Supporting Information

A class of 5-benzylidene-2-phenyl-thiazolinones with high potency as direct 5-lipoxygenase inhibitors

Bettina Hofmann, Sebastian Barzen, Carmen B. Rödl, Andreas Kiehl, Julia Borig, Aleksandra Živković, Holger Stark, Gisbert Schneider and Dieter Steinhilber

Contents:

I Chemical synthesis and analytical data of final compounds

All compounds are synthesized following the general procedure if not otherwise stated.

General Procedure.

A solution of the corresponding benzonitrile (1 equiv, 1-50 mmol), thioglycolic acid (1-1.1 equiv) and the corresponding benzaldehyde (1 equiv) and TEA in methanol or ethanol was refluxed for at least 12 h. The reaction mixture was evaporated under reduced pressure and the product was crystallized from ethanol and washed with acetone[1].

(*Z*)-5-(4-Methoxybenzylidene)-2-(p-tolyl)-5*H*-thiazol-4-one, 7. A solution of *p*-methylbenzonitrile (5.86 g, 50 mmol), thioglycolic acid (4.61 g, 55 mmol), *p*-methoxybenzaldehyde (6.8 g, 50 mmol) and 5 ml of TEA in 80 ml of ethanol was refluxed for 4 hours. Next, the reaction mixture was evaporated under reduced pressure and the product crystallized from ethanol. Yield: 40%; yellow-orange solid; Mp: 222 °C. $C_{18}H_{15}NO_2S$, M_r = 309.1. ESI-MS (*m/z*): 309.8 $[M + H]^+$. ^{1}H NMR (DMSO-d^6, δ (ppm)): 8.19 (d, 2H, *J* = 8.5, Ar*H),* 7.98 (s, 1H, -C*H*=), 7.78 (d, 2H, *J* = 8.8, Ar*H),* 7.48 (d, 2H, *J* = 8.0, Ar*H),* 7.14 (d, 2H, *J* = 8.75, Ar*H),* 3.85 (s, 3H, -OCH_3), 2.44 (s, 3H, -CH_3). ^{13}C NMR (DMSO-d^6, δ (ppm)):191.0, 163.8, 159.8, 141.2, 144.0, 134.2, 132.7, 130.3, 130.2, 129.3, 129.2, 129.1, 129.1, 128.1, 127.8, 115.0, 114.3, 114.2, 55.8, 21.3; Anal. Calcd: C (69.88%), H (4.89%), N (4.53%). Found: C (69.69%), H(5.00%), N (4.51%).

((Z)-2-(4-Chlorophenyl)-5-(4-methoxybenzylidene)-5*H*-thiazol-4-one), 18. 18 was prepared as described in General Procedure using *p*-chlorobenzonitrile (1.0 g, 7.3 mmol), thioglycolic acid (0.67 g, 7.3 mmol), *p*-methoxybenzaldehyde (0.99 g, 7.3 mmol), and 3 mL of TEA in 50 mL of methanol. After reflux for 12 h the mixture was evaporated under reduced pressure and the pure product recrystallized from ethanol in a yield of 45% as an orange solid. Mp: 186 °C; $C_{17}H_{12}ClNO_2S$, M_r=329.8. ESI-MS (*m/z*): 329.9 $[M + H]^+$; ^{1}H NMR ($CDCl_3$, δ (ppm)): 8.07 (d, 2H, *J* = 8.8, Ar*H*), 7.96 (s, 1H, -C*H*=), 7.58 (d, 2H, *J* = 8.8, Ar*H*), 7.46 (d, 2H, *J* = 8.8, Ar*H*), 6.95 (d, 2H, *J* = 8.9,

Ar*H*), 3.84 (s, 3H, -O*CH*$_3$); ^{13}C NMR ($CDCl_3$, δ (ppm)): 185.16, 183.26, 162.31, 141.37, 138.99, 132.80, 130.46, 129.87, 129.60, 126.38, 123.52, 114.95, 55.69; Anal. Calcd.: C (61.91%), H (3.67%), N (4.25%); Found: C (62.06%), H (3.69%), N (4.22%).

(*Z*)-5-(4-Methoxybenzylidene)-2-phenylthiazol-5*H*-thiazol-4-one, 19. Yield: 35%; orange solid. Mp: 195 °C. $C_{17}H_{13}NO_2S$, M_r = 295.4. ESI-MS (*m/z*): 295.9 $[M + H]^+$. ^{1}H NMR (DMSO-d^6, δ (ppm)): 8.23 (d, 2H, *J* = 7.5, Ar*H*), 8.05 (s, 1H, -C*H*=), 7.83 (m, 3H, Ar*H*), 7.70 (t, 2H, *J* = 8.9, Ar*H*), 7.17 (d, 2H, *J* = 9.0, Ar*H*), 3.89 (s, 3H, -O*CH*$_3$). ^{13}C NMR (DMSO-d^6, δ (ppm)): 185.94, 182.12, 161.89, 138.13, 135.49, 131,23, 132.56, 129.63, 128.45, 125.81, 123.18, 115.26, 55.72; Anal. Calcd: C (69.13%), H (4.44%), N (4.74%). Found: C (69.22%), H (4.25%), N (4.65%).

(*Z*)-Methyl-2-(4-((4-oxo-2-(*p*-tolyl)-4*H*-thiazol-5-ylidene)methyl)phenoxy)acetate, 20. *p*-Hydroxy-benzaldehyde (9 mmol, 1.1 g) was suspended with K_2CO_3 (1.5 equiv, 13.5 mmol,1.9 g) in DMF, after addition of ethyl chloroacetate (1.1 equiv, 9.9 mmol, 1.2 g) the mixture was refluxed in methanol for 12 h. When the suspension was cooled to room temperature, it was partioned between H_2O and ethyl acetate and the organic layer was washed with brine and dried over Mg_2SO_4[2]. The organic layer was evaporated to dryness under reduced pressure and the product was used as obtained. This building block was used according to the general procedure. Due to reflux in methanol a re-esterification reaction took place. Yield: 35%; yellow solid. Mp: 181 °C. $C_{20}H_{17}NO_4S$, M_r = 367.4. ESI-MS (*m/z*): 368.1 $[M + H]^+$. ^{1}H NMR (DMSO-d^6, δ (ppm)): 8.15 (d, 2H, *J* = 8.1, Ar*H*), 8.06 (s, 1H, -C*H*=), 7.86 (d, 2H, *J* = 8.6, Ar*H*), 7.56 (d, 2H, *J* = 8.0, Ar*H*), 7.22 (d, 2H, *J* = 8.7, Ar*H*), 5.02 (s, 2H, -O*CH*$_2$-), 3.80 (s, 3H, -O*CH*$_3$), 2.52 (s, 3H, -*CH*$_3$). ^{13}C NMR (DMSO-d^6, δ (ppm)): 185.68, 182.20, 168.74, 159.94, 146.57, 137.35, 132.70, 130.21, 128.47, 126.64, 123.65, 115.57, 64.74, 51.88, 21.42. Anal. Calcd: C (65.38%), H (4.66%), N (3.81%). Found: C (65.11%), H (4.69%), N (3.70%).

(*Z*)-Methyl-2-(4-(5-(4-methoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)phenoxy)acetate, 21. *p*-Hydroxybenzonitrile (9 mmol, 1.1 g) was suspended with K_2CO_3 (1.5 equiv, 13.5 mmol, 1.9 g) in

DMF, after addition of ethyl chloroacetate (1.1 equiv, 9.9 mmol,1.2 g) the mixture was refluxed in methanol for 12 h. When the suspension was cooled to room temperature, it was partioned between H_2O and ethyl acetate, the organic layer was extracted with brine and dried over Mg_2SO_4[2]. The organic layer was evaporated to dryness under reduced pressure and the product was used as obtained. This building block was used according to the general procedure. Due to reflux in methanol a re-esterification reaction took place. Yield: 35%; yellow solid. Mp: 190 °C. $C_{20}H_{17}NO_5S$, M_r = 383.4. ESI-MS (*m/z*): 384.1 $[M + H]^+$. ^{1}H NMR (DMSO-d^6, δ (ppm)): 8.17 (d, 2H, *J* = 8.8, Ar*H*), 7.97 (s, 1H, -C*H*=), 7.79 (d, 2H, *J* = 8.8, Ar*H*), 7.22 (d, 2H, *J* = 8.9, Ar*H*), 7.15 (d, 2H, *J* = 8.8, Ar*H*), 5.02 (s, 2H, -O*CH*$_2$-), 3.86 (s, 3H, -O*CH*$_3$), 3.72 (s, 3H, -O*CH*$_3$). ^{13}C NMR (DMSO-d^6, δ (ppm)): 184.79, 182.31, 168.60, 163.43, 161.86, 137.13, 132.86, 130.83, 126.11, 124.54, 123.42, 116.00, 114.87, 65.19, 55.75, 52.15. Anal. Calcd: C (62.65%), H (4.47%), N (3.65%). Found: C (62.41%), H (4.43%), N (3.51%).

(*Z*)-2-(4-Hydroxyphenyl)-5-(4-methoxybenzylidene)-5*H*-thiazol-4-one, 22. Yield: 45%; orange solid. Mp: 283 °C. $C_{17}H_{13}NO_3S$, M_r = 311.3. ESI-MS (*m/z*): 311.9 $[M + H]^+$. ^{1}H NMR (DMSO-d^6, δ (ppm)): 8.1 (d, 2H, *J* = 8.8, Ar*H*), 7.91 (s, 1H, -C*H*=), 7.75 (d, 2H, *J* = 8.7, Ar*H*), 7.14 (d, 2H, *J* = 8.8, Ar*H*), 6.99 (d, 2H, *J* = 8.8, Ar*H*), 3.85 (s, 3H, -O*CH*$_3$). ^{13}C NMR (DMSO-d^6, δ (ppm)): 184.68, 182.42, 164.81, 161.65, 136.37, 132.75, 131.40, 126.21, 123.72, 122.14, 116.50, 115.14, 55.77; Anal. Calcd: C (65.58%), H (4.21%), N (4.50%). Found: C (65.55%), H (4.23%), N (4.44%).

(*Z*)-5-(4-Methoxybenzylidene)-2-(4-methoxyphenyl)-5*H*-thiazol-4-one, 23. Yield: 35%; yellow solid. Mp: 242 °C. $C_{18}H_{15}NO_3S$, M_r = 325.3. ESI-MS (*m/z*): 325.9 $[M + H]^+$. ^{1}H NMR ($CDCl_3$, δ (ppm)): 8.11 (d, 2H, *J* = 8.7, Ar*H*), 7.91 (s, 1H, -C*H*=), 7.56 (d, 2H, *J* = 8.6, Ar*H*), 6.95 (m, 4H, Ar*H*), 3.87 (s, 3H, -O*CH*$_3$), 3.80 (s, 3H, -O*CH*$_3$). ^{13}C NMR ($CDCl_3$, δ (ppm)): 185.47, 183.57, 165.39, 161.87, 137.53, 132.69, 131.23, 126.83, 124.92, 124.04, 114.80, 55.72. Anal. Calcd: C (66.44%), H (4.65%), N (4.30%). Found: C (66.21%), H (4.56%), N (4.14%).

(***Z***)**-2-(4-Aminophenyl)-5-(4-methoxybenzylidene)-5*H*-thiazol-4-one, 24.** Yield: 35%; yellow solid. Mp: 252 °C. $C_{17}H_{14}N_2O_2S$, M_r = 310.3. ESI-MS (*m/z*): 310.8 $[M + H]^+$. ^1H NMR (DMSO-d^6, δ (ppm)): 7.92 (d, 2H, *J* = 8.0, Ar*H*), 7.80 (s, 1H, -C*H*=), 7.72 (d, 2H, *J* = 8.0, Ar*H*), 7.12 (d, 2H, *J* = 8.0, Ar*H*), 6.88 (s, 2H, -NH_2), 6.73 (d, 2H, *J* = 8.0, Ar*H*), 3.85 (s, 3H, -OCH_3). ^{13}C NMR (DMSO-d^6, δ (ppm)): 183.19, 182.08, 161.12, 156.70, 133.97, 132.19, 131.60, 126,39, 124,28, 117.50, 114.89, 113.44, 55.41; Anal. Calcd: C (65.79%), H (4.55%), N (9.03%). Found: C (65.53%), H (4.47%), N (8.99%).

(***Z***)**-2-(4-Acetylphenyl)-5-(4-methoxybenzylidene)-5*H*-thiazol-4-one, 25.** Yield: 45%; orange solid. Mp: 217 °C. $C_{19}H_{15}NO_3S$, M_r = 337.3; ESI-MS (*m/z*): 337.9 $[M + H]^+$. ^1H NMR (DMSO-d^6, δ (ppm)): 8.33 (d, 2H, *J* = 8.4, Ar*H*), 8.18 (d, 2H, *J* = 8.5, Ar*H*), 8.06 (s, 1H, -C*H*=), 7.81 (d, 2H, *J* = 8.9, Ar*H*), 7.16 (d, 2H, *J* = 8.8, Ar*H*), 3.87 (s, 3H, -OCH_3), 2.67 (s, 3H, -CH_3). ^{13}C NMR (DMSO-d^6, δ (ppm)): 197.12, 185.50, 183.12, 162.49, 141.61, 139.95, 135.68, 133.31, 129.04, 126.67, 123.58, 115.28, 55.74, 27.04. Anal. Calcd: C (67.64%), H (4.48%), N (4.15%). Found: C (67.41%), H (4.47%), N (4.04%).

(*Z*)-2-(3-Acetylphenyl)-5-(4-methoxybenzylidene)-5*H*-thiazol-4-one, 26. Yield: 40%; orange solid. Mp: 215 °C. $C_{19}H_{15}NO_3S$, M_r = 337.3. ESI-MS (*m/z*): 337.6 $[M + H]^+$. ^1H NMR ($CDCl_3$, δ (ppm)): 8.69 (s, 1H, Ar*H*), 8.32 (d, 1H, *J* = 7.7, Ar*H*), 8.19 (d, 1H, *J* = 7.8, Ar*H*), 8.00 (s, 1H, -C*H*=), 7.61 (m, 3H, Ar*H*), 6.97 (d, 2H, *J* = 8.6, Ar*H*), 3.84 (s, 3H, -OCH_3), 2.65 (s, 3H, -CH_3). ^{13}C NMR ($CDCl_3$, δ (ppm)): 196.71, 185.68, 183.36, 162.47, 139.51, 137.92, 134.01, 133.01, 132.69, 132.54, 129.66, 128.39, 126.54, 123.39, 115.07, 55.74, 26.97. Anal. Calcd: C (67.64%), H (4.48%), N (4.15%). Found: C (67.45%), H (4.54%), N (4.09%).

(*Z*)-2-(3-Fluorophenyl)-5-(4-methoxybenzylidene)-5*H*-thiazol-4-one, 27. Yield: 40%; yellow solid. Mp: 209 °C. $C_{17}H_{12}FNO_2S$, M_r = 313.3. ESI-MS (*m/z*): 314.0 $[M + H]^+$. ^1H NMR (DMSO-d^6, δ (ppm)): 8.05 (s, 1H, -C*H*=), 7.99 (d, 2H, *J* = 9.8, Ar*H*), 7.80 (d, 2H, *J* = 8.5, Ar*H*), 7.71 (m, 2H, Ar*H*), 7.15 (d, 2H, *J* = 8.5, Ar*H*), 3.86 (s, 3H, -OCH_3). ^{13}C NMR (DMSO-d^6, δ (ppm)): 185.39,

183.07, 164.79, 163.47, 139.55, 133.17, 130.85, 126.38, 124.38, 123.32, 121.79, 115.67, 115,25, 114.96, 55.54. Anal. Calcd: C (65.16%), H (3.86%), N (4.47%). Found: C (65.32%), H (4.07%), N (4.45%).

(*Z*)-2-(4-Chlorophenyl)-5-(4-hydroxybenzylidene)-5*H*-thiazol-4-one, 28. Yield: 35%; orange solid. Mp: 345 °C. $C_{16}H_{10}ClNO_2S$, M_r = 315.77. ESI-MS (*m/z*): 314.2 $[M - H]^+$. ^1H NMR (DMSO-d^6, δ (ppm)): 8.20 (d, 2H, *J* = 8.5, Ar*H*), 7.98 (s, 1H, -C*H*=), 7.74 (d, 2H, *J* = 8.6, Ar*H*), 7.69 (d, 2H, *J* = 8.7, Ar*H*), 6.97 (d, 2H, *J* = 8.6, Ar*H*). ^{13}C NMR (DMSO-d^6, δ (ppm)): 184.46, 182.19, 161.20, 140.05, 139.07, 133.41, 130.15, 130.02, 129.80, 124.24, 121.73, 116.58. Anal. Calcd: C (60.86%), H (3.19%), N (4.44%). Found: C (60.90%), H (3.16%), N (4.38%).

II X-ray structure of compound 7

We analyzed compound **7** by X-ray crystallography to identify the exact configuration the compounds are obtained in. A single crystal of compound **7** was measured on a SIEMENS SMART diffractometer at a temperature of about -131°C. The structure was determined using the program SHELXS.

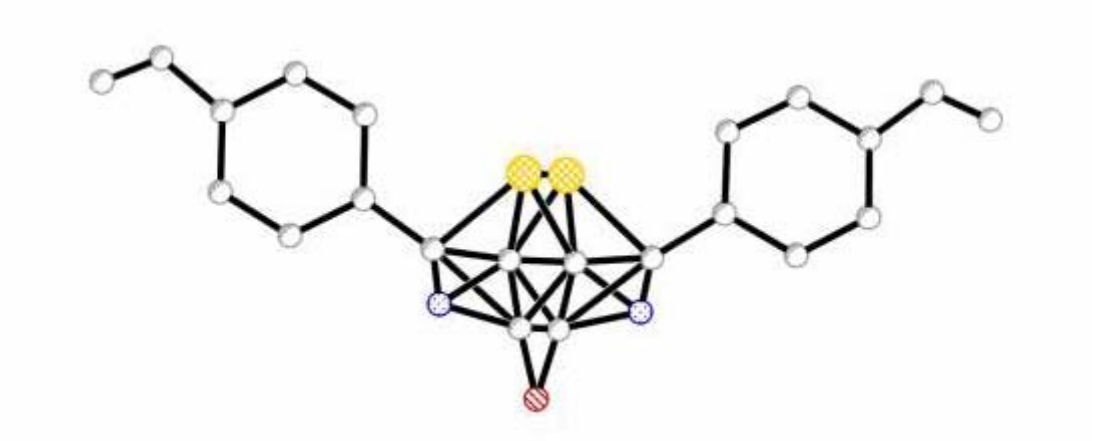


Figure 1. X-ray structure of two molecules of compound **7** in dimeric overlay.

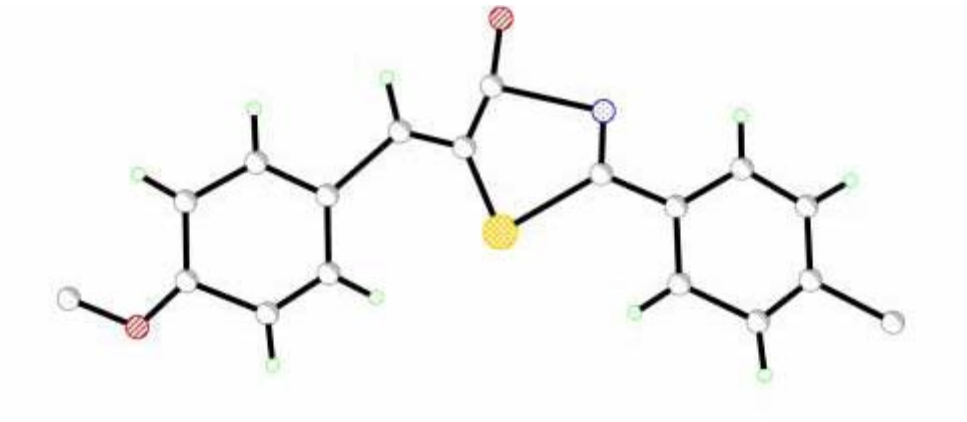


Figure 2. Molecular structure of compound **7** from X-ray analysis demonstrating the *Z*-orientation.

In figure 2 the second molecule is segregated out of figure 1. Due to the low resolution of the crystals obtained, the lengths and angles of the bindings are not in correct scale, but from the data it can clearly be stated that the *Z*-isomer is obtained. The resolution is insufficient to put these data in any data bank.

III Determination of 5-LO Product Formation

Cell Preparation. Human PMNL were freshly isolated from leukocyte concentrates obtained at Städtische Kliniken Höchst (Frankfurt, Germany). In brief, venous blood was taken from healthy adult donors and leukocyte concentrates were prepared by centrifugation at 4000g for 20 min at room temperature. PMNLs were immediately isolated by dextran sedimentation, centrifugation on Nycoprep cushions (PAA Laboratories, Linz, Austria), and hypotonic lysis of erythrocytes as previously described.[3] Cells were finally resuspended in phosphate-buffered saline (PBS), pH 7.4 containing 1 mg/mL glucose (purity >96-97%).

Determination of 5-LO Product Formation in Intact Cells. For whole-cell assay freshly isolated human polymorphonuclear leukocytes (PMNL) (5×10^6) were resuspended in 1 mL PBS, pH 7.4, containing 1 mg/mL glucose and 1 mM $CaCl_2$. After preincubation with test compounds for 15 min at 37 °C, 5-LO product formation was stimulated by calcium ionophore A23187 (2.5 μM) and arachidonic acid (20 μM). After 10 min at 37 °C, the reaction was stopped with 1 mL of

methanol. HCl (30 µL, 1 N), prostaglandin B_1 (200 ng), and PBS (500 µL) were added, 5-LO metabolites extracted and analyzed by HPLC as described.[4] 5-LO product formation was determined as nanogram of 5-LO products per 10^6 cells, which includes leukotriene B_4 (LTB_4) and its all-*trans* isomers, and 5-H(P)ETE (5(*S*)-hydroperoxy-6-*trans*-8,11,14-*cis*-eicosatetraenoic acid). Cysteinyl LTs C_4, D_4, and E_4 were not detected, and oxidation products of LTB_4 were not determined. Each compound was tested at least three times, and the mean and standard error of the mean were calculated.

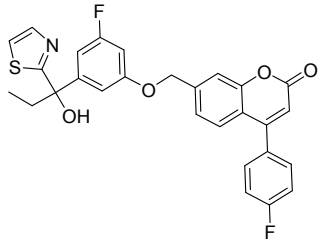
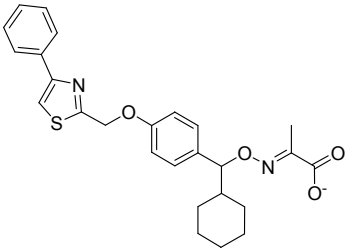
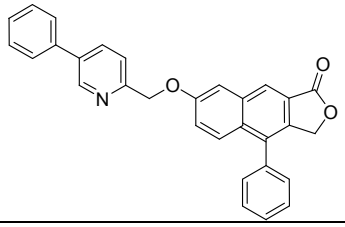
Determination of 5-LO Product Formation in Cell-Free Systems. For determination of 5-LO activity in 100000g supernatants (S100), freshly isolated PMNL cells were resuspended in 1 mL of PBS containing 1 mM EDTA and protease inhibitors, soybean trypsin inhibitor (60 µg/mL), 1 mM phenylmethylsulfonyl fluoride (PMSF), and leupeptine (10 µg/mL), cooled on ice for 10 min, and sonicated (three times for 10 s each) at 4 °C. The whole homogenate was then centrifuged (100000g for 70 min at 4 °C) to get the S100. For determination of 5-LO activity, S100 corresponding to 7.5×10^6 PMNL was added to 1 mL of a 5-LO reaction mix (PBS, pH 7.4, 1 mM EDTA, and 1 mM ATP). After preincubation with test compounds or vehicle (DMSO) for 15 min at 4 °C, samples were prewarmed for 30 s at 37 °C, and 20 µM AA and 2 mM $CaCl_2$ was added to start the 5-LO reaction. The reaction was stopped after 10 min at 37 °C by addition of 1 mL of ice-cold methanol. Formed metabolites were analyzed by HPLC as described for intact cells.

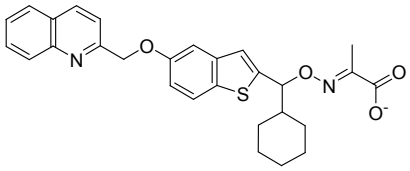
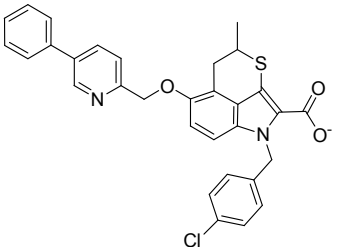
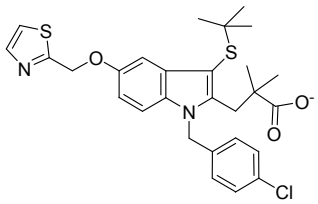
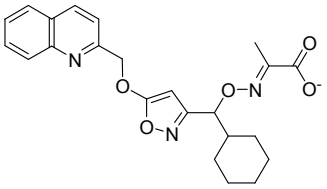
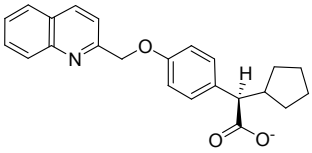
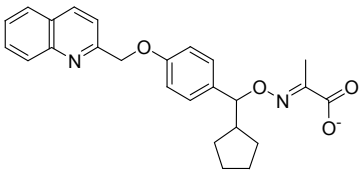
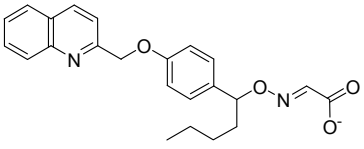
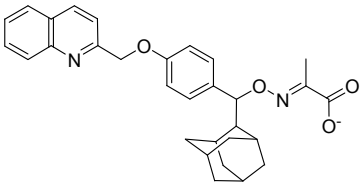
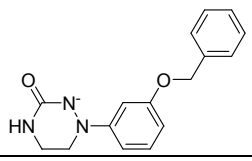
IV MACCS keys similarity search with compound 1 against published 5-LO inhibitors

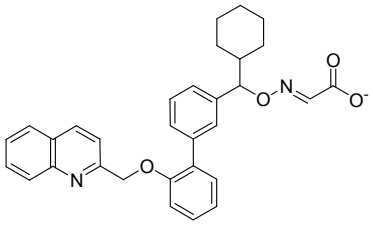
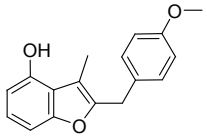
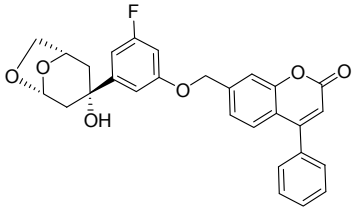
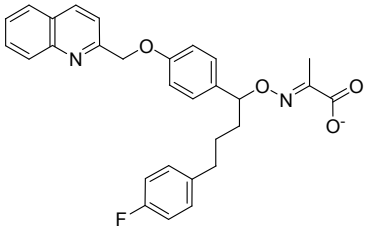
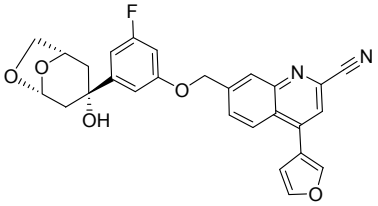
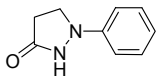
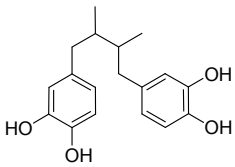
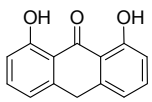
To range our compound class within already known 5 LO inhibitors, we performed a MACCS keys similarity search against publicly available 5-LO inhibitors using MOE (version 2009.10, Chemical Computing Group Ltd., Montreal, Canada). We screened the ChEMBLdb (https://www.ebi.ac.uk/chembldb), a database of bioactive drug-like small molecules with annotated bioactivities abstracted from the literature, with compound **1** as query structure for similarity search.

This involved the generation of MACCS keys from a given set of 166 predefined substructures for both database and query structures. A bit is set whenever one of these substructures is present in a molecule. Bit strings of the query and the database compounds were compared using the Tanimoto coefficient *T*. Molecules were retained with a Tanimoto coefficient >0.3. The resulting list was ranked in order of decreasing fingerprint similarity. Only those structures that do not contain the thiazolinone scaffold of compound **1** and that do exhibit unique scaffolds were retained. The 20 most similar structures from different structure series are shown with annotated bioactivities (Table S1).

Table S1. MACCS substructure keys similarity search results with compound **1** against known 5-LO inhibitors taken from the ChEMBLdb.

ID	Compound[#]	5-LO product formation IC_{50} [nM]	Reference	Tanimoto coefficient
36		2.7	Grimm, EL. et al. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2528-2531	0.5593
37		20	Kolasa, T. et al. J. *Med. Chem.* **2000**, *43*, 690-705	0.5345
38		22	Thérien, M., *Bioorg. Med. Chem. Lett.* **1993,** *3,* 2063-2066	0.5000

ID	Compound[#]	5-LO product formation IC_{50} [nM]	Reference	Tanimoto coefficient
39		33	Kolasa, T. et al. J. *Med. Chem.* **2000**, *43*, 690-705	0.4833
40		97	Hutchinson, JH. et al. J. *Med. Chem.* **1993**, *36*, 2771-2787	0.4762
41		7000	Woods, KW. et al. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1547-1552	0.4412
42		490	Kolasa, T. et al. J. *Med. Chem.* **2000**, *43*, 690-705	0.4063
43		60	Kolasa, T. et al. J. *Med. Chem.* **2000**, *43*, 690-705	0.4038
44		16	Kolasa, T. et al. J. *Med. Chem.* **2000**, *43*, 690-705	0.4000
45		52	Kolasa, T. et al. J. *Med. Chem.* **2000**, *43*, 690-705	0.4000
46		20	Kolasa, T. et al. J. *Med. Chem.* **2000**, *43*, 690-705	0.3966
47		200	Bhatia, PA. et al. J. *Med. Chem.* **1996**, *39*, 3938-3950	0.3939

ID	Compound[#]	5-LO product formation IC_{50} [nM]	Reference	Tanimoto coefficient
48		160	Kolasa, T. et al. J. *Med. Chem.* **2000**, *43*, 690-705	0.3934
49		574	Lau, CK. et al. J. *Med. Chem.* **1989**, *32*, 1190-1197	0.3800
50		3.7	Grimm, EL. et al. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2528-2531	0.3750
51		9	Kolasa, T. et al. J. *Med. Chem.* **2000**, *43*, 690-705	0.3710
52		2.3	Grimm, EL. et al. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2528-2531	0.3636
53		9200	Lau, CK. et al. J. *Med. Chem.* **1989**, *32*, 1190-1197	0.3155
54		85	Lau, CK. et al. J. *Med. Chem.* **1989**, *32*, 1190-1197	0.2885
55		7000	Müller, K. et al. J. *Med. Chem.* **1994**, *37*, 1660-1669	0.2766

[#]One representative (with the highest Tanimoto coefficient) of each scaffold class is shown.

V References

1. Zayed, E. M.; Elbannany, A. A. A.; Ghozlan, S. A. S. Studies on thiazolin-4-one: synthesis of some pyrano[2,3b]-thiazole derivatives. *Pharmazie* **1985**, *40*, 194-196.

2. Spurg, A.; Waldvogel, S. High-yielding cleavage of (aryloxy)acetates. *Eur. J. Org. Chem.* **2008**, *2*, 337-342.

3. Werz, O.; Bürkert, E.; Samuelsson, B.; Rådmark, O.; Steinhilber, D. Activation of 5-lipoxygenase by cell stress is calcium independent in human polymorphonuclear leukocytes. *Blood* **2002**, *99*, 1044-1052.

4. Brungs, M.; Rådmark, O.; Samuelsson, B.; Steinhilber, D. Sequential induction of 5-lipoxygenase gene expression and activity in Mono Mac 6 cells by transforming growth factor beta and 1,25-dihydroxyvitamin D3. *Proc. Natl. Acad. Sci.* **1995**, *92*, 107-111.