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Anacardic acid derived salicylates are inhibitors or activators of lipoxygenases

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ABSTRACT

Lipoxygenases catalyze the oxidation of unsaturated fatty acids, such as linoleic acid, which play a crucial role in inflammatory responses. Selective inhibitors may provide a new therapeutic approach for inflammatory diseases. In this study, we describe the identification of a novel soybean lipoxygenase-1 (SLO-1) inhibitor and a potato 5-lipoxygenase (5-LOX) activator from a screening of a focused compound collection around the natural product anacardic acid. The natural product anacardic acid inhibits SLO-1 with an IC_{50} of 52 μM, whereas the inhibitory potency of the novel mixed type inhibitor **23** is fivefold enhanced. In addition, another derivative (**21**) caused non-essential activation of potato 5-LOX. This suggests the presence of an allosteric binding site that regulates the lipoxygenase activity.

1. Introduction

Lipoxygenases (LOXs) are a family of non-heme iron-containing enzymes that catalyze the oxygenation of *cis*,*cis*-1,4-pentadiene moieties in lipids. In general, lipoxygenases (LOXs), which are widely distributed in both the plant and animal kingdom, are categorized into 5-LOX, 8-LOX-, 12-LOXand 15-LOX based on the position of oxygenation of their substrates. Lipoxygenases convert their natural substrates, arachidonic acid, to hydroperoxy eicosatetraenoic acids (HPETEs) by a radical mechanism.[1] Lipoxygenases found in plant oxygenate linoleic acid to generate 13-hydroperoxy-9(*Z*),11(*E*)-octadecadienoic acid (13-HPOD). 5-HPETE is transformed into Leukotriene A4, which contains an unstable epoxide. Subsequently, Leukotriene A4 is converted either into Leukotriene B4 by an enzymatic hydrolysis or into Leukotriene C4 by glutathione S-transferase. The resulting Leukotriene C4 is further metabolized to Leukotriene D4 and Leukotriene E4.[2] It has been reported that activities of lipoxygenases and their related products play an important role in numerous inflammatory and proliferative diseases such as asthma, atherosclerosis, and cancer.[3–5] Leukotriene B4 activates inflammatory cells such as neutrophils and macrophages.[6] This broad range of biological effects demonstrates the importance of lipoxygenases as a therapeutic target.

6-pentadecyl salicylic acid, commonly known as anacardic acid, is a natural product found in cashew nut shells. This compound is often associated with anti-inflammatory, anti-tumor, molluscicidal, and anti-microbial activities.[7–9] Previous studies reported that anacardic acid inhibits peroxidation of linoleic acid by soybean lipoxygenase-1 (SLO-1) with an IC_{50} of 85 μM.[10] In addition, anacardic acid and its derivatives inhibit histone acetyl transferases (HATs) and cyclooxygenases, which are also involved in inflammation and cancer.[11–13]

In this study, we investigate the affinity and selectivity of anacardic acid derived inhibitors for SLO-1 and potato 5-LOX as representatives of the lipoxygenase family. Although lipoxygenases are well-known drug targets, relatively little inhibitors with high selectivity and potency have been described (reviewed by Pergola and Werz[14]). Currently, the selective 5-LOX inhibitor Zileuton (IC_{50} = 0.5 μM) is marketed for treatment of asthma.[15] Although there are no 15-LOX inhibitors available for the clinic, recent studies identified inhibitors with nanomolar affinity.[16,17] Nevertheless, their efficacy in cell-based studies remains limited. Therefore, development of inhibitors of new-structural classes remains necessary in order to explore these enzymes further as drug targets.

Here, we describe the identification of lipoxygenase inhibitors and activators from a focused compound collection based on anacardic acid. Anacardic acid and its derivatives were synthesized following previous research[18] and inhibition of SLO-1 and potato 5-LOX were investigated. We found that derivative **23** inhibits SLO-1 selectively to potato 5-LOX, whereas derivative **21** shows a threefold activation on potato 5-LOX. The enzyme kinetics of these inhibitors indicate the presence of an allosteric site that influences the activity of the lipoxygenase active site.

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2. Results and discussion

2.1. Design

The fact that the lipoxygenases are iron-containing enzymes combined with the fact that salicylates are known iron-binding compounds justifies the hypothesis that the iron-binding properties of salicylates are key to their inhibitory potency. In addition, hydrophobic interactions between the hydrophobic tail of anacardic acid **18** and the lipoxygenase active site are probably important. Based on these hypotheses, we expect that the different 6-alkyl substituents in our focused compound collection can improve the potency for lipoxygenase inhibition.

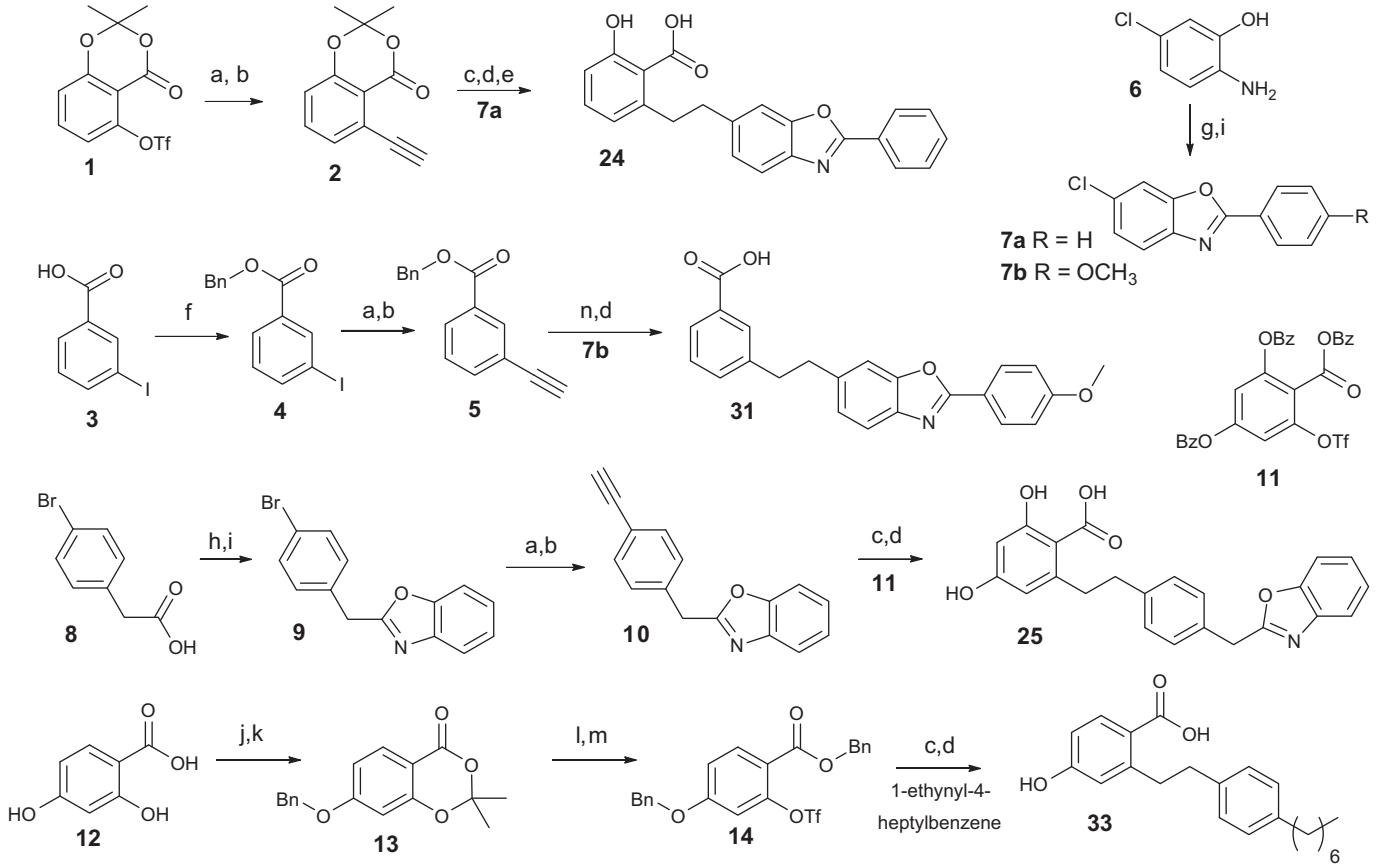
2.2. Synthesis

A compound collection was assembled around the natural product anacardic acid **18**. This collection comprises of the previously published salicylates **15**–**23**, **26**–**30**, and **32** and the newly synthesized salicylates **24**, **25**, **31**, and **33**. The synthesis of anacardic acid and its derivatives **15**–**23**, **26**–**30**, and **32** were described previously by Ghizzoni et al.[18,19] and compounds **24**, **25**, **31**, and **33** were synthesized using similar procedures (Scheme 1). Triflate **1** was synthesized as described by Uchiyama et al.[20] Alkynes **2**[21] and **5** were prepared from triflate **1** or 3-iodobenzoic acid **3** by Sonogashira coupling with trimethylsilyl (TMS) acetylene and subsequent cleavage of the TMS protective group to yield the corresponding products (Scheme 1). Benzoxazoles **7a** and **7b** were prepared from 2-amino-5-chlorophenol (**6**) and benzoic acid through amidation and cyclization.[22] Subsequently, **7a** was attached to **2** and **7b** was attached to **5** to give the corresponding alkynyls, which were reduced using catalytic hydrogenation to give **24** and **31** (Scheme 1).

Sonogashira coupling of aryl chlorides has been described to proceed with $PdCl_2(PPh_3)_2$, $P(tBu)_3$, and 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) as catalysts, and Cs_2CO_3 as a base to give >80% yields.[23] However, our attempt to synthesize compounds **24** and **31** under these conditions yielded 20–32% of the desired products. These relatively low yields are possibly due to electronic properties of the benzoxazole and/or the limited stability of the ester functionality in **2** or **5** under the basic coupling conditions.

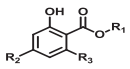
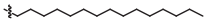
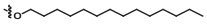
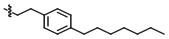
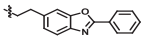
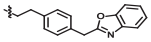
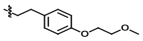
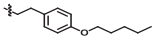
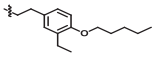
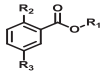
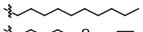
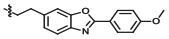
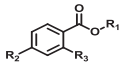
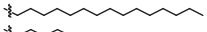
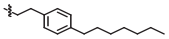
Benzoxazole **9** was prepared from commercially available 2-(4-bromophenyl)acetic acid (**8**) and 2-aminophenol following two reaction steps. Firstly, 2-(4-bromophenyl)acetic acid (**8**) was converted into the acyl chloride using thionyl chloride followed by amide bond formation with 2-aminophenol to give the amide with high yields (70%). Secondly, this amide was cyclized using *p*-toluenesulfonic acid in toluene at reflux for 4 h to give the product **9** with high yields (78–85%). Subsequently, the arylbromide (**9**) was coupled to trimethylsilyl acetylene by a Sonogashira coupling. The trimethylsilyl protective group was cleaved to give the corresponding alkyne **10**. This alkyne was coupled to triflate **11**[24] using a Sonogashira coupling to provide 55% yields of the corresponding alkyne (Scheme 1), which was hydrogenated to yield **25** in a single step.

Acetonide **13** was synthesized from 2,4-dihydroxybenzoic acid **12** as described by Tranchimand et al.[24] Furthermore, acetonide **13** was converted to triflate **14** as described previously.[20] Sonogashira reaction, coupling of 1-ethynyl-4-heptyl benzene with



Scheme 1. Reagent and conditions: (a) Trimethylsilylacetylene, CuI, $PdCl_2(PPh_3)_2$, Et_2NH, PPh_3, CH_3CN, (MW, 120 °C, 95 W), (b) TBAF, THF, 0 °C; (c) CuI, $PdCl_2(PPh_3)_2$, Et_2NH, HC≡CR, CH_3CN (MW, 100 °C, 70 W); (d) H_2, Pd/C, MeOH, 40 °C; (e) aqueous KOH 5 N, THF, 55 °C; (f) benzyl bromide, K_2CO_3, DMF, rt; (g) benzoic acid anhydride, pyridine, DMF, rt; (h) $SOCl_2$, 60 °C followed by 2-aminophenol, 0 °C; (i) *p*-toluensulfonic acid, toluene, reflux; (j) $SOCl_2$, DMAP, DME, acetone, rt; (k) Bn-Br, K_2CO_3, DMF, rt; (l) Bn-O^-Na^+, THF, rt; (m) Tf_2O, pyridine, CH_2Cl_2, 0 °C; (n) HC≡CR, aryl chloride, Cs_2CO_3, $PdCl_2(PPh_3)_2$, $P(tBu)_3$, DBU, DMF (MW, 150 °C, 95 W).

Table 1
Compound collection of anacardic acid and its derivatives

Compounds		R1	R2	R3
	**15**	H	H	
	16	H	H	
	17	H	OH	
	18	H	H	
	19	CH_3	H	
	20	H	OH	
	21	H	H	
	22	H	H	
	23	H	OH	
	24	H	H	
	25	H	OH	
	26	H	H	
	27	H	H	
	28	H	H	
	29	H	H	
	**30**	H	OH	
	31	H	H	
	**32**	H	H	
	33	H	OH	

triflate **14**, was performed to give the alkyne with high yield (79%), which was hydrogenated to give compound **33**.

The collection of compounds (Table 1) was screened for inhibition of the lipoxygenase activity of soybean lipoxygenase-1 (SLO-1) and potato 5-lipoxygenase (potato 5-LOX). The lipoxygenase activity was monitored in real time using a spectrophotometric assay to monitor the formation of conjugated diene 13-hydroperoxy-*cis*-9-*trans*-11-octadecadienoic acid (13-HPOD) from linoleic acid.[25,26] The residual enzyme activity was monitored after 10 min of pre-incubation with 50 μM of the respective inhibitor. The enzymatic activity without inhibitor present was taken as references and set to 100% and the activity without enzyme present was set to 0%. The percentages of the residual enzyme activity of SLO-1 and potato 5-LOX in the presence of the inhibitors are plotted in Figure 1.

Anacardic acid **18** inhibits both potato 5-LOX and SLO-1 about 50% at 50 μM and the IC_{50} value for SLO-1 was 52 μM (Fig. 2A and Table 2), which is in line with literature for SLO-1.[10] In

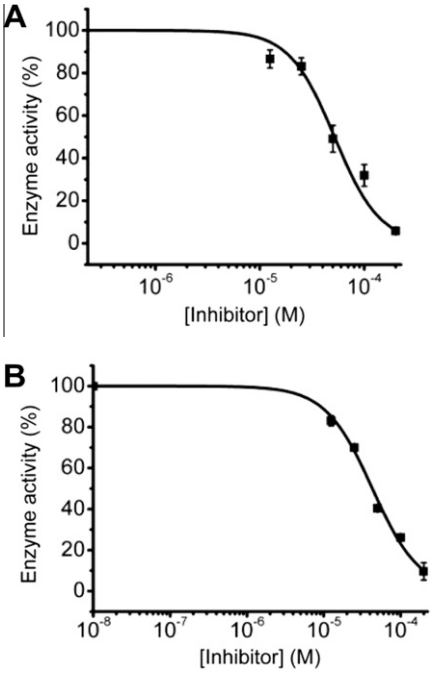


Figure 2. The IC_{50} value for inhibition of (A) SLO-1 and (B) potato 5-LOX by anacardic acid (**18**). The results were the average of three independent experiments with *error bars* (±S.D.).

contrast, we observed an IC_{50} of 43 μM for potato lipoxygenase (Fig. 2B), whereas literature reports a 30% activity inhibition at 6 μM.[12] This difference is probably due to a difference in the type of substrate that was used. Salicylates **21**, **23**, **24** and **25** show 50% inhibition or more at 50 μM for SLO-1, whereas this is not observed for potato 5-LOX. In contrast, compounds **21** and **22** activate the potato 5-LOX enzyme at these concentrations. This demonstrates that these compounds activate or inhibit lipoxygenase activity and that selectivity between both lipoxygenases can be obtained by variation of the substitution in the 4- and/or 6-position of the salicylate.

This salicylate compound collection shows interesting structure–activity relationships for SLO-1. The 6-pentadecyl substituent in **18** is important for inhibition, because inhibitors **15** and **16** with a 6-pentyl or 6-decyl substituents are less potent. The same is

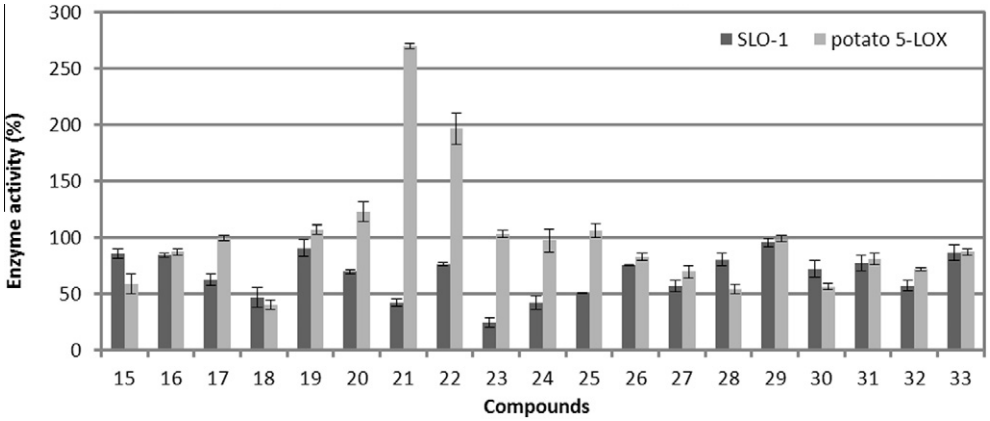


Figure 1. Residual enzyme activity that was observed for the screening of the salicylate compound collection for inhibition of the lipoxygenase activity. The bars show the residual activity of potato LOX-5 (light gray) and soybean lipoxygenase-1 (SLO1) (dark gray) in the presence of 50 μM of the respective inhibitor. The percentage activity for each compound was calculated in comparison with the blank in which no inhibitor was present. The results were the average of three independent experiments with the standard deviations.

Table 2
IC_{50} values for inhibition of SLO-1 by anacardic acid derivatives

Compounds	IC_{50} (μM)
18	51.9 ± 5.0
21	55.4 ± 6.3
23	11.1 ± 0.8
25	58.5 ± 3.6

Table 3
Enzyme kinetics parameter for SLO-1 inhibition

[**23**] (μM)	V_{max}^{app} (μM/s)	K_m^{app} (μM)	R^2
0	0.437	12.4	0.963
6	0.321	14.3	0.967
11	0.251	15.5	0.979

observed for the salicylates **26** and **27** without an aliphatic substituents in the 6-position. These results demonstrate that the side chain length of the 6-alkyl chain is important for the SLO-1 inhibitory potency. This is possibly due to the hydrophobic interactions between the inhibitor and the binding pocket of the enzyme. In addition, a complete loss of inhibition was observed if the carboxylate of anacardic acid **18** was converted into a methyl ester **19**, which demonstrates that the free carboxylate is also important for binding. Despite the presence of a 6-pentadecyl substitutent, compound **20** is slightly less active for SLO-1 and inactive for potato 5-LOX. Apparently, the extra hydroxyl in the *para*-position influences both the steric and electronic properties in such a way that binding is impaired. Furthermore, the importance of the 2-hydroxyl functionality of the salicylate is demonstrated by the inactivity of the inhibitors **31**–**33**, which show less than 50% inhibition 50 μM. These results demonstrate that the carboxylate and the hydroxyl of the salicylate core are both crucial for inhibition of SLO-1.

Salicylates **24** and **25** with a benzoxazole functionality in their side chain maintain their inhibition of SLO-1, whereas no inhibition of potato 5-LOX was observed. This demonstrates that the selectivity between potato 5-LOX and SLO-1 can be obtained by variation of the 6-alkyl substituent in anacardic acid.

Inhibitor **23** shows an IC_{50} of 11 μM (Table 2) for SLO-1, which is fivefold improved compared to anacardic acid **18**, whereas no inhibition of potato 5-LOX was observed. Furthermore, inhibitor **23** also shows its selectivity towards HATs, in which inhibitor **23** gives no inhibitory effect on the activity of p300, and PCAF and modest effect on Tip60 at 200 μM.[19] In comparison, the lower SLO-1 inhibition of **22** and **33** demonstrate that both hydroxyl groups of **23** are important for inhibition. In addition, the reduced potency of **20** shows that also the 1-ethyl-4-heptylbenzene substituent in **23** is important for inhibition.

In an attempt to improve the potency of inhibitor **23**, we designed a novel compound **25** in which the aliphatic chain was replaced for a heterocycle. However, this derivative did not provide a better inhibition of SLO-1 (Table 2).

The influence of **23** on the Michaelis–Menten kinetics for conversion of the substrate linoleic acid was determined in order to establish the mechanism of SLO-1 inhibition. Inhibitor **23** causes both a reduction of V_{max}^{app} and an increase of K_m^{app} (Table 3), which indicates a mixed type of inhibition (Fig. 3). The enzyme activity is expected to obey the model in Scheme 2, in which the inhibitor can bind to the free enzyme as well as to the substrate bound enzyme.

The values for V_{max} and K_m were determined from the Lineweaver–Burk plot using Eq. 1.1 (Fig. 4) in the absence of inhibitor **23**, respectively from the *y*-intercept and *x*-intercept. V_{max}^{app} and K_m^{app} for

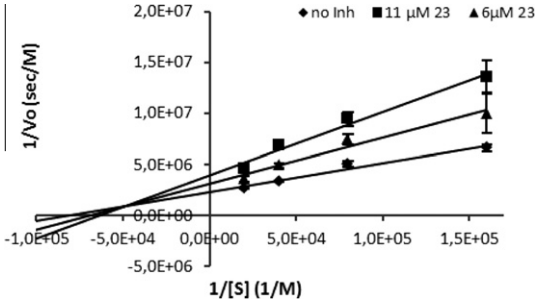
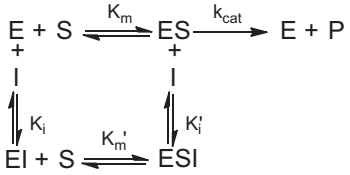


Figure 3. Conversion of the substrate linoleic acid by the enzyme SLO-1 with no inhibitor present (♦), after preincubation with 6 μM inhibitor **23** (▲), and with 11 μM inhibitor **23** (■). The results were the average of three independent experiments with *error bars* (±S.D.).



Scheme 2. Kinetic model for mixed enzyme inhibition.

$$v = \frac{V_{max} \times [S]}{\alpha K_m + \alpha' [S]} \quad \text{equation 1.1}$$

$$\alpha = 1 + \frac{[I]}{K_i} \quad \text{(eq1.2)} \qquad \alpha' = 1 + \frac{[I]}{K_i'} \quad \text{(eq1.3)}$$

Figure 4. Equation for the enzyme kinetics according to the model in Scheme 2. v is the reaction velocity, V_{max} is the maximal reaction velocity, [S] is the substrate concentration and K_m is the Michaelis–Menten constant. α and α', respectively, are the parameters to describe the change of substrate binding affinity to the enzyme and the change of the maximum velocities. K_i is the dissociation constant of inhibitor to the free enzyme and K_i' is the dissociation constant of inhibitor to the enzyme–substrate complex.

each inhibitor **23** concentration were calculated in the same manner as in the absence of inhibitor. α' and α/α' values, which are the change in V_{max} and K_m, are derived respectively from V_{max}^{app} divided by V_{max} and from K_m^{app} divided by K_m. The inhibitor binding constant, K_i and K_i' values, were calculated from the Eqs. 1.2 and 1.3 (Fig. 4) as described in Supplementary data. The binding constant binding for inhibition of the free enzyme (K_i) is 9.8 μM and the binding constant to the substrate bound enzyme (K_i') is 15.7 μM. The fact that inhibitor **23** binds to the free as well as the substrate bound enzyme in the mixed type inhibition suggests the presence of an allosteric binding site.[28–30]

Interestingly, inhibitor **21**, in which the 6-aliphatic side chain is replaced by an ether functionality, shows equal inhibition compared to anacardic acid **18** on SLO-1 (Table 2), whereas this inhibitor (and also inhibitor **22**) shows about threefold activation of potato 5-LOX. Compound **21** provided a concentration dependent activation with a maximal activation that is about threefold higher than the control activity at concentrations higher than 50 μM (Fig. 5).

We decided to study the enzyme kinetics for the activation of potato 5-LOX by **21** in order to investigate the binding mechanism. The concentration dependent effect of **21** on the Lineweaver–Burk plot of potato 5-LOX activity was investigated (Fig. 6A). Activator **21** causes an increase of the V_{max} and a decrease of the K_m values. This behavior, in which the reaction can occur in the presence or in the absence of the activator, indicates non-essential activation of

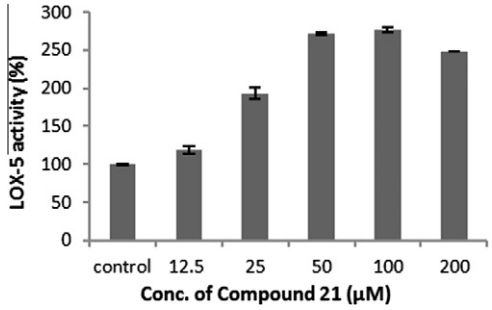


Figure 5. Compound **21** activates potato 5-LOX. The experiments were performed in the absence (control) or the presence of compound **21** with various concentrations. The results were the average of three independent experiments with *error bars* (±S.D.)

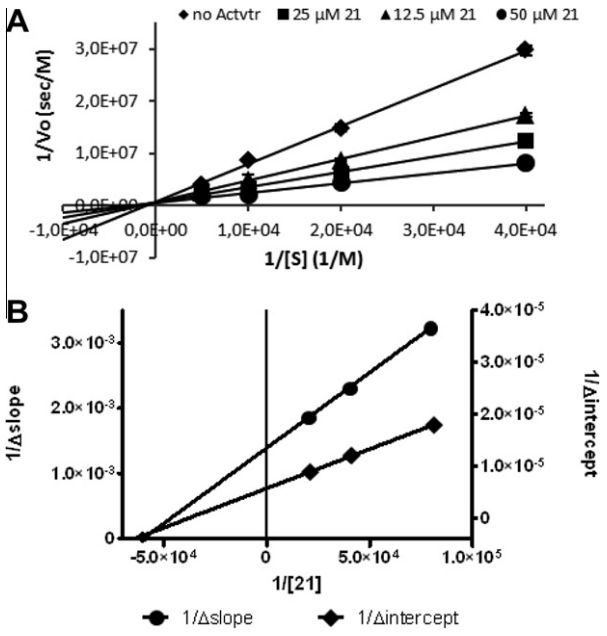


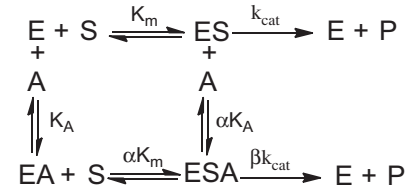
Figure 6. (A) Lineweaver–Burk plot of the potato 5-LOX activity with no activator present (♦), after preincubation with 12.5 μM activator **21** (▲), with 25 μM activator **21** (■), and with 50 μM activator **21** (●). The results were the average of three independent experiments with *error bars* (±S.D.) (B) Re-plot of 1/Δslope (●) and the 1/Δintercept (♦).

Table 4
Enzyme kinetics parameter for potato 5-LOX activation

[**21**] (μM)	V_{max}^{app} (μM/s)	K_m^{app} (mM)	R^2
0	1.597	1.160	0.998
12.5	1.754	0.733	0.999
25	1.852	0.537	0.995
50	1.949	0.370	0.992

potato 5-LOX[31] (Table 4). The enzyme kinetics for the activation of potato 5-LOX obeys the model shown in Scheme 3. The activator dissociation constants (K_A), the change in the affinity of substrate binding (α value) and the change in the catalytic constant (β value) were determined from the re-plot of 1/Δslope and the 1/Δintercept (Fig. 6B) according to Eq. 2 (Fig. 7) as described in Supplementary data.

The kinetic analysis shows that α is 0.013, β is 1.4 and K_A is 1.8 mM. The α value indicates that the substrate and the activator mutually enhance their binding by close to 100-fold. Consequently,



Scheme 3. Kinetic model for non-essential activation.

the affinity of the activator for the substrate bound enzyme is 24 μM, which explains the observed activation at concentrations of 25 μM and higher. In addition, activator binding increases the catalysis rate by 1.4-fold. Taking this together, activator **21** shows non-essential activation and binds with relatively high affinity to substrate bound lipoxygenase and enhances the enzymatic conversion of the substrate.

Furthermore, the critical micelle concentrations (CMCs) for both anacardic acid (**18**) and **23** at the assay conditions (0.2 M borate buffer, pH 9.0, rt) are, respectively, 390 μM and 436 μM (Fig. 8A,C) whereas for compound **21** (in 0.1 M phosphate buffer pH 6.3, rt), the CMC value is 208 μM (Fig. 8B). These results indicate that micelle formation does not occur at concentrations employed for inhibition or activation. In addition, we found a CMC value for linoleic acid of 163 μM (Fig. S2),[27] which demonstrates that the substrate concentration in the inhibition studies (100 μM) was below the CMC. Thus the enzyme kinetics were evaluated in a homogeneous system. We also performed a docking simulation of **18** and **23** to SLO-1 to generate plausible binding poses of the inhibitor in the SLO-1 active site (Fig. S3)

The kinetic studies on both potato 5-LOX and SLO-1 indicate the presence of an allosteric binding site that influences substrate binding and conversely is influenced by binding of the substrate. For potato 5-LOX we demonstrated activation of the enzyme activity and for SLO-1 we demonstrated inhibition. These indications for an allosteric binding pocket are in line with previous studies. The observation of substrate inhibition of soybean lipoxygenase by linoleic acid indicates the presence of an allosteric binding site.[32] It can be presumed that the salicylate based inhibitors resemble the lipid substrate linoleic acid and binds in a similar way to the enzyme, thereby inhibiting the enzyme activity via an allosteric binding pocket. In addition, mixed inhibition has been described previously for soybean lipoxygenase by the inhibitor oleyl sulfate, which also indicates the presence of an allosteric binding site.[28] Non-essential activation has been described previously for 5-LOX by compound (*R,S*)-2-hydroxy-2-trifluoromethyl-*trans*-*n*-octadec-4-enoic acid (HTFOA) and phosphatidic acid.[33,34] These findings also indicate the existence of allosteric site as enzyme activity regulator. Nevertheless, the location and structural properties of the allosteric binding pocket in these enzymes remain elusive.[35] This demonstrates that structural characterization of the allosteric binding pocket remains a major challenge in lipoxygenase research.

$$v = \frac{V_{max} \times [S]}{K_m\left(\frac{1+\frac{[A]}{K_A}}{1+\frac{\beta[A]}{\alpha K_A}}\right)+[S]\left(\frac{1+\frac{[A]}{\alpha K_A}}{1+\frac{\beta[A]}{\alpha K_A}}\right)} \quad \text{equation 2}$$

Figure 7. Equation for the enzyme kinetics according to the model in Scheme 3.[31] v is the reaction velocity, V_{max} is the maximal reaction velocity, [S] is the substrate concentration and K_m is the Michaelis–Menten constant, [A] is the activator concentration. α and β, respectively, are the parameters to describe the change in the affinity of substrate binding and the change in the catalytic constant.

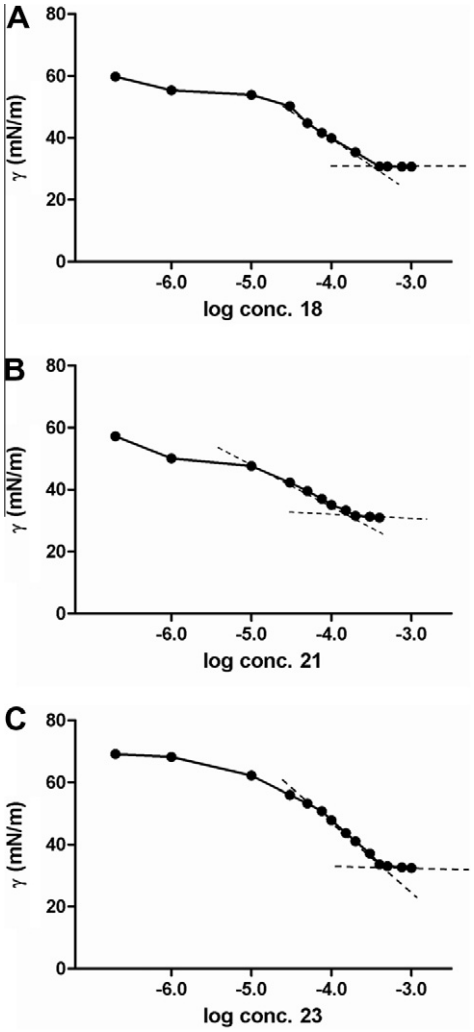


Figure 8. Surface tensions of (A) Anacardic acid **18** and (B) compound **21** (C) compound **23** against the logarithm of concentration. CMC values for A and C were measured in SLO-1 assay conditions, 0.2 M borate buffer, pH 9.0, rt (t = 19 °C), whereas CMC value for B was measured in potato 5-LOX assay conditions, 0.1 M phosphate buffer, pH 6.3, rt (t = 25 °C).

This study identifies salicylate based molecules as allosteric regulators of lipoxygenase enzyme activity. Such inhibitors might find applications as starting points for development of therapeutic agents for asthma and inflammations. Nevertheless, the potency and selectivity of this compound class for human lipoxygenases remains to be investigated. It is encouraging that the anacardic acid derived salicylates show clear structure–activity relationships, which indicates that further optimization of the affinity and selectivity of this compound class might be feasible.

3. Conclusions

This study demonstrates that anacardic acid **18** and its derivatives are lipoxygenase inhibitors and that their potency depends on the substitution pattern in the 4- and 6-position of the salicylate core. A novel inhibitor **23** was identified for soybean lipoxygenase-1 with a fivefold improved IC_{50} value compared to anacardic acid **18**. Enzyme kinetics reveal a mixed type inhibition pattern for **23** with a K_i of 9.8 μM and a K_i' of 15.7 μM (Scheme 2). In addition, an activator **21** of potato 5-lipoxygenase was identified for which K_A is 1.8 mM, α is 0.013 and β is 1.4 (Scheme 3). The affinity of **21** for the substrate bound enzyme (αK_A) is 24 μM. To our knowledge, this is the first activator with micromolar potency for potato lipoxygenase. These inhibitors might provide valuable starting points for development of inhibitors that target lipoxygenases, which is relevant for inflammatory diseases.

Supplementary data

Supplementary data (synthetic procedures and compounds analytical data as well as kinetic studies, assay description and molecular docking) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2012.06.019. These data include MOL files and InChiKeys of the most important compounds described in this article.

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