Design and Synthesis of 1-Indol-1-yl-propan-2-ones as Inhibitors of Human Cytosolic Phospholipase $A_2\alpha$

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The synthesis and structure−activity relationship study of a series of 1-indol-1-yl-3-phenoxypropan-2-one inhibitors of cytosolic phospholipase $A_2\alpha$ ($cPLA_2\alpha$) are described. The compounds were evaluated in a vesicle assay with isolated $cPLA_2\alpha$ and in cellular assays with intact human platelets. Systematic variation led to 3-methylhydrogen 1-[3-(4-decyloxyphenoxy)-2-oxopropyl]indole-3,5-dicarboxylate (**57**), which revealed the highest activity against the isolated enzyme. With an IC_{50} value of 4.3 nM in this assay, it is one of the most potent in vitro $cPLA_2\alpha$ inhibitors known today.

Introduction

Phospholipase A_2 (PLA_2) enzymes are a class of esterases that catalyze the hydrolysis of membrane phospholipids at the *sn*-2 position, leading to the production of lysophospholipids and free fatty acids including arachidonic acid. Arachidonic acid is further converted by cyclooxygenase and lipoxygenase enzymes to bioactive eicosanoids, such as prostaglandins and leukotrienes. In addition, a subset of lysophospholipids released by PLA_2 can be acetylated to the platelet-activating factor (PAF). Prostaglandins, leukotrienes, lysophospholipids, and PAFs are potent mediators of inflammation.[1−3] Thus, the inhibition of PLA_2 is considered to be an interesting target for the design of new anti-inflammatory drugs.[4−9] The special attraction of this approach is based on the evidence that unlike cyclooxygenase inhibitors the inhibitors of PLA_2 not only reduce the formation of prostaglandins but also suppress the generation of proinflammatory leukotrienes, lysophospholipids, and PAFs. Therefore, it can be expected that inhibitors of PLA_2 will possess improved therapeutic activities in comparison to those of the cyclooxygenase inhibitors therapeutically applied today.

One problem associated with the in vitro search for anti-inflammatory PLA_2 inhibitors is the selection of the appropriate enzyme because many different PLA_2 enzymes are present in the mammalian organism.[10,11] They can be divided into PLA_2 enzymes utilizing a catalytic histidine and PLA_2 enzymes with a serine in the active site. The small molecular weight (approximately 14 kDa) secretory PLA_2 enzymes ($sPLA_2$) are members of the first group. The second group consists of cytosolic PLA_2 enzymes ($cPLA_2$), calcium-independent PLA_2 enzymes ($iPLA_2$), and lipoprotein-associated PLA_2 enzymes, which have higher molecular weights than those of the $sPLA_2$ enzymes. From all of these PLA_2 enzymes, the α-subtype of $cPLA_2$ ($cPLA_2\alpha$) seems to play the central role in the arachidonic acid cascade and during the inflammatory response as supported by experiments with cells overexpressing $cPLA_2\alpha$[12] and $cPLA_2\alpha$ knockout animals.[13−18]

$cPLA_2\alpha$, also classified as group IVA PLA_2, is an 85 kDa protein, which is present in the cytosol of resting cells and translocates to intracellular membranes following stimulation with a variety of agonists.[11] The activation of the enzyme is tightly regulated by different factors, including intracellular Ca^{2+} levels and phosphorylation. $cPLA_2\alpha$ is unique among the PLA_2 enzymes in having a preference for phospholipids with arachidonic acid at the *sn*-2 position. The catalytic mechanism of $cPLA_2\alpha$ is thought to be similar to that of serine proteases, proceeding through a serine-arachidonoyl intermediate.

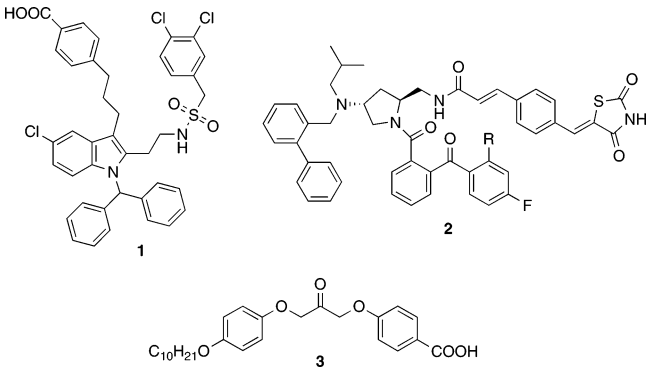

Figure 1.

Although there have been intense efforts made in finding inhibitors of $cPLA_2\alpha$, no such compound has emerged as an anti-inflammatory drug to date. The identification of $cPLA_2\alpha$ inhibitors is complicated by the fact that they have to partition into the phospholipid membrane to interfere with the enzyme in its active status. For enrichment in the phospholipid layer, the inhibitors must possess a substantial lipophilicity. Such compounds, however, often do not have suitable pharmaceutical properties for in vivo measurements of anti-inflammatory activity. The only $cPLA_2\alpha$ inhibitor reported to undergo clinical development as an anti-inflammatory drug is the indole derivative efipladib (**1**) from Wyeth.[19,20] Extreme potent in vitro $cPLA_2\alpha$ inhibitors discovered are pyrrolidine **2** of Shionogi[21] and propan-2-one **3** (AR−C70484XX) of AstraZeneca[22] (Figure 1). In vivo data for **2** and **3** have not been published until now.

We have found that several indole-2-carboxylic acid derivatives such as **4** and **5** (Figure 2) are inhibitors of $cPLA_2\alpha$-mediated arachidonic acid release in intact human platelets in the low micromolar and submicromolar ranges.[23,24] However, these compounds did not inhibit the isolated enzyme, indicating that they do not directly interact with the catalytic site of the enzyme.[25]

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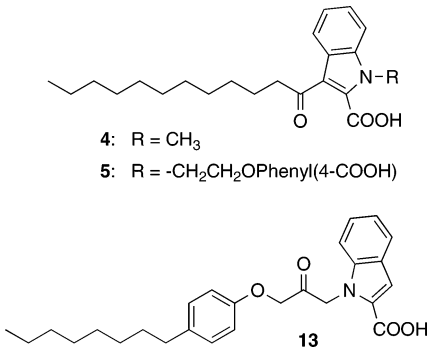


Figure 2.

An important pharmacophoric element of the propan-2-one cPLA$_2\alpha$ inhibitor **3** from AstraZeneca is the 4-decyloxyphenoxy-2-oxopropyl group. In an effort to gain true inhibitors of the enzyme, we synthesized and evaluated indole derivatives, which contain an analogous residue. In this approach, we first prepared compounds with the related equilipophilic 4-octylphenoxy-2-oxopropyl moiety such as indole **13**. The reason for the selection of this residue was the fact that the precursor 4-octylphenol required for its synthesis was commercially available, in contrast to the 4-decyloxyphenol needed for the preparation of the 4-decyloxyphenoxy-2-oxopropyl moiety. In the course of this approach, compounds were obtained, which proved to be highly active against the isolated enzyme as well as the cellular production of arachidonic acid.

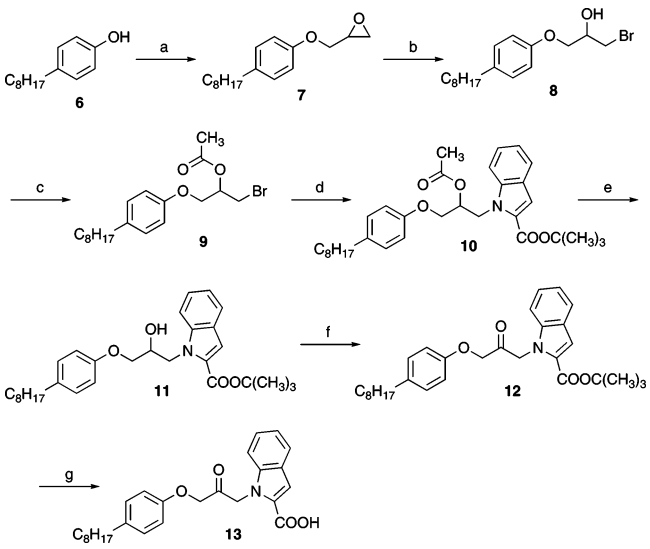
Chemistry

Indole-2- and -3-carboxylic acid derivatives **13** and **14** were synthesized by the route outlined for compound **13** in Scheme 1. 4-Octylphenol (**6**) was reacted with epichlorohydrin in the presence of powdered KOH and tetrabutylammonium bromide to give the intermediate **7**[26] in excellent yield. The epoxide ring of **7** was opened regioselectively with LiBr, applying silica gel as a catalyst to afford **8**. Acetylation of this compound with acetyl chloride led to **9**, which was coupled with *tert*-butyl indole-2-carboxylate[27] in DMSO in the presence of potassium *tert*-butylate. Treatment of obtained compound **10** with sodium methoxide in methanol yielded the hydroxy intermediate **11**. The alcohol moiety of **11** was oxidized by the Albright−Goldman procedure with acetic anhydride-DMSO to provide keto-ester **12**. Deprotection of the *tert*-butyl ester under standard conditions afforded target compound **13**.

The synthesis of indole-4-, -5-, and -6-carboxylic acids **17**−**19** was conducted in a manner similar to that described for the synthesis of cPLA$_2\alpha$ inhibitor **3**.[22] Scheme 2 outlines the synthesis of compound **17**. Thus, *tert*-butyl indole-4-carboxylate[27] was reacted with sodium hydride and **7** in DMF to give the hydroxy intermediate **15**. Subsequent oxidation of the alcohol group of this compound with the acetic anhydride-DMSO system afforded keto-ester **16**, which was treated with trifluoroacetic acid to yield desired acid **17**. During the synthesis of **18**, an indole-5-carboxylic acid derivative with a *tert*-butyl group in position 3 of the indole **39** was obtained as a side product.

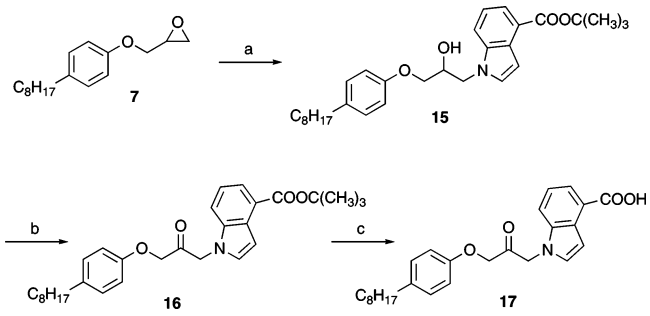
The analogues of **18** with varying substituents at the indole-5-position (**20**−**26**) were synthesized in a fashion similar to the synthesis of **16**. For the preparation of indole-5-carboxamide **28**, the nitrile moiety of the hydroxy intermediate of **24** was hydrolyzed to carboxamide **27** by KOH in *tert*-butyl alcohol. Oxidation of **27** by acetic anhydride-DMSO yielded keto-amide product **28**.

Scheme 1



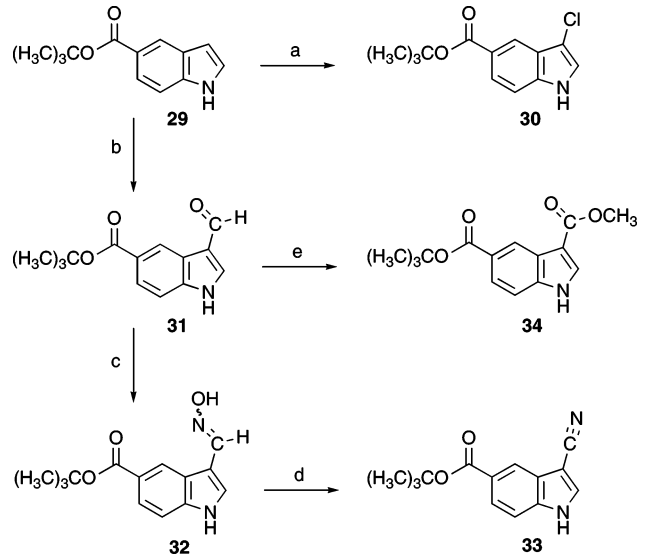
(a) Epichlorohydrin, KOH, $Bu_4N^+Br^-$, room temp.; (b) LiBr, silica gel, CH_2Cl_2, room temp.; (c) acetyl chloride, pyridine, CH_2Cl_2, 0 °C; (d) *tert*-butyl indole-2-carboxylate, *tert*-BuOK, DMSO, 110 °C; (e) CH_3ONa, CH_3OH; room temp.; (f) acetic anhydride, DMSO, room temp.; (g) TFA, CH_2Cl_2, room temp.

Scheme 2



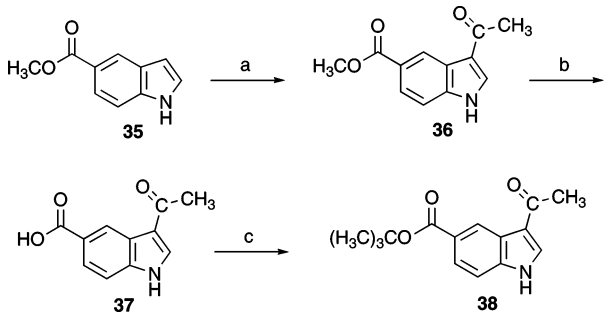
(a) *tert*-Butyl indole-4-carboxylate, NaH, DMF, 60 °C; (b) acetic anhydride, DMSO, room temp.; (c) TFA, CH_2Cl_2, room temp.

Scheme 3



(a) *N*-Chlorosuccinimide, CH_3OH, room temp.; (b) oxalyl chloride, DMF, CH_2Cl_2, 0 °C−room temp; (c) hydroxylammonium chloride, pyridine, reflux; (d) 2-chloro-1-methylpyridinium iodide, THF, triethylamine, room temp.; (e) NaCN, activated MnO_2, CH_3OH, room temp.

Scheme 4



(a) 1. $ZnCl_2$, BuLi, CH_2Cl_2, room temp., 2. acetyl chloride, $AlCl_3$, 0 °C−room temp.; (b) KOH, THF, ethylen glycol, reflux; (c) *N*,*N*-dimethylformamide di-*tert*-butyl acetal, benzene, reflux.

The 3-functionalized indole-5-carboxylic acid derivatives **40**−**44** were prepared in the same way as **17**, starting from the appropriate 3-substituted *tert*-butyl indole-5-carboxylates. The syntheses of the latter compounds are described in Schemes 3 and 4. Chlorination of *tert*-butyl indole-5-carboxylate (**29**)[27] with *N*-chlorosuccinimide[28] provided 3-chloro substituted indole **30**. The formylation of **29** in position 3 was achieved with oxalyl chloride/DMF in CH_2Cl_2. 3-Formyl intermediate **31** was converted to 3-cyano indole **33** via oxime **32** by reaction with hydroxylammonium chloride in pyridine followed by dehydration with 2-chloro-1-methylpyridinium iodide. Treatment of formylindole derivative **31** with sodium cyanide and activated MnO_2 provided diester intermediate **34**. The synthesis of *tert*-butyl 3-acetylindole-5-carboxylate (**38**) started from methyl indole-5-carboxylate (**35**) (Scheme 4). This was acetylated in position 3 to provide **36**. Hydrolysis of the methyl ester of **36** by KOH followed by esterfication of obtained carboxylic acid **37** with *N*,*N*-dimethylformamide di-*tert*-butyl acetal led to intermediate **38**.

The indole-3,5-dicarboxylic acid **50** was synthesized as shown in Scheme 5. Thus, methyl 3-formylindole-5-carboxylate (**45**) was converted to dimethylester **46** by reaction with NaCN/MnO_2. Transesterfication with benzyl alcohol/potassium benzylate gave dibenzyl ester **47**. The introduction of the 3-aryloxy-2-oxopropyl residue in position 1 of this indole compound was carried out in a fashion similar to that described for the synthesis of **16**. Hydrogenation of intermediate **49** with palladium on charcoal afforded **50**.

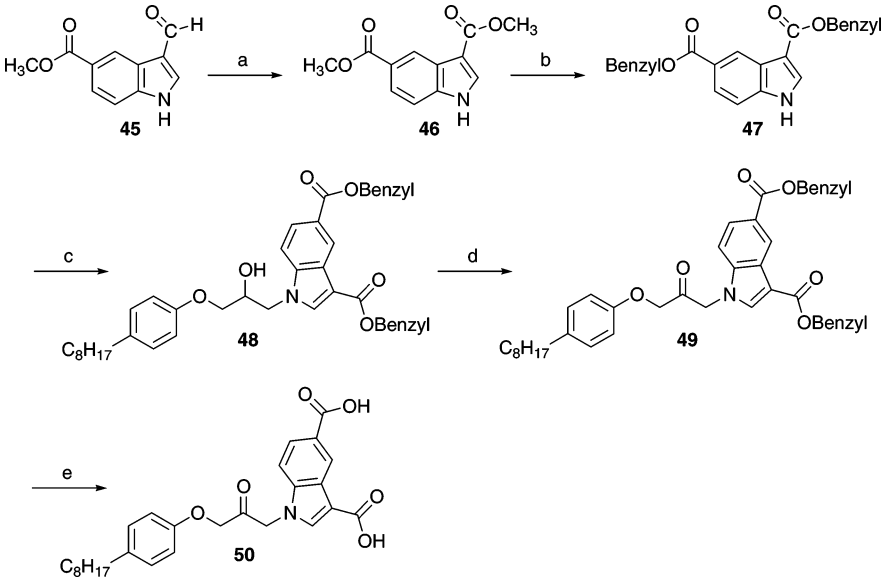
Decyloxy substituted target compounds **54** and **57** were prepared as shown in Scheme 6, starting from 2-(4-decyloxyphenoxymethyl)oxirane[22] and the appropriate indole-*tert*-butylester.

{1-[3-(4-Octylphenoxy)-2-oxopropyl]indol-3-yl}acetic acid (**59**) (Figure 3) was synthesized from *tert*-butyl indol-3-ylacetate applying the synthetic route described for the synthesis of **17**.

Evaluation of Inhibitors. All newly synthesized indole derivatives were evaluated in an assay applying cPLA$_2\alpha$ isolated from human platelets.[29] Like other lipases, cPLA$_2\alpha$ has evolved to work optimally at a lipid−water interface. For this reason, sonicated covesicles consisting of 1-stearoyl-2-arachidonoyl-*sn*-glycero-3-phosphocholine and 1,2-dioleoyl-*sn*-glycerol[30] were used as enzyme substrates. A possible problem of assays using such an aggregated form of phospholipids is that a test compound could inhibit the enzyme not by binding to its active site but by merely altering the substrate assembly and, hence, causing the enzyme to desorb from the lipid−water interface. To exclude this path of action, the mole fraction of the inhibitor in the interface has to be kept low.[31] Thus, the highest concentration of test compounds evaluated was 10 μM, whereas the concentration of the vesicle-forming lipids was 300 μM. The enzyme activity was determined by measuring the enzyme product arachidonic acid formed after an incubation time of 60 min with HPLC and UV detection at 200 nm. Several of the active compounds were also tested in cellular situations. In this assay, cPLA$_2\alpha$ of intact human platelets was stimulated with calcium ionophore A23187.[24] The cPLA$_2\alpha$-catalyzed liberation of arachidonic acid from membrane phospholipids was measured with HPLC and UV detection at 200 nm. To avoid the metabolism of arachidonic acid via the cyclooxygenase-1 and 12-lipoxygenase pathways, the dual cyclooxygenase/12-lipoxygenase inhibitor 5,8,11,14-eicosatetraynoic acid (ETYA) was added to the platelets in these experiments.

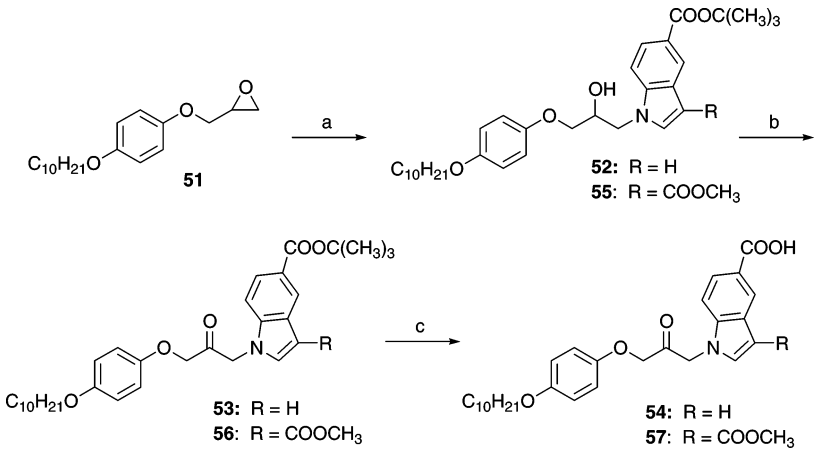
Besides, phorbolester 12-*O*-tetradecanoylphorbol-13-acetate (TPA) was used as an alternative stimulant. Although A23187

Scheme 5



(a) NaCN, activated MnO_2, CH_3OH, room temp.; (b) KH (30% dispersion in mineral oil), benzyl alcohol, 100 °C; (c) 2-(4-octylphenoxy)methyloxirane, NaH, DMF, 100 °C; (d) acetic anhydride, DMSO, room temp.; (e) H_2, Pd/C, THF, room temp.

Scheme 6



(a) NaH, DMF, *tert*-butyl indole-5-carboxylate, 60 °C, or 5-*tert*-butyl-3-methyl indole-3,5-dicarboxylate (**34**), 100 °C; (b) acetic anhydride, DMSO, room temp.; (c) TFA, CH_2Cl_2, room temp.

activates cPLA$_2\alpha$ by increasing the cytosolic Ca^{2+} concentration, TPA stimulates the enzyme via phosphorylation as a consequence of the activation of protein kinases, probably, in combination with the elevation of local Ca^{2+} levels.[32] The kinetics of arachidonic acid formation after stimulation with A23187 and TPA differ remarkably. Whereas A23187 causes a fast and short rise of the arachidonic acid liberation, TPA leads to a slower and long-lasting arachidonic acid release by the cells. For this reason, different incubation times were used for both stimuli: 1 min for A23187 and 60 min for TPA.

Because the lysis of the platelets by a test compound may falsely indicate enzyme inhibition, we also determined the cell lytic potency of each compound by turbidimetry.[33] In these experiments, it was found that none of the compounds showed cell lytic properties against human platelets at a concentration of 10 μM.

Results and Discussion

Our investigations started from the 1-substituted indole-2-carboxylic acid **13**. This compound possessed inhibitory properties against isolated and cellular cPLA$_2\alpha$ similar to those of structurally related 3-acylindole-2-carboxylic acid **4** (Figure 2). Although **13** inhibited the cellular arachidonic acid release after A23187 stimulation with an IC_{50} value somewhat below 10 μM, it was inactive against the isolated enzyme at 10 μM (Table 1). Shifting the carboxylic acid group from position 2 of the indole ring to the 3- or 4-positions (compounds **14** and **17**), slightly reduced the activity in the cellular assay. However, in contrast to **13**, both substances showed some inhibition of isolated cPLA$_2\alpha$ at 10 μM. A dramatic increase of inhibitory potency was registered when the carboxy moiety was moved to the 5-position of the indole. With an IC_{50} value of 0.035 μM against the isolated enzyme and an IC_{50} value of 0.41 μM against A23187-induced cellular arachidonic acid liberation, indole-5-carboxylic acid **18** was nearly as potent as AstraZeneca compound **3**, which had been tested as a reference (Table 1). Switching the carboxy group from the 5- to the 6-position led to a significant decrease in activity. The IC_{50} value of obtained compound **19** in the two assays was 1.1 and 4.7 μM, respectively.

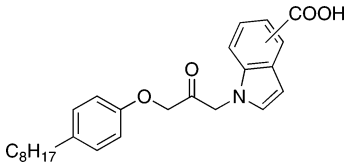
The importance of the 5-carboxy moiety for the eminent activity of **18** was seen when this group was omitted or replaced by several other substituents (Table 2). Unsubstituted indole derivative **20** and the compounds with a chloro, methyl, or methoxy groups in position 5 (**21**−**23**) were inactive against the isolated enzyme at 10 μM. Nitrile **24** and carboxylic acid methylester **25** possessed IC_{50} values greater than 10 μM in this assay, whereas the IC_{50} value of carbaldehyde **26** was 4.3 μM. The most active compound of this series was 5-carboxamide **28**. With an IC_{50} value of 0.12 μM, it was about three times less active against the isolated enzyme than 5-carboxylic acid **18**. Similar structure−activity relationships could be observed when the substances were tested in cellular situations with A23187 as the stimulant.

Next, we investigated the influence of substituents at position 3 of indole **18** on its enzyme inhibitory properties. Although the introduction of the lipophilic *tert*-butyl and chloro residues (**39**, **40**) caused a marked loss of activity against isolated cPLA$_2\alpha$, the more polar electron-withdrawing groups CN, CHO, $COCH_3$, and $COOCH_3$ (**41**−**44**) significantly increased inhibitory potency (Table 3). The most active compound of this series was the indole-5-carboxylic acid with a methylester moiety at position 3 (**44**). With an IC_{50} value of 0.0049 μM, this compound was about 7-fold more active in the assay with the isolated enzyme than the parent **18**. Interestingly, the cleavage of the ester group of **44** was accompanied by a large decrease of inhibitory potency. The IC_{50} value of dicarboxylic acid **50** was only 0.89 μM.

All derivatives of **18** with substituents at position 3 of the indole also inhibited the A23187-induced arachidonic acid release in human platelets. However, the IC_{50} values obtained with this assay were much higher than those in the test system with the isolated enzyme. Furthermore, the inhibition data did not correlate between the assays. Although 3-acetyl and 3-methoxycarbonyl derivatives **43** and **44** were significantly more active than the 3-unsubstituted indole **18** in the assay with isolated cPLA$_2\alpha$, they showed poorer activity than **18** in the cellular assay.

This decrease of activity in the cellular assay may be because of an impaired penetration of the compounds into the cells or the transformation of the compounds into inactive or less active metabolites in the cells. Besides, in our opinion, a third reason for the observed results must be considered. The indole-5-carboxylic acids synthesized are structurally related to the recently published 1,3-diaryloxypropan-2-ones such as **3**.[22] This compound was reported to form covalent bonds with the serine of the active site of cPLA$_2\alpha$ via its activated electrophilic ketone moiety. With the 3-aryloxy-2-oxopropyl-group in position 1 of the indole, our cPLA$_2\alpha$ inhibitors also possess such a serine trap. This can be concluded by the fact that the keto group of

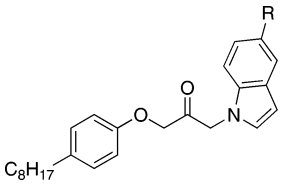
Table 1. Inhibition of cPLA$_2\alpha$ Activity



compd	position of the carboxylic acid moiety at the indole ring	vesicle assay with the isolated enzyme IC_{50} (μM)[a]	cellular assay with human platelets; stimulant A23187 IC_{50} (μM)[a]
13	2	n.a.[b]	8.0
14	3	>10[c]	>10[c]
17	4	>10[c]	>10[c]
18	5	0.035	0.41
19	6	1.1	4.7
3		0.011	0.25

[a] Values are the means of at least two independent determinations; errors are within ±20%. [b] Not active at 10 μM. [c] About 40% inhibition of enzyme activity at 10 μM.

Table 2. Inhibition of cPLA$_2\alpha$ Activity

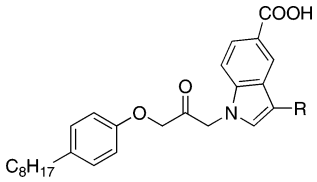


compd	R	vesicle assay with the isolated enzyme IC_{50} (μM)[a]	cellular assay with human platelets; stimulant A23187 IC_{50} (μM)[a]
18	COOH	0.035	0.41
20	H	n.a.[b]	>10[c]
21	CH_3	n.a.[b]	n.a.[b]
22	Cl	n.a.[b]	n.a.[b]
23	OCH_3	n.a.[b]	>10[d]
24	CN	>10[e]	>10[f]
25	$COOCH_3$	>10[g]	>10[h]
26	CHO	4.3	4.9
28	$CONH_2$	0.12	0.77

[a] Values are the means of at least two independent determinations; errors are within ±20%. [b] Not active at 10 μM. [c] Indicates 43% inhibition of enzyme activity at 10 μM. [d] Indicates 37% inhibition of enzyme activity at 10 μM. [e] Indicates 25% inhibition of enzyme activity at 10 μM. [f] Indicates 46% inhibition of enzyme activity at 10 μM. [g] Indicates 36% inhibition of enzyme activity at 10 μM. [h] Indicates 40% inhibition of enzyme activity at10 μM.

our active inhibitors easily forms hydrates as indicated by reversed-phase HPLC/MS investigations performed with aqueous eluents.[34] In the cellular assay applying A23187 as the stimulant, an incubation time of only 1 min was applied because of the fast and short rise of arachidonic acid liberation after the addition of A23187. This time is probably not sufficient for the quantitative formation of covalent bonds between serine trap inhibitors and the enzyme. In the assay with the isolated enzyme, the incubation time is much longer (60 min), and the inhibitors can exert their full effect against the enzyme. This assumption is supported by the results obtained with a cellular inhibitor assay using the phorbol ester TPA as the stimulant. Here, cellular liberation of arachidonic acid occurs during a longer period than that after stimulation with A23187, allowing the enzyme reaction to be performed for 60 min as in the assay with the isolated enzyme. Under these conditions, the cellular inhibition data of

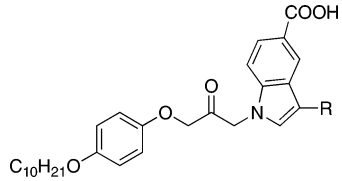
Table 3. Inhibition of cPLA$_2\alpha$Activity



compd	R	vesicle assay with the isolated enzyme IC_{50} (μM)[a]	cellular assay with human platelets: stimulant A23187 IC_{50} (μM)[a]	cellular assay with human platelets: stimulant TPA IC_{50} (μM)[a]
18	H	0.035	0.41	0.018
39	$C(CH_3)_3$	0.34	3.3	0.23
40	Cl	0.11	1.5	0.12
41	CN	0.015	0.37	0.011
42	CHO	0.016	0.38	0.0097
43	$COCH_3$	0.016	1.0	0.0064
44	$COOCH_3$	0.0049	1.4	0.0011
50	COOH	0.89	6.5	0.56
2		0.031	0.019	0.0045
3		0.011	0.25	0.0047

[a] Values are the means of at least two independent determinations; errors are within ±20%.

Table 4. Inhibition of cPLA$_2\alpha$ Activity



compd	R	vesicle assay with the isolated enzyme IC_{50} (μM)[a]	cellular assay with human platelets: stimulant A23187 IC_{50} (μM)[a]	cellular assay with human platelets: stimulant TPA IC_{50} (μM)[a]
54	H	0.020	0.21	0.0078
57	$COOCH_3$	0.0043	0.57	0.0009

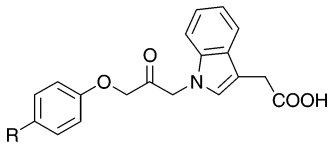
[a] Values are the means of at least two independent determinations; errors are within ± 20%.

our compounds and of reference compound **3** lie in the same order of magnitude as that of the data obtained in the enzymatic assay with isolated cPLA$_2\alpha$ (Table 3). Furthermore, the correlation of the IC_{50} values between the cellular and isolated enzyme assays is much better in this case. Interestingly, potent pyrrolidine cPLA$_2\alpha$ inhibitor **2**, which we have also tested as a reference, does not show such great discrepancies in the IC_{50} values in the cellular assays than our indoles and **3**. In summary, the high activity of our most active compounds in the platelet assay applying TPA as the stimulant makes it unlikely that the substances cannot penetrate into the platelets or that they are metabolized to inactive compounds in the platelets. The reason for the lower activity of the inhibitors in the cellular assay using A23187 for activation of cPLA$_2\alpha$ seems to lie in the slow-binding kinetics of the propane-2-ones.

Because AstraZeneca has found that a 4-decyloxyphenyl-moiety was the most preferable lipophilic residue in their cPLA$_2\alpha$ inhibitors, we replaced the 4-octylphenyl moiety in compound **18** and **44** by such a residue. Obtained derivative **54** was about 2-fold more active in the cellular assays as well as in the assay with the isolated enzyme than parent **18** (Table 4). For 3-substituted derivative **57**, a significant increase of activity could only be observed in the assay with A23187 compared with that of **44**. However, with an IC_{50} value of 0.0043 μM in

the isolated enzyme assay and 0.0009 μM in the cellular assay with TPA as the stimulant, compound **57** was found to be one of the most potent in vitro cPLA$_2\alpha$ inhibitors known today.

While this work was in progress, AstraZeneca reported that 1-indol-1-yl-propanone **58** (Figure 3) is an inhibitor of cPLA$_2\alpha$.[35] Closely related compound **59**, which we synthesized independently, inhibited cPLA$_2\alpha$ activity in our isolated enzyme assay with an IC_{50} value of 1.3 μM.



58: R = $OC_{10}H_{21}$
59: R = C_8H_{17}

Figure 3.

In summary, we have described the synthesis of novel, highly potent cPLA$_2\alpha$ inhibitors with indole-scaffolds. In future articles, we will report studies on the synthesis of less lipophilic cPLA$_2\alpha$ inhibitors of this series.

Experimental Section

Column chromatography was performed on Merck silica gel 60, 230−400 mesh (= flash chromatography) or 70−230 mesh. Preparative HPLC was performed on a RP18 column (Kromasil 100, 5 μm, 10 mm (i.d.) × 250 mm, protected with an analogously filled guard column of 10 mm (i.d.) × 50 mm; CS-chromatographie service, Langerwehe, Germany). Melting points were determined on a Büchi B-540 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Mercury Plus 400 spectrometer (400 MHz). Mass spectra were obtained on Finnigan GCQ and LCQ apparatuses applying electron beam ionization (EI) and electrospray ionization (ESI), respectively. The purity of the target compounds was determined using two diverse HPLC systems with UV detection at 254 nm. The first one applied an amino phase (Spherisorb NH_2, 5 μm, 4.0 mm (i.d.) × 250 mm; Latek, Heidelberg, Germany), eluting the compounds with an isohexane/THF gradient at a flow rate of 0.75 mL/min. In the second system, separation was performed using a cyano phase (LiChrospher 100 CN, 5 μm, 3.0 mm (i.d.) × 250 mm; Merck, Darmstadt, Germany) with a isohexane/THF gradient containing 0.1% trifluoroacetic acid at a flow rate of 0.5 mL/min. With the exception of **41**, all target compounds showed purities greater than 97% in both HPLC systems. The purity evaluated for **41** was 95% (cyano phase) and 99% (amino phase). Reference inhibitor **2** (*N*-{(2*S*,4*R*)-4-[biphenyl-2-ylmethyl-(isobutyl)amino]-1-[2-(2,4-difluorobenzoyl)benzoyl]pyrrolidin-2-ylmethyl}-3-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenyl]-acrylamide)[21] was a gift from Merckle (Blaubeuren, Germany). Reference inhibitor **3** (4-[3-(4-decyloxyphenoxy)-2-oxopropoxy]-benzoic acid) was synthesized according to published procedures.[22]

2-(4-Octylphenoxy)methyloxirane[26] (7). To a mixture of powdered KOH (88%, 3.10 g, 48.4 mmol), 4-octylphenol (5.00 g, 24.2 mmol) (**6**), and tetrabutylammonium bromide (0.81 g, 2.44 mmol) was added epichlorohydrin (13.5 g, 146 mmol). The reaction mixture was stirred at room temperature for 5 h, treated with water, and extracted three times with diethyl ether. The combined organic layers were washed with water and dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate, 95:5) to give **7** as a solid (6.34 g, 99%); mp 25 °C.

1-Bromo-3-(4-octylphenoxy)propan-2-ol (8). To a solution of **7** (1.17 g, 4.46 mmol) in dry CH_2Cl_2 (10 mL) was added silica gel (1.34 g) and lithium bromide (1.16 g, 13.4 mmol). The mixture was evaporated to near dryness and allowed to stand at room temperature for 3 h. After the addition of CH_2Cl_2, the reaction mixture was filtered through a cotton pad. The filtrate was evaporated, and the residue was treated with diethyl ether. The organic phase was washed with water and dried (Na_2SO_4), and the solvent was evaporated to give **8** as an oil (1.52 g, 99%).

[1-Bromo-3-(4-octylphenoxy)propan-2-yl]acetate (9). A cooled (0 °C) mixture of dry pyridine (0.41 g, 5.18 mmol) and dry CH_2Cl_2 (10 mL) was treated under a nitrogen atmosphere with acetyl chloride (0.41 g, 5.22 mmol) and stirred for 30 min. Then, a solution of **8** (0.50 g, 1.46 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise, and the reaction mixture was stirred an additional 3 h at 0 °C. After the addition of CH_2Cl_2, the organic phase was washed twice with 5% aqueous $NaHCO_3$ solution. The aqueous phases were re-extracted with CH_2Cl_2, and the combined CH_2Cl_2 phases were washed with water. The organic layer was separated, dried (Na_2SO_4), and concentrated. The residue was treated with toluene, and the solvent was evaporated. This procedure was repeated twice. Purification by silica gel chromatography (petroleum ether/ethyl acetate, 19:1) gave **9** as an oil (0.56 g, 99%).

***tert*-Butyl 1-[2-acetoxy-3-(4-octylphenoxy)propyl]indole-2-carboxylate (10).** A solution of *tert*-butyl indole-2-carboxylate[27] (0.33 g, 1.52 mmol) in dry DMSO (15 mL) was treated under a nitrogen atmosphere with potassium *tert*-butylate (0.18 g, 1.60 mmol) and stirred at 110 °C for 15 min. A solution of **9** (0.58 g, 1.51 mmol) in dry DMSO (15 mL) was added dropwise, and the reaction mixture was stirred at 110 °C for an additional 30 min. The mixture was cooled, diluted with brine, and extracted four times with diethyl ether. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 99:1) to give **10** as an oil (0.25 g, 32%).

***tert*-Butyl 1-[2-hydroxy-3-(4-octylphenoxy)propyl]indole-2-carboxylate (11).** A solution of **10** (0.21 g, 0.40 mmol) in dry methanol (10 mL) was treated under a nitrogen atmosphere with 0.5 M sodium methoxide in methanol (1.60 mL). The mixture was stirred for 15 min at room temperature, concentrated approximately to one-half of its original volume, and diluted with diethyl ether. The organic solution was washed with half-saturated brine and dried (Na_2SO_4), and the solvent was evaporated. The residue was separated by silica gel chromatography (petroleum ether/ethyl acetate, 19:1) to give **11** as an oil (0.15 g, 78%).

***tert*-Butyl 1-[3-(4-octylphenoxy)-2-oxopropyl]indole-2-carboxylate (12).** Acetic anhydride (1.02 g, 9.99 mmol) was added to dry DMSO (10 mL), and the mixture was stirred under a nitrogen atmosphere at room temperature for 10 min. Then, this solution was added dropwise to a solution of **11** (120 mg, 0.25 mmol) in dry DMSO (10 mL). The mixture was stirred under a nitrogen atmosphere for 8 h and poured into a mixture of 5% aqueous $NaHCO_3$ and brine (1:1). After 10 min, the mixture was extracted four times with diethyl ether. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate, 49:1) to give **12** as an oil (113 mg, 96%).

1-[3-(4-Octylphenoxy)-2-oxopropyl]indole-2-carboxylic Acid (13). To the solution of **12** (46 mg, 0.096 mmol) in dry CH_2Cl_2 (10 mL) was added trifluoroacetic acid (1.49 g, 13 mmol), and the mixture was stirred at room temperature for 1.5 h. Then, the reaction mixture was concentrated to dryness. The residue was treated twice with toluene, and the solvent was evaporated each time. The residue was recrystallized from petroleum ether/ethyl acetate (2:1) to give **13** as a white solid (31 mg, 77%); mp 173 °C.

1-[3-(4-Octylphenoxy)-2-oxopropyl]indole-3-carboxylic Acid (14). Compound **14** was prepared from *tert*-butyl indole-3-carboxylate utilizing the reaction sequence described for the synthesis of **13**; mp 182−183 °C.

***tert*-Butyl 1-[2-hydroxy-3-(4-octylphenoxy)propyl]indole-4-carboxylate (15).** Under a nitrogen atmosphere, a suspension of NaH (60% in mineral oil; 48 mg, 1.20 mmol) in dry DMF (10 mL) was stirred at room temperature for 10 min. After the addition of a solution of *tert*-butyl indole-4-carboxylate[27] (0.25 g, 1.15 mmol) in dry DMF (10 mL), the mixture was stirred for 1 h. A solution of 2-(4-octylphenoxymethyl)oxirane (**7**) (0.30 g, 1.14 mmol) in dry DMF (10 mL) was added dropwise at room temperature, and the reaction mixture was heated at 60 °C for 3 h. After it was cooled

to room temperature, the mixture was treated with half-saturated brine and extracted with diethyl ether four times. The combined organic phases were washed three times with half-saturated brine and dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 9:1) followed by chromatography on an octadecyl reversed-phase material (acetonitrile/H_2O, 4:1) to give **15** as an oil (0.36 g, 66%).

***tert*-Butyl 1-[3-(4-octylphenoxy)-2-oxopropyl]indole-4-carboxylate (16).** Acetic anhydride (1.55 g, 15.2 mmol) was added to dry DMSO (10 mL), and the mixture was stirred under a nitrogen atmosphere at room temperature for 10 min. Then, this solution was added dropwise to a solution of **15** (182 mg, 0.38 mmol) in dry DMSO (10 mL). The mixture was stirred for 15 h under a nitrogen atmosphere and poured into a mixture of 5% aqueous $NaHCO_3$ and half-saturated brine (1:1). After 10 min, the mixture was extracted four times with diethyl ether. The combined organic phases were washed three times with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 93:7) to give **16** as a solid (131 mg, 71%); mp 100 °C.

1-[3-(4-Octylphenoxy)-2-oxopropyl]indole-4-carboxylic Acid (17). To the solution of **16** (63 mg, 0.132 mmol) in dry CH_2Cl_2 (15 mL) was added trifluoroacetic acid (1.1 g, 9.8 mmol), and the mixture was stirred at room temperature for 2 h. Then, the reaction mixture was concentrated to dryness. The residue was treated three times with petroleum ether/ethyl acetate (1:2), and the solvents were evaporated each time. The residue was recrystallized from petroleum ether/ethyl acetate (2:1) to give **17** as a solid (48 mg, 86%); mp 160−161 °C.

Compounds **18** and **19** were prepared in a manner similar to that described for the synthesis of **17**, utilizing the appropriate *tert*-butyl indolecarboxylates and purifying by the method indicated.

1-[3-(4-Octylphenoxy)-2-oxopropyl]indole-5-carboxylic Acid (18). Compound **18** was purified by RP-HPLC, applying acetonitrile/H_2O (4:1) as the mobile phase. The eluates were concentrated under reduced pressure until most of the acetonitrile was removed. Freeze-drying the remaining solution gave **18** as a solid; mp 122−124 °C.

1-[3-(4-Octylphenoxy)-2-oxopropyl]indole-6-carboxylic Acid (19). The purification of **19** was performed by RP-HPLC as described for **18**, except that acetonitrile/H_2O (9:1) was used as the eluent; mp 180 °C.

Compounds **20**−**26** were prepared in a manner similar to that described for the synthesis of **16** utilizing the appropriate indole and purified by the method indicated. In case of the synthesis of **23**, the coupling of 5-methoxyindole with **7** was performed at room temperature with protection from light.

1-Indol-1-yl-3-(4-octylphenoxy)propan-2-one (20). Purification by silica gel chromatography (petroleum ether/ethyl acetate, 19:1) and recrystallization from petroleum ether gave **20** as a solid; mp 65 °C.

1-(5-Methylindol-1-yl)-3-(4-octylphenoxy)propan-2-one (21). Purification by silica gel chromatography (petroleum ether/ethyl acetate, 97:3) gave **21** as a solid; mp 75 °C.

1-(5-Chloroindol-1-yl)-3-(4-octylphenoxy)propan-2-one (22). Purification by silica gel chromatography (petroleum ether/ethyl acetate, 19:1) and recrystallization from petroleum ether gave **22** as a solid; mp 77 °C.

1-(5-Methoxyindol-1-yl)-3-(4-octylphenoxy)propan-2-one (23). Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate, 19:1) gave **23** as a solid; mp 85 °C.

1-[3-(4-Octylphenoxy)-2-oxopropyl]indole-5-carbonitrile (24). Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate, 9:1) and recrystallization from petroleum ether/ethyl acetate (19:1) gave **24** as a solid; mp 96 °C.

Methyl 1-[3-(4-octylphenoxy)-2-oxopropyl]indole-5-carboxylate (25). Recrystallization from petroleum ether/ethyl acetate (47:3) gave **25** as a solid; mp 118 °C.

1-[3-(4-Octylphenoxy)-2-oxopropyl]indole-5-carbaldehyde (26). Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate, 9:1) gave **26** as a solid; mp 96 °C.

1-[2-Hydroxy-3-(4-octylphenoxy)propyl]indole-5-carboxamide (27). 0.18 g (0.44 mmol) of 1-[2-hydroxy-3-(4-octylphenoxy)-propyl]indole-5-carbonitrile, previously synthesized from indole-5-carbonitrile and 2-(4-octylphenoxy)methyloxirane (**7**) using a method similar to that for **15**, was dissolved in *tert*-butyl alcohol (15 mL) and treated with 0.23 g (3.6 mmol) powdered KOH (88%). The mixture was heated under reflux for 11 h. The reaction mixture was cooled, diluted with water, acidified with 1 M HCl, and extracted three times with diethyl ether. The combined organic phases were washed with brine and water, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate, 1:1) to give **27** as a solid (0.13 g, 70%); mp 118−119 °C.

1-[3-(4-Octylphenoxy)-2-oxopropyl]indole-5-carboxamide (28). Compound **27** was oxidized to **28** using the procedure described for the preparation of **16**. The product was recrystallized from petroleum ether/ethyl acetate (1:1) and further purified by RP-HPLC applying acetonitrile/H_2O (4:1) as the mobile phase. The eluates were concentrated under reduced pressure until most of the acetonitrile was distilled off. The remaining solvent was removed by freeze-drying, yielding **28** as white solid; mp 158−159 °C.

***tert*-Butyl 3-chloroindole-5-carboxylate (30).** A solution of 389 mg (1.79 mmol) of *tert*-butyl indole-5-carboxylate[27] (**29**) in methanol (12 mL) was treated with 335 mg (2.50 mmol) *N*-chlorosuccinimide and stirred overnight at room temperature. The solvent was distilled off and the residue dissolved in 15 mL of ethyl acetate. The organic solution was washed twice with 1 M aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated. The residue was purified by silica gel chromatography (hexane/ethyl acetate, 9:1) to give **30** as a solid (190 mg, 42%); mp 120 °C.

***tert*-Butyl 3-formylindole-5-carboxylate (31).** A solution of oxalyl chloride (0.4 mL, 4.87 mmol) in dry CH_2Cl_2 (15 mL) was treated at 0 °C with a solution of dry DMF (0.4 mL) in dry CH_2Cl_2 (15 mL). The mixture was stirred at 0 °C for 20 min. After the addition of *tert*-butyl indole-5-carboxylate[27] (**29**) (1.0 g, 4.6 mmol), the mixture was allowed to warm to room temperature and then stirred for a further 20 min. The solvent was evaporated and the residue treated with THF (40 mL) and 20% aqueous ammonium acetate (50 mL). The mixture was heated under reflux for 30 min, cooled, treated with 5% aqueous $NaHCO_3$, and extracted three times with ethyl acetate. The combined organic phases were washed with brine and dried (Na_2SO_4), and the solvent was evaporated. The residue was recrystallized from hexane/ethyl acetate to yield **31** as a solid (0.81 g, 71%); mp 190 °C.

***tert*-Butyl 3-(hydroxyiminomethyl)indole-5-carboxylate (32).** Hydroxylammonium chloride (0.28 g, 4.08 mmol) was added to a solution of **31** in pyridine (10 mL) in several portions. The mixture was heated under reflux for 5 h. Then, the solvent was distilled off. The residue was dissolved in ethyl acetate and washed with 1 M HCl. The organic phase was separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with water, dried (Na_2SO_4), and concentrated. The residue was treated several times with hexane/ethyl acetate (1:1), and the solvents were evaporated each time to give a mixture of (*E*)- and (*Z*)-*tert*-butyl 3-(hydroxyiminomethyl)indole-5-carboxylate as a solid (0.50 g, 94%); mp 188−189 °C (decomp.).

***tert*-Butyl 3-cyanoindole-5-carboxylate (33).** 2-Chloro-1-methylpyridinium iodide (0.29 g, 1.14 mmol) was added under nitrogen to a solution of **32** (0.27 g, 1.04 mmol) in dry THF (30 mL). The mixture was stirred at room temperature for 10 min, then treated dropwise with triethylamine (0.55 mL, 3.94 mmol), and stirred for a further 20 h at room temperature. Dilute HCl (5%, 20 mL) was added, and the mixture was extracted three times with ethyl acetate. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography on silica gel (hexane/ethyl acetate, 3:2) to give **33** as a solid (0.21 g, 87%); mp 188−189 °C.

5-*tert*-Butyl-3-methyl indole-3,5-dicarboxylate (34). A solution of **31** (0.70 g, 2.83 mmol) in methanol (30 mL) was treated with NaCN (0.70 g, 14.3 mmol). Then, activated MnO_2 (4.92 g, 57.2 mmol) was added in several portions, and the reaction mixture was stirred at room temperature for 48 h. After the addition of CH_2Cl_2 (80 mL) and Celite (5 g), the suspension was filtered off by suction and the residue washed with CH_2Cl_2. The combined filtrates were subsequently washed with saturated aqueous $FeSO_4$ solution and brine, dried (Na_2SO_4), and concentrated to give **34** as a solid (0.74 g, 94%); mp 196 °C.

Methyl 3-acetylindole-5-carboxylate (36). To a mixture of $ZnCl_2$ solution in dry diethyl ether (2.2 M, 4.2 mL) and dry CH_2Cl_2 (20 mL) was slowly added under nitrogen at 0 °C a solution of butyllithium in dry hexane (1.6 M, 5.6 mL). The mixture was allowed to warm to room temperature, stirred for 1 h at room temperature, treated with a solution of methyl indole-5-carboxylate (**35**) (1.5 g, 8.6 mmol) in dry CH_2Cl_2 (20 mL), and stirred again for 1 h. The reaction mixture was cooled to 0 °C, acetyl chloride (1.28 mL, 18 mmol) was added, and stirring was continued for 1 h at room temperature. Then, the mixture was treated with $AlCl_3$ (0.93 g, 7.0 mmol) and further stirred for 1 h. After the addition of half-saturated brine and THF (20 mL), the mixture was extracted four times with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate, 3:2) to give **36** as a solid (0.70 g, 38%); mp 235−236 °C.

3-Acetylindole-5-carboxylic Acid (37). Methyl 3-acetylindole-5-carboxylate (**36**) (0.69 g, 3.16 mmol) was dissolved in THF (10 mL) and ethylene glycol (10 mL) by heating. After the addition of KOH (88%, 7.08 g, 0.13 mol), the mixture was heated under reflux for 30 min. The THF was distilled off under reduced pressure, and the remaining solution was acidified at 0 °C with dilute HCl. The precipitate formed was filtered off by suction, washed with water, and dried to provide **37** as a solid (0.64 g, 99%); mp 364 °C.

***tert*-Butyl 3-acetylindole-5-carboxylate (38).** A solution of *N*,*N*-dimethylformamide di-*tert*-butyl acetal (90% purity, 6.3 mL, 26.3 mmol) in dry benzene (50 mL) was added dropwise under nitrogen to the refluxing suspension of **37** (1.34 g, 6.60 mmol) in dry benzene (100 mL) within 30 min. The solution was refluxed for a further 30 min, cooled, diluted with diethyl ether, and washed with $NaHCO_3$ solution (5%) and brine. The organic layer was dried (Na_2SO_4) and the solvent evaporated. The residue was purified by silica gel chromatography (hexane/ethyl acetate, 3:2) to give **38** (0.39 g, 23%) as a solid; mp 214 °C.

3-*tert*-Butyl-1-[3-(4-octylphenoxy)-2-oxopropyl]indole-5-carboxylic Acid (39). Compound **39** was a side product of the synthesis of **18**. It was separated during the course of the RP-HPLC purification of **18**; mp 146−147 °C.

Compounds **40**−**44** were prepared in a manner similar to that described for the synthesis of **17**, starting from the appropriate 3-substituted *tert*-butyl indole-5-carboxylates (**30**, **33**, **31**, **38**, and **34**). The coupling of these compounds with **7** was performed at 60 °C (**30**, **33**) and 120 °C (**31**, **34**, **38**), applying a reaction time of 8−26 h. The target compounds were purified by the method indicated.

3-Chloro-1-[3-(4-octylphenoxy)-2-oxopropyl]indole-5-carboxylic Acid (40). Recrystallization from hexane/THF gave **40** as a solid; mp 157 °C.

3-Cyano-1-[3-(4-octylphenoxy)-2-oxopropyl]indole-5-carboxylic Acid (41). Recrystallization from hexane/ethyl acetate gave **41** as a solid; mp 197−198 °C (decomp.).

3-Formyl-1-[3-(4-octylphenoxy)-2-oxopropyl]indole-5-carboxylic Acid (42). The purification of **42** was performed by RP-HPLC as described for **18** except that acetonitrile/H_2O (9:1) was used as the eluent; mp 193 °C.

3-Acetyl-1-[3-(4-octylphenoxy)-2-oxopropyl]indole-5-carboxylic Acid (43). Recrystallization from hexane/THF gave **43** as a solid; mp 197 °C.

3-Methylhydrogen 1-[3-(4-octylphenoxy)-2-oxopropyl]indole-3,5-dicarboxylate (44). Recrystallization from hexane/THF gave **44** as a solid; mp 208 °C.

Dimethyl indole-3,5-dicarboxylate (46). The treatment of methyl 3-formylindole-5-carboxylate (**45**) (2.30 g, 11.3 mmol) according to the procedure described above for the preparation of **34** provided **46** as a solid (0.75 g, 29%); mp 223−225 °C (decomp.).

Dibenzyl indole-3,5-dicarboxylate (47). A mixture of KH (30% dispersion in mineral oil, 0.10 g, 0.75 mmol) and dry benzyl alcohol (10 mL) was stirred at room temperature for 15 min. After the addition of **46** (0.70 g, 3.0 mmol), the mixture was heated at 100 °C for 5 h. Then, the reaction mixture was cooled, diluted with brine, and extracted three times with diethyl ether. The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was treated twice with methanol, and the solvent was evaporated each time to give **47** as a solid (0.58 g, 50%); mp 173−174 °C.

Dibenzyl 1-[2-hydroxy-3-(4-octylphenoxy)propyl]indol-3,5-dicarboxylate (48). Starting from **7** (0.30 g,1.17 mmol) and **47** (0.45 g, 1.17 mmol), **48** was prepared in a manner similar to that described for the synthesis of **15**. The reaction mixture was heated at 100 °C for 40 h. Purification by silica gel chromatography (hexane/ethyl acetate, 4:1) gave **48** as a solid (0.20 g 27%); mp 102−103 °C.

Dibenzyl 1-[3-(4-octylphenoxy)-2-oxopropyl]indole-3,5-dicarboxylate (49). Compound **49** was prepared from **48** (160 mg, 0.25 mmol) in a manner similar to that described for the synthesis of **16**. Purification by flash chromatography on silica gel (hexane/ethyl acetate, 4:1) gave **49** (63 mg, 39%) as an oil.

1-[3-(4-Octylphenoxy)-2-oxopropyl]indole-3,5-dicarboxylic Acid (50). A solution of **49** (54.0 mg, 0.08 mmol) in THF (10 mL) was stirred at room temperature with Pd/C (10%; 15 mg) under H_2 supplied by a balloon for 5 h. The mixture was filtered through a cotton pad and concentrated to give **50** as a solid (21 mg, 56%); mp 225−225.5 °C (decomp.).

1-[3-(4-Decyloxyphenoxy)-2-oxopropyl]indole-5-carboxylic Acid (54). Compound **54** was prepared in a manner similar to that described for the synthesis of **17**, starting from *tert*-butyl indole-5-carboxylate[27] and 2-(4-decyloxyphenoxymethyl)oxirane (**51**).[22] It was purified by RP-HPLC as described for the purification of **18** using acetonitrile/H_2O (9:1) as the eluent; mp 137 °C.

5-*tert*-Butyl-3-methyl 1-[3-(4-decyloxyphenoxy)-2-hydroxypropyl]indole-3,5-dicarboxylate (55). A solution of 5-*tert*-butyl-3-methyl indole-3,5-dicarboxylate (**34**) (0.50 g, 1.82 mmol) in dry DMF (20 mL) was reacted with NaH (60% in mineral oil; 73 mg, 3.03 mmol) in dry DMF (20 mL) and a solution of 2-(4-decyloxyphenoxymethyl)oxirane (**51**)[22] (0.56 g, 1.82 mmol) in dry DMF (20 mL) in a manner similar to that described for the synthesis of **15**, except that the reaction mixture was heated at 100 °C for 26 h. Purification was performed by flash chromatography on silica gel (petroleum ether/ethyl acetate, 7:3) followed by chromatography on an octadecyl reversed-phase material (acetonitrile/H_2O, 4:1) to give **55** as an oil (0.26 g, 25%).

5-*tert*-Butyl-3-methyl 1-[3-(4-decyloxyphenoxy)-2-oxopropyl]-indole-3,5-dicarboxylate (56). A solution of **55** (240 mg, 0.41 mmol) in dry DMSO (10 mL) was treated with a mixture of acetic anhydride (1.69 g, 16.5 mmol) and dry DMSO (10 mL) in a manner similar to that described for the synthesis of **16**, except that the reaction time was 17 h. Purification was achieved by flash chromatography on silica gel (hexane/ethyl acetate, 4:1) to give **56** as an oil (135 mg, 56%).

3-Methylhydrogen 1-[3-(4-decyloxyphenoxy)-2-oxopropyl]indole-3,5-dicarboxylate (57). A solution of **56** (107 mg, 0.18 mmol) in dry CH_2Cl_2 (20 mL) was treated with trifluoroacetic acid (1.68 g, 14.7 mmol) in a manner similar to that described for the synthesis of **17**, except that the reaction time was 3 h. The reaction mixture was concentrated to dryness. The residue was treated twice with hexane, and the solvent was evaporated each time. The residue was recrystallized from hexane/ethyl acetate to give **57** as a solid (79 mg, 82%).

{1-[3-(4-Octylphenoxy)-2-oxopropyl]indol-3-yl}acetic Acid (59). Indol-3-ylacetic acid was converted to its *tert*-butylester with *N*,*N*-dimethylformamide di-*tert*-butyl acetal applying the method described for the synthesis of **38**. *tert*-Butyl indol-3-yl acetate was

reacted with 2-(4-octylphenoxymethyl)oxirane (**7**) at room temperature for 14 h using a procedure analogous to the procedure described for the synthesis of **15**. The intermediate obtained was converted to **59** using the procedures for the synthesis of **16** and **17**. Compound **59** was purified by RP-HPLC applying acetonitrile/H_2O/formic acid (85:15:0.05) as the mobile phase. The eluates were concentrated under reduced pressure until most of the acetonitrile was removed. Freeze-drying the remaining solution gave **59** as a solid; mp 121−122 °C.

Assay of cPLA$_2\alpha$ Inhibition Using the Isolated Enzyme. The inhibition of cPLA$_2\alpha$ isolated from human platelets was performed as previously described.[29] Briefly, sonicated co-vesicles consisting of 1-stearoyl-2-arachidonoyl-*sn*-glycero-3-phosphocholine (0.2 mM) and 1,2-dioleoyl-*sn*-glycerol (0.1 mM) were used as enzyme substrates. The cPLA$_2\alpha$ activity was determined by measuring the arachidonic acid released by the enzyme with reversed-phase HPLC and UV detection at 200 nm after cleaning up the samples using solid-phase extraction.

Ionophore- and Phorbolester-Induced Arachidonic Acid Release from Human Platelets. The ability of the compounds to inhibit cPLA$_2\alpha$ activity in intact cells was determined by monitoring calcium ionophore A23187-induced and phorbolester-induced arachidonic acid release from human platelets by HPLC with UV detection.

The inhibition of the A23187-induced arachidonic acid release was measured according to a procedure previously described, applying a final A23187 concentration of 1 μM and an incubation time of 1 min.[24] Deviating, the HPLC separation of arachidonic acid was achieved on a RP18 multospher 100 column, 3 μm, 3.0 mm (i.d.) × 125 mm, with a RP18 multospher 100 guard column, 5 μm, 3.0 mm (i.d.) × 20 mm (CS-chromatographie service, Langerwehe, Germany). The mobile phase consisted of an acetonitrile/$(NH_4)_2HPO_4$ buffer (10 mM) adjusted to pH 7.4 with *ortho*-phosphoric acid (50:50, v/v). The flow rate was 0.33 mL/min, and the injected sample volume was 300 μL. The detection wavelength was 200 nm, applying a Waters 2487 UV-detector. After each run, the column was washed with 0.6 mL of methanol. 3-(4-Decyloxyphenyl)propanoic acid was applied as internal standard.

The inhibition of the phorbolester (TPA)-induced arachidonic acid release was measured similarly, applying a final TPA concentration of 2 μM and an incubation time of 60 min. The sample volume injected to HPLC was 600 μL. Control incubations in the absence of the stimulant TPA were carried out in parallel and used to calculate specific hydrolysis. In intact human platelets, iPLA$_2$ is not involved in TPA-induced arachidonic acid release because the iPLA$_2$ inhibitor bromoenol lactone (BEL) did not reduce arachidonic acid liberation at a test concentration of 10 μM.

Supporting Information Available: ^{1}H NMR and MS data of all compounds, purity of all target compounds evaluated with two diverse HPLC systems, and HRMS data of target compounds **42**−**44**, **54**, and **57**. This material is available free of charge via the Internet at http://pubs.acs.org.

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