play a critical role in modulating 15-LOX-1 activity. Selectivity studies demonstrated that the compounds display species- and substrate-specific modulation of lipoxygenase activity. Enzyme kinetic analysis confirmed a competitive mechanism for both inhibition and activation. Molecular modeling provided structural insights, highlighting key interactions with the active site iron and surrounding residues. Overall, our findings expand the chemical space for 15-LOX-1 modulation and offer promising leads for the development of selective enzyme regulators.

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Introduction

The pursuit of small molecules to modulate biological targets remains a central goal of drug discovery. Traditionally, efforts have focused primarily on the development of inhibitors, compounds that decrease the activity of target proteins, to achieve therapeutic benefits.^{1,2} However, pharmacological research is undergoing a meaningful transformation, driven by a growing need for more precise regulatory strategies. Increasing attention is being paid to molecules capable of enhancing protein function, known as activators, which offer promising avenues for innovative therapeutic interventions.³

Activators are designed to augment or restore protein function, providing novel strategies for the treatment of a broad spectrum of diseases, including; metabolic disorders, neurodegenerative diseases, cancer, and inflammatory conditions.³ Recent clinically successful small molecule examples include **Mitapivat**, a pyruvate kinase allosteric activator evaluated for sickle cell disease, thalassemia, and hemolytic anemias,^{4,5} and, **Riociguat**, an activator of

soluble guanylate cyclase approved for the treatment of pulmonary hypertension.^{6–8} Beyond approved drugs, candidate activators, such as, **LY-2608204**, developed for type II diabetes, further demonstrate the expanding potential of this approach.^{9–11} Despite these successes, many pharmacologically relevant targets still lack identified activators, limiting our ability to fully understand and therapeutically exploit their biology. One notable example is human 15-lipoxygenase-1 (15-LOX-1), for which numerous inhibitors have been developed, but for which activators remain virtually absent.¹²

15-LOX-1 is a lipid-modifying enzyme implicated in a wide range of biological processes, particularly inflammation, ferroptosis and its resolution.^{13–20} Exhibiting “double-edged sword” attributes, 15-LOX-1 can produce either pro- or anti-inflammatory lipid mediators depending on the cellular context and substrate availability.^{21–23} This dual role underscores the urgent need for small molecule probes, both inhibitors and activators, to dissect the complex biological mechanisms associated with 15-LOX-1 activity under different physiological and pathological conditions.²⁴ While substantial research efforts have yielded potent and selective inhibitors of 15-LOX-1,^{25–34} the development of activators has lagged behind significantly, despite the potential therapeutic benefits of promoting the biosynthesis of pro-resolving mediators.^{1,35} The absence of well-defined 15-LOX-1 activators represents a major limitation in functional studies and hampers the exploration of novel lipid signaling pathways.³⁶

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In this context, the discovery and characterization of small-molecule activators of 15-LOX-1 could provide critical insights into the enzyme's regulation and pave the way for novel therapeutic strategies targeting inflammation and tissue repair. In this study, our aim was to identify and characterize small molecule modulators of human 15-LOX-1 activity. Through a structure-guided screening approach, we discovered distinct families of compounds capable of either inhibiting or activating the enzyme. From this starting point, we developed focused chemical libraries to explore structure–activity relationships (SAR) and evaluated the effects on enzyme activity. The most potent compounds were characterized by kinetic analysis, selectivity profiling and molecular modeling in order to propose binding modes. Our findings provide the first examples of small molecule activators for 15-LOX-1 and offer valuable chemical tools for studying the enzyme's dual biological roles.

Results and discussion

Exploring previously identified bioactive 15-LOX-1 compounds

Several inhibitors of human 15-lipoxygenase-1 (15-LOX-1) have been identified to date, exhibiting moderate to good inhibitory potency. In previous studies, we have developed a virtual database comprising over 6000 15-LOX-1 inhibitors.³⁴ Cheminformatic analysis of their physicochemical properties and molecular features revealed that the vast majority of these compounds contained at least one aromatic ring (>95%, Fig. 1A). We also demonstrated that the enzyme shows a pronounced tendency to bind tightly to lipophilic molecules ($\log P > 5$).³⁴ Moreover, we had previously underscored the importance of non-aromatic, sp^3 -rich elements in effective 15-LOX-1 inhibitors, exemplified by such compounds as PE and Eleftheriadis 14d.^{27,33} These structural features align with those of the enzyme's natural substrates, thereby facilitating improved binding affinity. Based on these crucial observations, our primary objective became to expand away from over-explored chemical space to identify novel bioactive leads that deviated from traditional flat, aromatic structures.

Using DataWarrior software, we performed a scaffold analysis of compounds lacking aromatic rings, identifying common ring systems such as lactones, pyrrolidines, and cyclohexanones. This analysis highlighted some recurring structural motifs (Fig. 1B). Based on the resulting pharmacophore model, we employed our substitution-oriented fragment screening (SOS) approach to develop a focused screening library,^{27,30,37,38} incorporating these non-aromatic rings along with other aliphatic compounds featuring diverse substitution patterns (Table S1†).

15-LOX-1 activity was assessed using our previously established UV absorbance assay in a 96-well format, monitoring the enzymatic product at 234 nm following the conversion of linoleic acid.^{26,27,29,30,32} Encouragingly, five hit compounds were identified as bioactive: three exhibited a greater than 10% increase in enzyme activity, while two compounds induced a 25% decrease at a concentration of 50 μ M (Fig. 1C).

Interestingly, all active hits (Fig. 1C) contained a five-membered ring system bearing a carbonyl group. Moreover, unlike the inhibitors, the activating compounds did not feature any aromatic systems. To confirm these results and to further investigate the influence of substitution patterns on inhibitory or activating potency, we focused on the common five-membered ring scaffold, specifically examining compounds C9 (BT6), D9(CP4), and D16(LC9).

Structure-based analysis to identify suitable substitution patterns

Based on the results of our initial screening, we expanded our chemical library by developing more focused derivatives from the three compound families that had demonstrated enzyme inhibition or activation. A target library was generated to systematically assess the contribution of substituents at selected positions of the five-membered ring scaffolds.

Specifically, guided by our initial findings; for inhibitors, we designed α,β -unsaturated- γ -lactams (3-pyrrolin-2-ones) derivatives (LC) incorporating *N*-benzyl or *N*-alkyl groups with a spirocyclic ring at the 5-position. For the activators, butenolide (BT) derivatives and cyclopentanone (CP) scaffolds were selected for further modification. We synthesized a series of derivatives, introducing a range of aliphatic and aromatic substituents at specific positions of the five-membered ring systems. All compounds were made using previously published synthetic protocols established by the Vassilikogiannakis group (Scheme 1).^{39–41} These syntheses all use operationally simple photocatalytic sequences beginning with the [4 + 2]-cycloaddition of photocatalytically-generated singlet oxygen to a furan substrate; in most cases, the sequences continue with different types of additional photocatalysed transformations. The designed and synthesized compounds from our focused chemical library were screened against 15-LOX-1 at the same concentration used in the initial screening. Consistent with our earlier observations, members of the γ -lactam compound family exhibited inhibitory activity, whereas both butenolide and cyclopentanone derivatives promoted activation of 15-LOX-1.

Specifically, γ -lactams induced up to a 45% decrease in enzyme activity, while derivatives of both butenolide and cyclopentanone scaffolds resulted in up to a 48% increase in activity (Fig. 2A). These preliminary results provided valuable insights regarding the influence of the C, N, and O atoms α to the carbonyl, as well as other substituents at key positions of the active compounds, as will be discussed further below.

Comparative analysis of the three compound families. Our results clearly demonstrate that only the γ -lactam derivatives, characterized by the presence of a nitrogen atom adjacent to the carbonyl, exhibit 15-LOX-1 inhibitory activity. By contrast, compounds featuring either an oxygen or carbon atom at this same position, such as, the butenolide and cyclopentanone derivatives, respectively, consistently induced enzyme activation (Fig. 2). This observation suggests that the nature of the (hetero)atom at this position significantly influences the biological outcome. Variations in the ring (hetero)atom influence



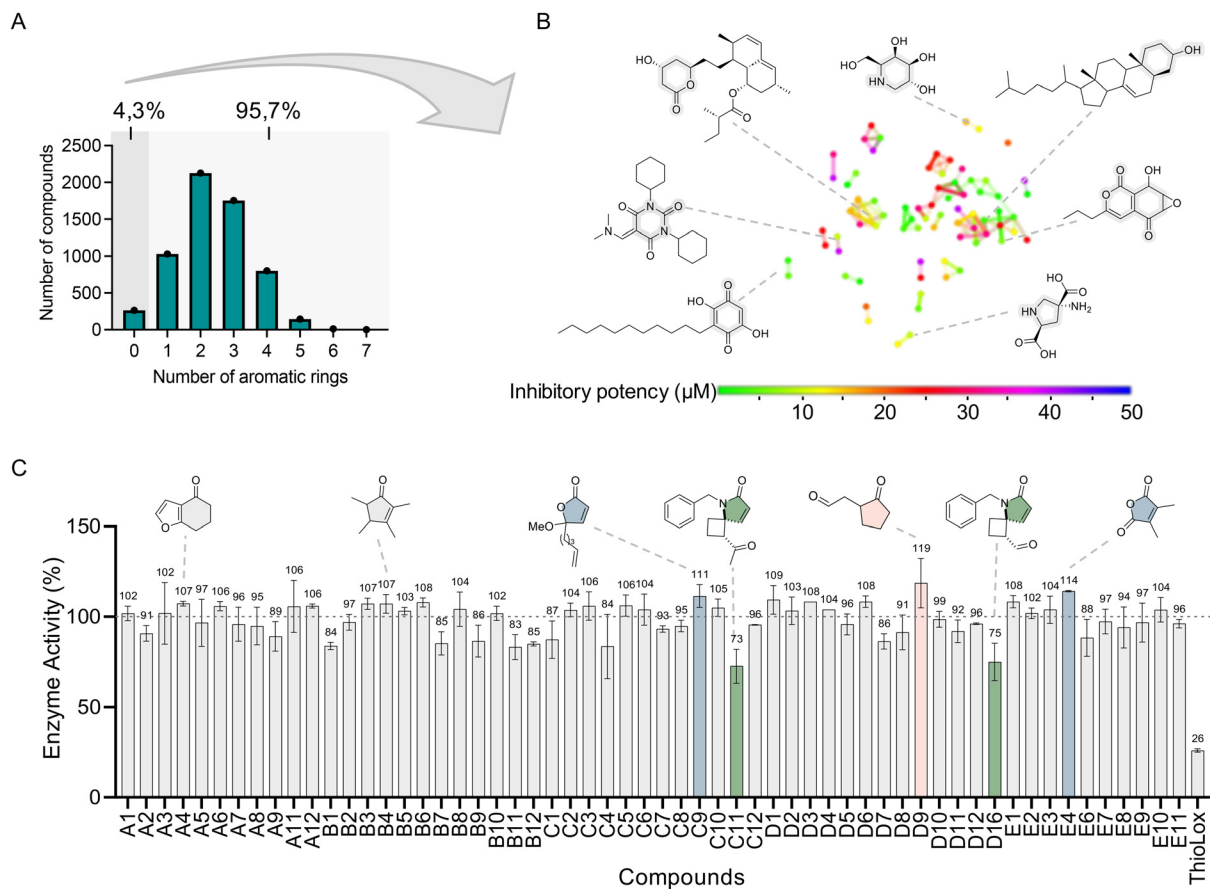
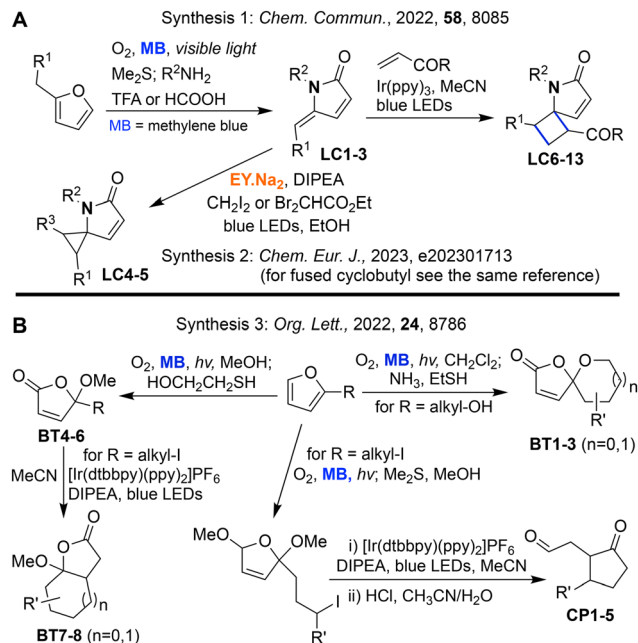


Fig. 1 (A) Chemoinformatic analysis of a virtual database comprised of over 6000 reported 15-LOX-1 inhibitors, categorized by the number of aromatic rings per compound. (B) SALI plot of non-aromatic compound scaffolds generated using DataWarrior software, based on structural similarity and IC_{50} values. The size and color of each dot represent the number of similar scaffolds and their inhibitory potency (μM), respectively. Representative active fragments are shown, with common structural features highlighted in grey. (C) Results of focused fragment screening against 15-LOX-1 at a concentration of 50 μM . Compounds that decreased enzyme activity by more than 25% are shown in green, while those that increased activity by more than 10% are shown in pink (ThioLox was used as reference compound). All experiments were performed in triplicate ($n = 3$), and the standard error is reported.

both the electronic properties of the carbonyl and the ring conformation, with cyclopentanones uniquely adopting a flexible “envelope” conformation while the butenolides and γ -lactams have a flatter and more rigid ring. Interestingly, the presence of a double bond within the ring does not appear to significantly affect activity, as both γ -lactam and butenolide derivatives possess a double bond yet show opposing biological effects (Fig. 2). Likewise, cyclopentanone derivatives, which lack a double bond in the ring, produce a similar activation effect as the butenolides. Additionally, substitution at the β -position (relative to the ring carbonyl, adjacent to the heteroatom) appears to be critical for activity across all compound families. It is likely that substituents at this position occupy an adjacent cavity in the binding pocket, enhancing interactions. Modifications at the 3- and 4-positions do not seem to improve binding affinity, as evidenced by a comparison of compounds B6, D6, B7, C7 and B8 (Table S1[†]). The inhibitory and activating activities of the most promising compounds were confirmed through determination of their IC_{50} and EC_{50} values, respectively (Fig. 3A).

SAR analysis of γ -lactams. Comparison of compounds LC10–13 with LC6–9 indicates that the presence of a benzyl group on the nitrogen does not impair inhibitory potency and may slightly enhance it compared to *N*-methyl-substituted derivatives (Fig. 3A). The good inhibitory activities of LC9 ($\text{IC}_{50} = 97.5 \pm 13.2 \mu\text{M}$), LC6 ($\text{IC}_{50} = 109.9 \pm 21.4 \mu\text{M}$), LC10 ($\text{IC}_{50} = 125.1 \pm 24.4 \mu\text{M}$) and LC13 ($\text{IC}_{50} = 108.1 \pm 30.6 \mu\text{M}$) further validated our initial screening results (Fig. 3A and S3[†]). These findings are consistent with our cheminformatic analysis of known 15-LOX-1 inhibitors, which highlighted the acceptance for the inclusion of some flat, aromatic systems that likely engage in π - π interactions within the enzyme’s active site. Modifications at the 5-position, such as the introduction of a cyclobutane ring, which feature in many biologically active compounds,³⁹ did not significantly alter inhibitory potency compared to cyclopropane-substituted (*e.g.*, LC4, LC5) or other aliphatic-substituted analogues (*e.g.*, LC1). However, variations in the carbonyl group attached to the cyclobutane ring, including; the ester (LC10) and its corresponding acid (LC11), ketone (LC12), and aldehyde (LC9), revealed a preference for the ester





Scheme 1 Overview of the synthetic protocols utilized for the development of (A) LC; and, (B) BT and CP compound derivatives.

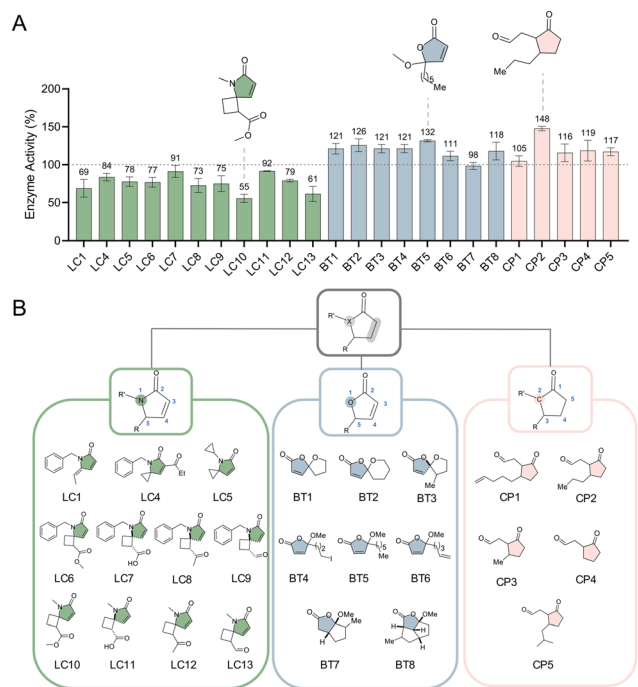


Fig. 2 (A) Focused screening of a chemical library against 15-LOX-1 at a concentration of 50 μM . γ -Lactam derivatives (green) exhibited up to 45% inhibition of enzyme activity, whereas butenolide (blue) and cyclopentanone (pink) families induced up to 48% activation. (B) Representation of three core scaffold families featuring either a nitrogen, oxygen or a carbon atom α to the carbonyl, and further diversification through various substituents. All experiments were performed in triplicate ($n = 3$), and the standard error is reported.

and aldehyde, both of which positively influenced activity, indicating these substitutions may confer additional inhibitory benefit (Fig. 2, 3A and S3[†]).

SAR analysis of butenolides. To evaluate the contribution derived from changes in butenolide substituents, we synthesized and tested (non-)spiro and open-chain derivatives (**BT1–8**). Comparison of the open-chain derivatives **BT5** and **BT6** with the spiro derivatives **BT1**, **BT2**, and **BT3**, as well as a comparison between different spirocycle ring sizes (**BT1**: 5,5-spiro system; **BT2**: 5,6-spiro system), revealed no significant differences in enzyme activation potency. This observation is perhaps not surprising since all these compounds have a sterically and electronically very similar quaternary centre adjacent to the heteroatom, which is equivalent to the 5-position of the γ -lactams. All compounds exhibited a maximum enzyme activation of up to 30%, with EC_{50} values in the low micromolar range (Fig. 2, 3A and S3[†]). Specifically, **BT1** showed a maximum enzyme activation of 27% with an EC_{50} value of $30.0 \pm 4.9 \mu\text{M}$, **BT5** exhibited 19% activation with an EC_{50} of $4.3 \pm 2.9 \mu\text{M}$, and **BT3** demonstrated 23% activation with an EC_{50} of $6.6 \pm 4.9 \mu\text{M}$ (Fig. 3A). By contrast, removal of the double bond from the butenolide core and fusion to a cyclopentane ring (**BT7**) resulted in complete loss of activity, highlighting the critical role of the butenolide's conformation in maintaining biological function.

SAR analysis of cyclopentanones. Based on our initial screening results, we sought to explore the introduction of various aliphatic chains at the 3-position of the cyclopentanone scaffold to enhance enzyme activation (this position equates to the 5-position of the γ -lactams and the butenolides that is key to the activity profile). We observed that unsubstituted analogue (**CP4**) or analogues with an increase in the length of the aliphatic chain up to three carbon atoms resulted in more active compounds (**CP2**, **CP3** and **CP5**), whereas longer linear chains, such as in **CP1**, led to reduced activation (Fig. 2). The highest activation, 45%, was observed for **CP2**, with an EC_{50} value of $12.6 \pm 6.7 \mu\text{M}$ (Fig. 3A). Compounds **CP4** and **CP5** exhibited enzyme activations of 27% and 33%, respectively, with corresponding EC_{50} values of $10.8 \pm 7.2 \mu\text{M}$ and $6.8 \pm 4.5 \mu\text{M}$ (Fig. 3A). We hypothesize that a short aliphatic chain at the 3-position enhances binding by occupying an adjacent hydrophobic pocket within the enzyme's active site, providing additional lipophilic interactions that may stabilize the enzyme–substrate complex.

Selectivity profile

Next, we examined the selectivity profile of one of our most potent activators, compound **CP5**, in human 15-LOX-1 and soybean lipoxygenase (sLOX), a plant isoenzyme with high structural similarity to 15-LOX-1.⁴² Interestingly, **CP5** displayed an opposing effect in the two enzymes, causing partial inhibition of sLOX with an IC_{50} value of $32.3 \pm 20.2 \mu\text{M}$, thereby demonstrating a substantial degree of selectivity (Fig. 3B and S4[†]). These findings suggest that our compounds do not merely interfere with the generic lipoxygenase redox mechanism, but rather engage in specific molecular interactions with



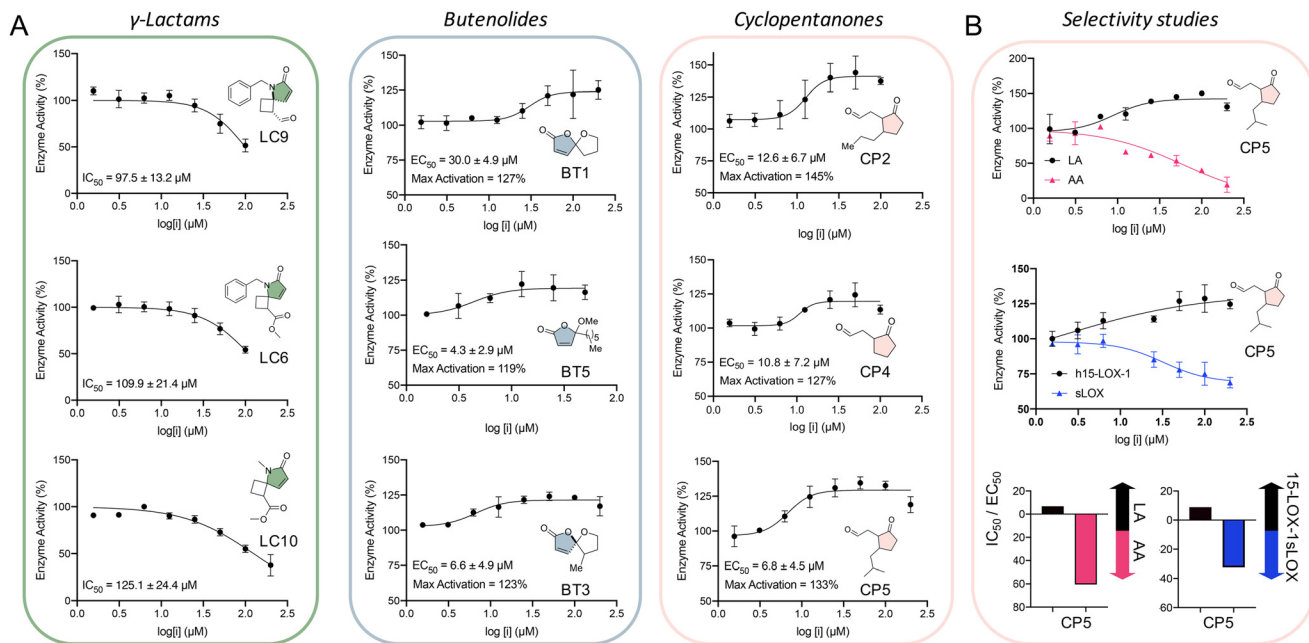


Fig. 3 (A) Chemical structures of the most active derivatives from the three compound families, along with their corresponding IC₅₀ (inhibitors) or EC₅₀ (activators) values against human 15-LOX-1. Maximum percentage of enzyme activation is also indicated for each compound. (B) Selectivity profiling of compound CP5. Top: Substrate selectivity, comparing enzyme activity with linoleic acid (black, EC₅₀) versus arachidonic acid (pink, IC₅₀). Bottom: Enzyme selectivity, comparing activity between human 15-LOX-1 (black, EC₅₀) and soybean LOX (sLOX, blue, IC₅₀). Bar graphs represent relative potency of CP5 across different substrate and enzyme combinations. All experiments were performed in triplicate ($n = 3$), and the standard error is reported.

15-LOX-1. We propose that the contrasting effects observed between the enzymes arise from differences in active site architecture, with sLOX possessing a significantly larger active site pocket compared to 15-LOX-1.³³

Another notable finding is that this selectivity also extends to substrate-specific activation. This could allow for the selective regulation of particular lipid mediators without affecting the biosynthesis of others derived from different fatty acids.⁴³ As previously shown, CP5 once again activated 15-LOX-1 when linoleic acid (LA) was used as the substrate. However, when arachidonic acid (AA) served as the substrate, the same compound exhibited the opposite effect, acting as a selective inhibitor of AA oxygenation with an IC₅₀ value of 60.5 ± 28.1 μM (Fig. 3B and S4†).

Enzyme kinetic analysis

To investigate the binding mechanisms of our activators and inhibitors, we performed Michaelis–Menten kinetic analyses in the presence of compounds CP2 and LC9. As anticipated based on our design, both compounds exhibited competitive binding behavior, as demonstrated by Lineweaver–Burk plots (Fig. 4A and B).

Specifically, LC9, our inhibitor, induced an increase in the apparent K_M values while leaving V_{max} unchanged (Fig. 4B and Table S2†), consistent with a competitive inhibition mechanism. In contrast, CP2, our activator, caused a decrease in the K_M values while also maintaining constant V_{max} values (Fig. 4A

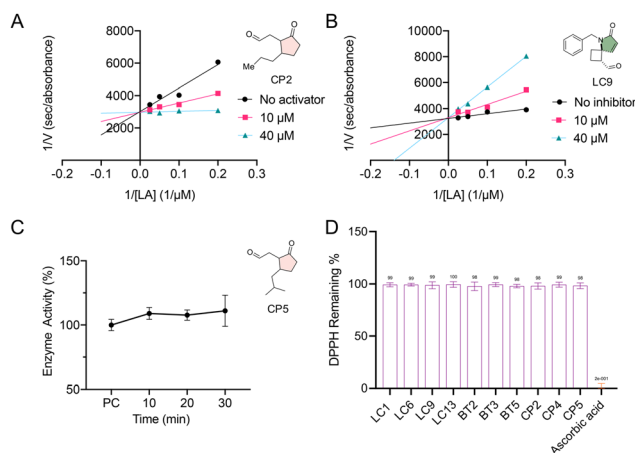


Fig. 4 Steady-state kinetic analysis of human 15-LOX-1 in the presence of increasing concentrations of compound (A) CP2 and (B) LC9, represented using Lineweaver–Burk plots. (C) Time-dependent activation assay of h15-LOX-1 by compound CP5. The enzyme was pre-incubated with the activator (at the EC₅₀ concentration) for three different time points to evaluate potential time-dependent effects. (D) DPPH assay screening of selected compounds to assess potential antioxidant or radical-generating activity, showing that none exhibited radical-generating properties.

and Table S3†), indicative of a competitive activation mechanism of 15-LOX-1.

These findings confirm our initial hypothesis that the compounds target the active site of 15-LOX-1. To further exclude



the possibility of covalent binding or nonspecific redox effects, we performed time-dependent inhibition studies (Fig. 4C) and DPPH assays (Fig. 4D). Specifically, in the time-dependent activation assay of h15-LOX-1 by compound CP5, the enzyme was pre-incubated with the activator at three different time intervals to assess potential time-dependent effects. The observed trends further support the proposed mechanism of action.

Molecular modeling

To rationalize our experimental results and propose possible binding modes of our compounds, we conducted molecular modeling studies. In order to correlate the observed inhibitory and activation potencies, as well as kinetic behaviors, with structural information, selected representative compounds from each chemical family were docked into the active site of the enzyme. Due to the lack of an available crystal structure for human 15-LOX-1, we employed the structure of rabbit 15-LOX as determined by Gillmor *et al.*⁴⁴ Molecular modeling was performed using the MOE software package. Docking experiments were conducted using the London dG scoring function for initial ranking (refinement: forcefield), followed by rescoring with the GBVI/WSA dG method and energy minimization (forcefield: MMFF94X; dielectric constant: r ; cutoff: {8,10}).

Compounds with the highest potencies, such as activators CP2, BT5, and CP5, exhibited the best docking scores compared to less active or inactive compounds (Fig. 5A). Analysis of the top-ranked docking poses revealed consistent binding configurations, with only the activator compounds, correlating with stronger binding (lower EC₅₀ values), anchoring in the active site *via* a key interaction between the carbonyl group of the five-membered ring and the catalytic iron atom (Fig. 5 and S5[†]), in agreement with our enzyme kinetic findings.

Specifically, cyclopentanone and butenolide activators (*e.g.*, CP4 and BT5) not only coordinate the catalytic iron through their

carbonyl groups, but also form additional interactions with His360, while their aliphatic side chains engage the hydrophobic pocket through lipophilic interactions (Fig. 5B, C and S5[†]). By contrast, the more rigid γ -lactam inhibitors, such as LC6 and LC8, interact with His365 and establish potential π - π interactions between their phenyl rings and aromatic residues Phe414 and/or Phe352, thereby extending deeper into the active site and likely obstructing substrate access (Fig. 5D and S5, 6[†]).

Conclusions

Through a multidisciplinary approach combining fragment-based screening, SAR analysis, enzyme kinetics, and molecular modeling, we have uncovered novel non-aromatic 15-LOX-1 modulators with distinct inhibitory and activating profiles. Our work highlights the critical influence of scaffold architecture and substitution patterns in dictating enzyme behavior, with γ -lactam derivatives emerging as good inhibitors and butenolide/cyclopentanone derivatives as effective activators. Importantly, we demonstrate selective modulation not only between enzyme isoforms, but also across different lipid substrates, offering a new level of precision in lipoxygenase targeting. Kinetic and computational analyses confirmed active site engagement through competitive mechanisms, underscoring the rational design of our compounds. These findings significantly broaden the chemical and mechanistic space of 15-LOX-1 regulation and open new avenues for the development of selective chemical modulators and therapeutic candidates.

Experimental

For complete experimental procedures, spectroscopic and analytical data, copies of NMR, see the ESI.[†]

Author contributions

Marina Somaraki, Ioannis Zachilas, Elvira Tsapinou, Georgianna Boulkou: writing, investigation, validation, methodology. Tamsyn Montagnon, Georgios Vassilikogiannakis and Nikolaos Eleftheriadis: writing, editing, reviewing, and supervision. All authors reviewed and approved the final manuscript. Nikolaos Eleftheriadis conceived and managed the project.

Conflicts of interest

There are no conflicts to declare.

Data availability

All data supporting the findings of this study are available within the article and its ESI.[†]

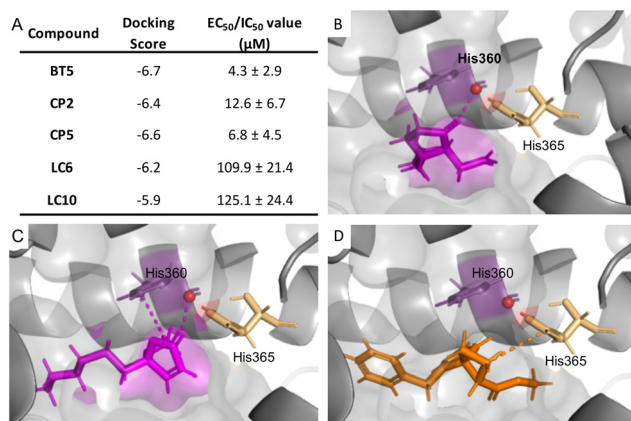


Fig. 5 (A) Comparative table summarizing the inhibitory or activating effects of selected compounds on human 15-LOX-1, alongside their corresponding docking scores obtained from molecular modeling studies targeting the enzyme's active site. Predicted binding poses of representative compounds in the h15-LOX-1 active site as modeled using MOE software: (B) CP2 (cyclopentanone activator), (C) BT5 (butenolide activator), and (D) LC6 (γ -lactam inhibitor). Key interactions such as coordination to the active-site iron, are highlighted.



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References

- 1 A. Turberville, H. Semple, G. Davies, D. Ivanov and G. A. Holdgate, *SLAS Discovery*, 2022, **27**, 419–427.
- 2 K. Singh, J. K. Gupta, D. Pathak and S. Kumar, *Curr. Enzyme Inhib.*, 2023, **19**, 157–166.
- 3 L. F. Dow, A. M. Case, M. P. Paustian, B. R. Pinkerton, P. Simeon and P. C. Trippier, *RSC Med. Chem.*, 2023, **14**, 2206–2230.
- 4 H. Al-Samkari and E. J. van Beers, *Ther. Adv. Hematol.*, 2021, **12**, 20406207211066070.
- 5 A. Matte, E. Federti, C. Kung, P. A. Kosinski, R. Narayanaswamy, R. Russo, G. Federico, F. Carlomagno, M. A. Desbats, L. Salviati, C. Leboeuf, M. T. Valenti, F. Turrini, A. Janin, S. Yu, E. Beneduce, S. Ronseaux, I. Iatcenko, L. Dang, T. Ganz, C.-L. Jung, A. Iolascon, C. Brugnara and L. De Franceschi, *J. Clin. Invest.*, 2021, **131**(10), e144206.
- 6 N. Hambly and J. Granton, *Expert Rev. Respir. Med.*, 2015, **9**, 679–695.
- 7 D. Conole and L. J. Scott, *Drugs*, 2013, **73**, 1967–1975.
- 8 D. Khaybullina, A. Patel and T. Zerilli, *P & T*, 2014, **39**, 749–758.
- 9 S. Zheng, F. Shao, Y. Ding, Z. Fu, Q. Fu, S. Ding, L. Xie, J. Chen, S. Zhou, H. Zhang, H. Zhou, Y. Chen, C. Sun, J. Zhu, X. Zheng and T. Yang, *Clin. Drug Invest.*, 2020, **40**, 1155–1166.
- 10 Y. Zhou, Y. Zhang, D. Zhao, X. Yu, X. Shen, Y. Zhou, S. Wang, Y. Qiu, Y. Chen and F. Zhu, *Nucleic Acids Res.*, 2024, **52**(D1), D1465–D1477.
- 11 C.-Y. Yang, C.-R. Liu, I. Y.-F. Chang, C.-N. OuYang, C.-H. Hsieh, Y.-L. Huang, C.-I. Wang, F.-W. Jan, W.-L. Wang, T.-L. Tsai, H. Liu, C.-P. Tseng, Y.-S. Chang, C.-C. Wu and K.-P. Chang, *Cancers*, 2020, **12**(7), 1726.
- 12 H. Meng, C. L. McClendon, Z. Dai, K. Li, X. Zhang, S. He, E. Shang, Y. Liu and L. Lai, *J. Med. Chem.*, 2016, **59**, 4202–4209.
- 13 I. Ivanov, D. Heydeck, K. Hofheinz, J. Roffeis, V. B. O'Donnell, H. Kuhn and M. Walther, *Arch. Biochem. Biophys.*, 2010, **503**, 161–174.
- 14 H. Kuhn, S. Banthiya and K. van Leyen, *Biochim. Biophys. Acta, Mol. Cell Biol. Lipids*, 2015, **1851**, 308–330.
- 15 B. Samuelsson, S. E. Dahlén, J. A. Lindgren, C. A. Rouzer and C. N. Serhan, *Science*, 1987, **237**, 1171–1176.
- 16 J. Z. Haeggström and C. D. Funk, *Chem. Rev.*, 2011, **111**, 5866–5898.
- 17 J. Zhao, V. B. O'Donnell, S. Balzar, C. M. St. Croix, J. B. Trudeau and S. E. Wenzel, *Proc. Natl. Acad. Sci. U. S. A.*, 2011, **108**, 14246–14251.
- 18 K. van Leyen, *CNS Neurol. Disord.: Drug Targets*, 2013, **12**, 191–199.
- 19 D. Praticò, V. Zhukareva, Y. Yao, K. Uryu, C. D. Funk, J. a. Lawson, J. Q. Trojanowski and V. M.-Y. Lee, *Am. J. Pathol.*, 2004, **164**, 1655–1662.
- 20 W. S. Yang, K. J. Kim, M. M. Gaschler, M. Patel, M. S. Shchepinov and B. R. Stockwell, *Proc. Natl. Acad. Sci. U. S. A.*, 2016, **113**, E4966–E4975.
- 21 C. N. Serhan, *Nature*, 2014, **510**, 92–101.
- 22 A. J. Klil-Drori and A. Ariel, *Prostaglandins Other Lipid Mediators*, 2013, **106**, 16–22.
- 23 M. A. Vaezi, B. Safizadeh, A. R. Eghtedari, S. S. Ghorbanhosseini, M. Rastegar, V. Salimi and M. Tavakoli-Yaraki, *Lipids Health Dis.*, 2021, **20**, 169.
- 24 J. Z. Haeggström and C. D. Funk, *Chem. Rev.*, 2011, **111**, 5866–5898.
- 25 G. Rai, V. Kenyon, A. Jadhav, L. Schultz, M. Armstrong, J. B. Jameson, E. Hoobler, W. Leister, A. Simeonov, T. R. Holman and D. J. Maloney, *J. Med. Chem.*, 2010, **53**, 7392–7404.
- 26 N. Eleftheriadis, S. Thee, J. te Biesebeek, P. van der Wouden, B.-J. J. Baas and F. J. Dekker, *Eur. J. Med. Chem.*, 2015, **94**, 265–275.
- 27 N. Eleftheriadis, C. G. Neochoritis, N. G. J. Leus, P. E. van der Wouden, A. Dömling and F. J. Dekker, *J. Med. Chem.*, 2015, **58**, 7850–7862.
- 28 K. Traven, N. Eleftheriadis, S. Seršen, J. Kljun, J. Bezenšek, B. Stanovnik, I. Turel and F. J. Dekker, *Polyhedron*, 2015, **101**, 306–313.
- 29 N. Eleftheriadis, S. A. Thee, M. R. H. Zwinderman, N. G. J. Leus and F. J. Dekker, *Angew. Chem., Int. Ed.*, 2016, **55**, 12300–12305.
- 30 N. Eleftheriadis, H. Poelman, N. G. J. Leus, B. Honrath, C. G. Neochoritis, A. Dolga, A. Dömling and F. J. Dekker, *Eur. J. Med. Chem.*, 2016, **122**, 786–801.
- 31 H. Guo, N. Eleftheriadis, N. Rohr-Udilova, A. Dömling and F. J. Dekker, *Eur. J. Med. Chem.*, 2017, **139**, 633–643.
- 32 R. van der Vlag, H. Guo, U. Hapko, N. Eleftheriadis, L. Monjas, F. J. Dekker and A. K. H. Hirsch, *Eur. J. Med. Chem.*, 2019, **174**, 45–55.
- 33 N. Spacho, M. Casertano, C. Imperatore, C. Papadopoulos, M. Menna and N. Eleftheriadis, *Chem. – Eur. J.*, 2024, **30**, e202402279.
- 34 A. Louka, N. Spacho, D. Korovesis, K. Adamis, C. Papadopoulos, E.-E. Kalaitzaki, N. Tavernarakis, C. G. Neochoritis and N. Eleftheriadis, *Angew. Chem., Int. Ed.*, 2025, **64**, e202418291.



- 35 C. N. Serhan and B. D. Levy, *J. Clin. Invest.*, 2018, **128**, 2657–2669.
- 36 J. N. Fullerton and D. W. Gilroy, *Nat. Rev. Drug Discovery*, 2016, **15**, 551–567.
- 37 M. Wójcik, N. Eleftheriadis, M. R. H. Zwinderman, A. S. S. Dömling, F. J. Dekker and Y. L. Boersma, *Eur. J. Med. Chem.*, 2019, **161**, 93–100.
- 38 T. Kok, H. Wapenaar, K. Wang, C. G. Neochoritis, T. Zarganes-Tzitzikas, G. Proietti, N. Eleftheriadis, K. Kurpiewska, J. Kalinowska-Thuścik, R. H. Cool, G. J. Poelarends, A. Dömling and F. J. Dekker, *Bioorg. Med. Chem.*, 2018, **26**, 999–1005.
- 39 D. Kalaitzakis, I. Kampouropoulos, M. Sofiadis, T. Montagnon and G. Vassilikogiannakis, *Chem. Commun.*, 2022, **58**, 8085–8088.
- 40 L.-P. Apostolina, A. Bosveli, A. Profyllidou, T. Montagnon, V. Tsopanakis, M. Kaloumenou, D. Kalaitzakis and G. Vassilikogiannakis, *Org. Lett.*, 2022, **24**, 8786–8790.
- 41 A. Bosveli, N. Griboura, I. Kampouropoulos, D. Kalaitzakis, T. Montagnon and G. Vassilikogiannakis, *Chem. – Eur. J.*, 2023, **29**, e202301713.
- 42 M. M. Gleason, C. J. Rojas, K. S. Learn, M. H. Perrone and G. E. Bilder, *Am. J. Physiol.*, 1995, **268**, C1301–C1307.
- 43 A. Golovanov, A. Zhuravlev, A. Cruz, V. Aksenov, R. Shafiullina, K. R. Kakularam, J. M. Lluch, H. Kuhn, À. González-Lafont and I. Ivanov, *J. Med. Chem.*, 2022, **65**, 1979–1995.
- 44 S. A. Gillmor, A. Villaseñor, R. Fletterick, E. Sigal and M. F. Browner, *Nat. Struct. Biol.*, 1997, **4**, 1003–1009.

