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1-(5-Carboxy- and 5-carbamoylindol-1-yl)propan-2-ones as inhibitors of human cytosolic phospholipase $A_2\alpha$: Bioisosteric replacement of the carboxylic acid and carboxamide moiety

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Abstract—Indole-5-carboxylic acids and -carboxamides with 3-aryloxy-2-oxopropyl residues in position 1 were previously reported to be potent inhibitors of cytosolic phospholipase $A_2\alpha$ ($cPLA_2\alpha$) isolated from human platelets. In continuation of our attempts to develop novel $cPLA_2\alpha$ inhibitors, a number of derivatives of these substances characterized by bioisosteric replacement of the carboxylic acid and carboxamide functionality, respectively, were prepared. The results of the biological evaluation of the obtained compounds enabled us to gain further insight into structural features critical for $cPLA_2\alpha$ inhibition.

1. Introduction

Cytosolic phospholipase $A_2\alpha$ ($cPLA_2\alpha$) is an esterase that selectively cleaves the *sn*-2 position of arachidonoyl-glycerophospholipids of biomembranes to generate free arachidonic acid and lysophospholipids.[1] Arachidonic acid in turn is metabolized to a variety of inflammatory mediators including prostaglandins and leukotrienes. Lysophospholipids with an alkyl ether moiety at the *sn*-1 position can be acetylated to platelet activating factor (PAF), another mediator of inflammation.[2] Thus, inhibition of $cPLA_2\alpha$ is considered as an attractive target for the design of new anti-inflammatory drugs.[3–5]

First-generation inhibitors of $cPLA_2\alpha$ were analogues of arachidonic acid with the COOH group replaced by $COCF_3$ ($AACOCF_3$, **1**) or $PO(OCH_3)F$ (MAFP).[3] Compounds with very high in vitro $cPLA_2\alpha$-inhibitory potency reported later are thiazolidinedione compounds from Shionogi[6] and propan-2-ones, such as **2**, from AstraZeneca (Fig. 1).[7] Recently, we have found that 1-[3-(4-octylphenoxy)-2-oxopropyl]indoles, which are structurally related to **2**, as compounds **3**–**5**, are also potent inhibitors of $cPLA_2\alpha$.[8] Structure–activity relationship studies revealed that a carboxylic acid or carboxamide moiety in position 5 of the indole nucleus is important for a pronounced inhibition of the enzyme by these substances.

Since bioisosteric replacement is a valuable tool in lead optimization and structure–activity relationship studies,[9] we now replaced the carboxylic acid and carboxamide substituents of **4** and **5**, respectively, by bioisosteric groups.

2. Chemistry

Indole-5-carboxamide derivatives **12** and **13** were synthesized by the route outlined in Scheme 1. Indole-5-carboxylic acid (**6**) was reacted with *N*,*N*′-carbonyldiimidazole to give the stable imidazolide **7**,[10] which upon reaction with methylamine and dimethylamine, respectively, afforded the *N*-methylated indole-5-carboxamides **8** and **9**.[11,12] These compounds were coupled with 2-(4-octylphenoxy)methyloxirane[8] in DMF in the presence of NaH. The alcohol moieties of the obtained intermediates **10** and **11** were oxidized by the Albright–Goldman procedure with acetic anhydride/DMSO to provide the target compounds **12** and **13**.

Keywords: Cytosolic phospholipase $A_2\alpha$ inhibitors; Indol-1-ylpropan-2-ones; Bioisosteric replacement.
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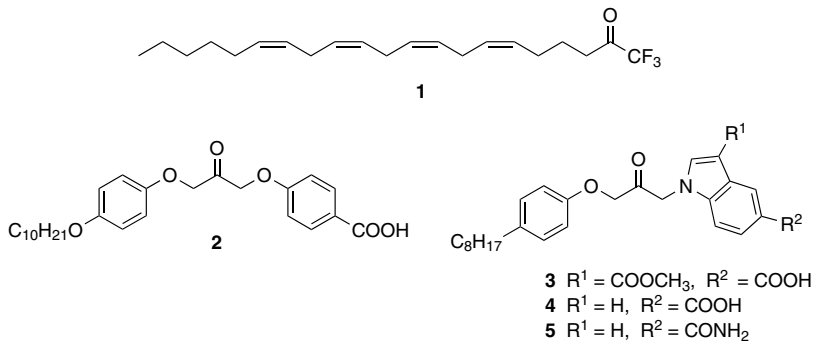
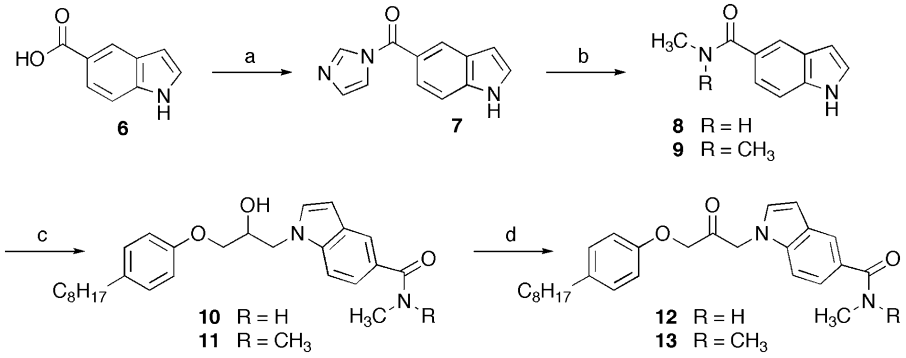


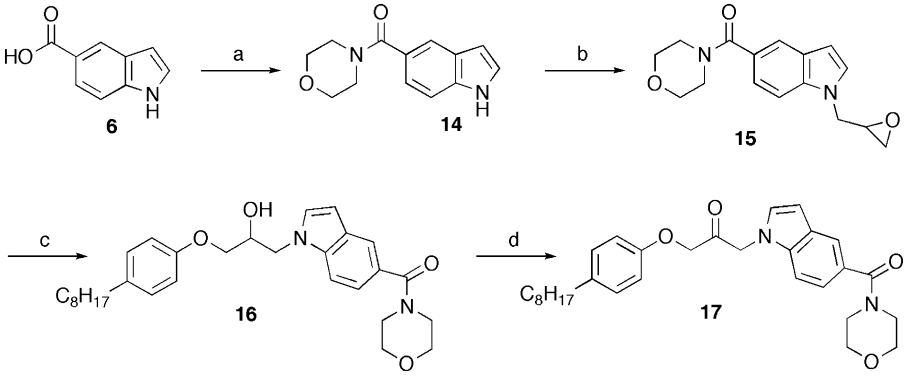
Figure 1.



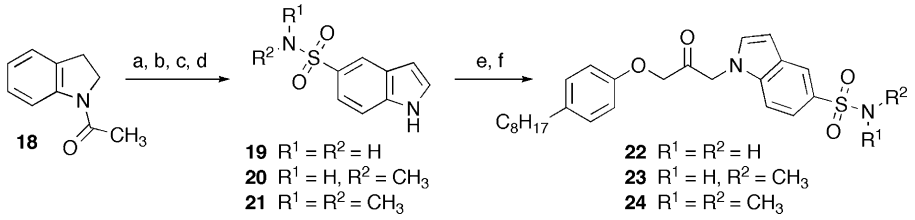
Scheme 1. Reagents and conditions: (a) *N*,*N*′-Carbonyldiimidazole, THF, room temperature; (b) methylamine HCl or dimethylamine HCl, triethylamine, THF, aqueous $NaHCO_3$, room temperature; (c) 2-(4-octylphenoxymethyl)oxirane, NaH, DMF, 100 °C; (d) acetic anhydride, DMSO, room temperature.

The preparation of morpholinocarbonyl-substituted indole derivative **17** is shown in Scheme 2. Treatment of indole-5-carboxylic acid with *N*,*N*′-carbonyldiimidazole and morpholinium chloride/triethylamine gave 5-morpholinocarbonylindole (**14**).[13] This compound was further reacted with epichlororhydrin to afford the epoxy intermediate **15**. Ring opening of **15** with 4-octylphenol was achieved without solvent in the presence of catalytic amounts of 4-dimethylaminopyridine. Oxidation of the resulting alcohol intermediate **16** to the desired ketone **17** was carried out with Dess–Martin reagent.

Indole-5-sulfonamides **19**–**21**[14–16] were synthesized starting from 1-acetylindoline by known reaction sequences involving chlorosulfonation with chlorosulfonic acid, sulfonamide formation with ammonia, methylamine or dimethylamine, deacetylation with concentrated HCl, and rearomatization of the indoline to the indole with 2,3-dichloro-5,6-dicyanobenzoquinone (Scheme 3). Reaction of **19**–**21** with 2-(4-octylphenoxy)methyloxirane as described for the synthesis of **10** and subsequent oxidation with acetic anhydride/DMSO or Dess–Martin reagent led to the target sulfonamides **22**–**24**.



Scheme 2. Reagents and conditions: (a) *N*,*N*′-Carbonyldiimidazole, THF, morpholinium chloride, triethylamine, room temperature; (b) epichlorohydrin, KOH, $Bu_4N^+Br^-$, room temperature; (c) 4-octylphenol, 4-dimethylaminopyridine, 95 °C; (d) Dess–Martin reagent, CH_2Cl_2, room temperature.



Scheme 3. Reagents and conditions: (a) Chlorosulfonic acid, 70 °C; (b) aqueous NH_3, THF, room temperature, or methylamine HCl, triethylamine, THF, aqueous $NaHCO_3$, reflux, or dimethylamine HCl, triethylamine, THF, aqueous $NaHCO_3$, reflux; (c) conc. HCl, dioxane, reflux; (d) 2,3-dichloro-5,6-dicyanobenzoquinone, dioxane, 80 °C; (e) 2-(4-octylphenoxymethyl)oxirane, NaH, DMF, 60 °C or room temp; (f) acetic anhydride, DMSO, room temperature, or Dess–Martin reagent, CH_2Cl_2, room temperature.

Indol-5-ylmethylidenethiazolidine-2,4-dione derivative **26** was prepared by treatment of indole-5-carbaldehyde **25** with thiazolidine-2,4-dione in toluene in the presence of catalytical amounts of piperidine and acetic acid, followed by oxidation with Dess–Martin reagent (Scheme 4).

Oxadiazoles **30** and **31** were synthesized in the same way as **12** starting from 5-(3-benzyl- and 3-ethyl-1,2,4-oxadiazol-5-yl)indole (**28** and **29**) (Scheme 5). The preparation of the latter compounds was achieved by reaction of methyl indole-5-carboxylate with *N*-hydroxy-2-phenylacetamidine[17] and *N*-hydroxypropionamidine,[18] respectively.

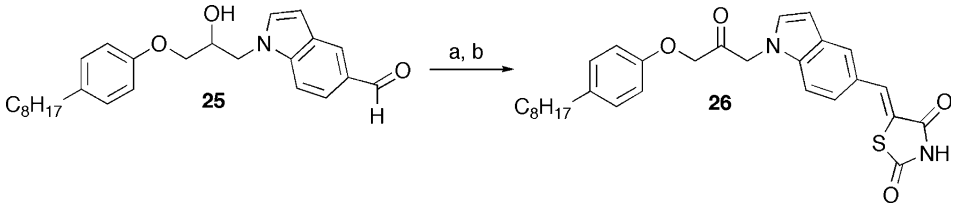
Scheme 6 outlines the synthesis of the target compounds with 4,5-dihydro-1,2,4-oxadiazol-5-one and 1*H*-tetrazole moieties **36** and **38**. Indole-5-carbonitrile (**32**) was alkylated in position 1 with epichlorohydrin to afford **33**. Coupling of this compound with 4-octylphenol in a fashion similar to that described for the synthesis of **16** provided the hydroxy intermediate **34**. This was converted to the oxadiazol-5-one **35** by subsequent treatment with hydroxylammonium chloride/NaOH and diethyl carbonate, and to the 1*H*-tetrazole **37** by reaction with trimethylsilyl azide/tetrabutylammonium fluoride. Dess–Martin-oxidation of **35** and **37** gave the desired compounds **36** and **38**.

3. Evaluation of inhibitors

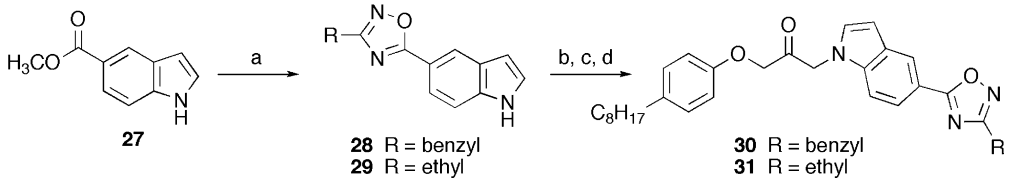
All newly synthesized indole derivatives were evaluated in an assay applying cPLA$_2\alpha$ isolated from human platelets.[19] Like other lipases, cPLA$_2\alpha$ has evolved to work optimally at a lipid–water interface. For this reason, sonicated covesicles consisting of 1-stearoyl-2-arachidonoyl-*sn*-glycero-3-phosphocholine and 1,2-dioleoyl-*sn*-glycerol were used as enzyme substrate. 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 merely by altering the substrate assembly and hence causing the enzyme to desorb from the lipid–water-interface. To exclude this way of action, the mole fraction of inhibitor in the interface has to be kept low.[20] Thus, the highest concentration of test compounds evaluated was 10 μM, while 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.

4. Results and discussion

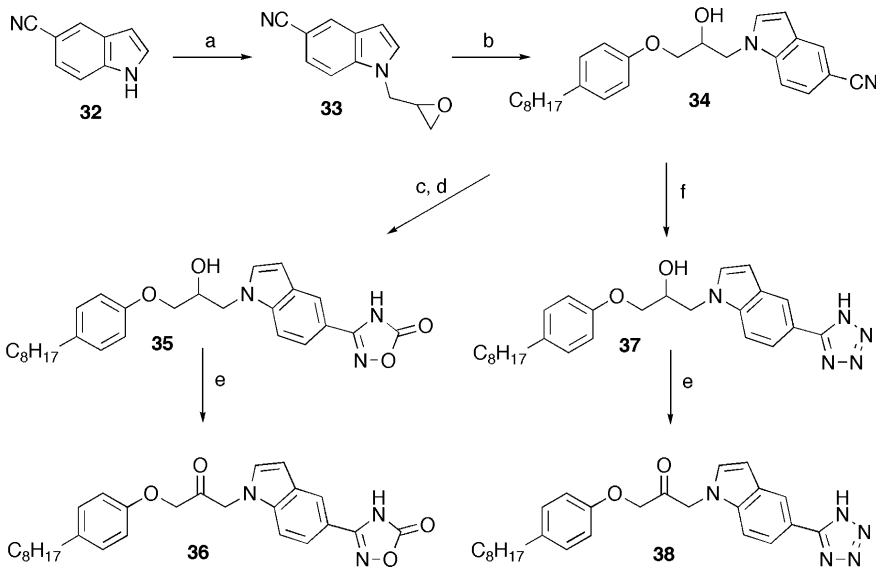
Bioisosteric replacement is a well-known medicinal chemistry technique. It consists of replacing one frag-



Scheme 4. Reagents and conditions: (a) Thiazolidine-2,4-dione, acetic acid, piperidine, toluene, reflux; (b) Dess–Martin reagent, CH_2Cl_2, THF, room temperature.



Scheme 5. Reagents and conditions: (a) *N*-Hydroxy-2-phenylacetamidine or *N*-hydroxypropionamidine, NaH, THF, reflux; (b) 2-(4-octylphenoxymethyl)oxirane, NaH, DMF, 60 °C; (c) acetic anhydride, DMSO, room temperature.

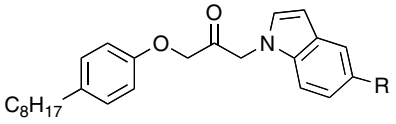


Scheme 6. Reagents and conditions: (a) Epichlorohydrin, KOH, $Bu_4N^+Br^-$, room temperature; (b) 4-octylphenol, 4-dimethylaminopyridine, 60 °C; (c) hydroxylammonium chloride, methanol, aqueous NaOH, reflux; (d) diethyl carbonate, NaOEt, ethanol, reflux; (e) Dess–Martin reagent, CH_2Cl_2, THF, room temperature; (f) trimethylsilyl azide, $Bu_4N^+F^-$ hydrate, 120 °C.

ment in a bioactive molecule with another fragment possessing similar spatial and electronic character. Bioisosteric transformation has been extensively and successfully used in the optimization of lead candidates in drug discovery.[9]

Indole-5-carboxylic acid **4** and its carboxamide derivative **5** have been found to be potent inhibitors of cPLA$_2\alpha$ with IC_{50}-values of 0.035 and 0.12 μM against the enzyme isolated from human platelets.[8] Since the carboxylic acid and carboxamide moieties of **4** and **5**, respectively, are important parts of the pharmacophore of these inhibitors, we now replaced these functionalities by several bioisosteric groups. First, we synthesized the *N*-methylated and *N*,*N*-dimethylated carboxamides **12** and **13**. With IC_{50}-values of 0.37 and 0.84 μM these compounds were about threefold and sevenfold less active than the unsubstituted parent **5** (Table 1). Replacement of the amide nitrogen by a morpholino substituent (**17**) decreased activity to a similar extent. Introduction of unsubstituted and methyl substituted sulfonamide residues also did not result in more active compounds. The sulfonamides **22**, **23**, and **24** possessed an IC_{50} against cPLA$_2\alpha$ in the range of 0.3–0.5 μM. In contrast

Table 1. Inhibition of cPLA$_2\alpha$-activity



Compound	R	Vesicle assay IC_{50}[a] (μM)
4	COOH	0.035
5	$CONH_2$	0.12
12	$CONHCH_3$	0.37
13	$CON(CH_3)_2$	0.84
17	Morpholin-4-ylcarbonyl	0.50
22	SO_2NH_2	0.39
23	SO_2NHCH_3	0.31
24	$SO_2N(CH_3)_2$	0.50
26	2,4-Dioxothiazolidin-5-ylidenemethyl	>10[b]
30	3-Benzyl-1,2,4-oxadiazol-5-yl	n.a.[c]
31	3-Ethyl-1,2,4-oxadiazol-5-yl	n.a.[c]
36	5-Oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl	3.5
38	1*H*-Tetrazol-5-yl	1.1
1		2.3
2		0.011
3		0.005

[a] Values are means of at least two independent determinations; errors are within ±20%.
[b] 29% inhibition at 10 μM.
[c] n.a., not active at 10 μM.

to the corresponding amides, the unsubstituted sulfonamide **22** was not significantly more active than the *N*-methylated compounds **23** and **24**.

Since a series of 3-methylidenethiazolidine-2,4-dione derivatives had been found to inhibit cPLA$_2\alpha$ very potently,[6] we synthesized a compound with such a residue in position 5 of the indole scaffold (**26**). This modification led to a drastic decrease of enzyme inhibition in our case. The IC_{50}-value of **26** was greater than 10 μM. 3-Benzyl- and 3-ethyl-1,2,4-oxadiazole residues, known as bioisosteric to amide groups, even led to a total loss of activity at a concentration of 10 μM when introduced instead of the 5-carboxamide residue. With the introduction of a 4,5-dihydro-1,2,4-oxadiazol-5-one system some inhibitory potency could be regained; the IC_{50} of compound **36** was 3.5 μM.

Since the tetrazole group possesses bioisosteric relationships to the carboxylic acid moiety, we finally synthesized 1*H*-tetrazole **38**. With an IC_{50} of 1.1 μM this compound was about 30-fold less active than the lead compound **4**.

In conclusion, in contrast to many other medicinal chemistry investigations,[9] in our case bioisosteric replacement of a carboxylic acid and carboxamide functionality, respectively, did not lead to more potent bioactive molecules.

5. Experimental

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 (ID) × 250 mm protected with an analogously filled guard column 10 mm (ID) × 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. For ESI-MS a mixture of acetonitrile/H_2O/formic acid (85:15:0.1) containing ammonium formiate (12 mM) was used.[21] 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 (ID) × 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 (ID) × 250 mm, Merck, Darmstadt, Germany) with an isohexane/THF gradient containing 0.1% trifluoroacetic acid at a flow rate of 0.5 mL/min. With exception of **24** and **38**, all target compounds showed purities greater than 97% in both HPLC systems. The purity evaluated for **24** was 95%, and for **38** 96% each time. The reference inhibitor arachidonyltrifluoromethyl ketone (AACOCF$_3$) was purchased from Biomol, Hamburg, Germany. The reference inhibitor AR-C70484XX (4-[3-(4-decyloxyphenoxy)-2-oxopropoxy]benzoic acid, **2**), was sythesized according to published procedures.[7]

5.1. (Imidazol-1-yl)indol-5-ylmethanone (7)[10]

A solution of indole-5-carboxylic acid (1.0 g, 6.2 mmol) in dry THF (15 mL) was treated under a nitrogen atmosphere with *N*,*N*′-carbonyldiimidazole (1.0 g, 6.2 mmol), and the mixture was stirred at room temperature until the gas development was finished. After addition of water, the reaction mixture was extracted exhaustively with diethyl ether. The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was recrystallized from acetone/toluene (1:1) to give **7** as a solid (1.1 g, 81%); mp 162 °C. ^{1}H NMR (DMSO-d_6): δ 6.66–6.67 (m, 1H), 7.16 (m, 1H), 7.55–7.56 (m, 1H), 7.59 (m, 2H), 7.71 (m, 1H), 8.13 (s, 1H), 8.23–8.24 (m, 1H), 11.66 (br, 1H). MS (EI) *m*/*z* (%): 211 (4) $[M]^+$, 144 (100).

5.2. *N*-Methylindole-5-carboxamide (8)[11]

To a solution of **7** (211 mg, 1 mmol) in THF were added subsequently methylamine hydrochloride (135 mg, 2 mmol), triethylamine (0.28 mL), and a saturated aqueous $NaHCO_3$ solution (2 mL). The mixture was stirred at room temperature for 1 h. Then, methylamine hydrochloride (135 mg, 2 mmol) and saturated aqueous $NaHCO_3$ solution (2 mL) were added a second time, and stirring was continued for additional 2 h. After dilution with water, the mixture was extracted exhaustively with diethyl ether. The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate, 3:2) to give **8** as a solid (142 mg, 82%); mp 144 °C. ^{1}H NMR (DMSO-d_6): δ 2.77–2.78 (m, 3H), 6.50 (m, 1H), 7.38–7.40 (m, 2H), 7.58–7.60 (m, 1H,), 8.08 (s, 1H), 8.25 (br, 1H), 11.28 (br, 1H). MS (EI) *m*/*z* (%): 174 (60) $[M]^+$, 144 (100).

5.3. *N*,*N*-Dimethylindole-5-carboxamide (9)[12]

Compound **7** was reacted with dimethylamine hydrochloride according to the methodology described for **8** to give **9** as a solid; mp 237 °C. ^{1}H NMR (DMSO-d_6): δ 2.96 (s, 6H), 6.46–6.47 (m, 1H), 7.12 (dd, 1H), 7.38–7.40 (m, 2H), 7.59–7.60 (m, 1H), 11.25 (br, 1H). MS (EI) *m*/*z* (%): 188 (27) $[M]^+$, 144 (100).

5.4. 1-[2-Hydroxy-3-(4-octylphenoxy)propyl]-*N*-methylindole-5-carboxamide (10)

Under a nitrogen atmosphere a suspension of NaH (60% in mineral oil; 29 mg, 0.72 mmol) in dry DMF (7 mL) was stirred at room temperature for 10 min. After addition of a solution of **8** (115 mg, 0.66 mmol) in dry DMF (7 mL), the mixture was further stirred for 1 h. Then, a solution of 2-(4-octylphenoxymethyl)oxirane[8] (173 mg, 0.66 mmol) in dry DMF (10 mL) was added, and the reaction mixture was heated at 100 °C for 3 h. After it was cooled to room temperature, the mixture was treated with half-saturated brine and

extracted exhaustively with diethyl ether. The combined organic phases were washed three times with half-saturated brine, dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by silica gel chromatography (1) hexane/ethyl acetate, 1:1; (2) ethyl acetate) to give **10** as an oil (150 mg, 52%). ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H), 1.26–1.30 (m, 10H), 1.55–1.58 (m, 2H), 2.54 (t, 2H), 2.86 (br, 1H), 3.01 (d, 3H), 3.84 (dd, 1H), 3.91 (dd, 1H), 4.28–4.33 (m, 2H), 4.40–4.44 (m, 1H), 6.21 (d, 1H), 6.55 (d, 1H), 6.79 (d, 2H), 7.08 (d, 2H), 7.21 (d, 1H), 7.36 (d, 1H), 7.56 (d, 1H), 8.03 (s, 1H). MS (EI) *m*/*z* (%): 436 (100) $[M]^+$.

5.5. 1-[2-Hydroxy-3-(4-octylphenoxy)propyl]-*N*,*N*-dimethylindole-5-carboxamide (11)

Compound **9** was reacted with 2-(4-octylphenoxymethyl)oxirane for 50 h at 100 °C following the procedure for the synthesis of **10** to give **11** as an oil in 60% yield. ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H), 1.26–1.30 (m, 10H), 1.56 (quint, 2H), 2.53 (t, 2H), 3.06 (br, 6H), 3.17 (d, 1H), 3.78 (dd, 1H), 3.85 (dd, 1H), 4.24–4.30 (m, 2H), 4.37–4.43 (m, 1H), 6.51 (d, 1H), 6.77 (d, 2H), 7.06 (d, 2H), 7.18–7.20 (m, 2H), 7.30 (d, 1H), 7.68 (d, 1H). MS (EI) *m*/*z* (%): 450 (100) $[M]^+$.

5.6. *N*-Methyl-1-[3-(4-octylphenoxy)-2-oxopropyl]indole-5-carboxamide (12)

Acetic anhydride (1.0 mL, 10 mmol) was added to dry DMSO (5 mL), and the mixture was stirred under a nitrogen atmosphere at room temperature for 10 min. Then, this solution was added to a solution of **10** (120 mg, 0.27 mmol) in dry DMSO (7 mL). The mixture was stirred under a nitrogen atmosphere for 18 h, and poured into a mixture of 5% aqueous $NaHCO_3$ and brine (1:2). After being stirred for 5 min, the mixture was extracted exhaustively with diethyl ether. The combined organic phases were washed three times with half-saturated brine, dried (Na_2SO_4), and the solvent was distilled off. The residue was purified by silica gel chromatography ($CHCl_3$/methanol, 49:1). The product fractions were concentrated, and the residue was crystallized from ethyl acetate/hexane. The product was further purified by RP-HPLC applying acetonitrile/H_2O (85:15) as 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 to give **12** as a solid (83 mg, 71%); mp 138 °C. ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H), 1.26–1.30 (m, 10H), 1.58 (quin, 2H), 2.57 (t, 2H), 3.03 (d, 3H), 4.62 (s, 2H), 5.21 (s, 2H), 6.20 (br, 1H), 6.64 (d, 1H), 6.83 (d, 2H), 7.09–7.10 (m, 2H), 7.14 (d, 2H), 7.63 (dd, 1H), 8.07 (d, 1H). MS (EI) *m*/*z* (%) 434 (57) $[M]^+$, 230 (100).

5.7. *N*,*N*-Dimethyl-1-[3-(4-octylphenoxy)-2-oxopropyl]indole-5-carboxamide (13)

Compound **11** was oxidized using the procedure described for the preparation of **12**. Silica gel chromatography (hexane/ethyl acetate, 1:1) afforded **13** as a solid; mp 136 °C. ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H), 1.27–1.30 (m, 10H), 1.58 (quint, 2H), 2.56 (t, 2H), 3.08 (br, 6H), 4.62 (s, 2H), 5.20 (s, 2H), 6.62 (d, 1H), 6.83 (d, 2H), 7.09 (d, 1H), 7.12–7.15 (m, 3H), 7.29 (dd, 1H), 7.73 (d, 1H). MS (EI) *m*/*z* (%): 448 (92) $[M]^+$, 244 (100).

5.8. (Indol-5-yl)morpholin-4-ylmethanone (14)[13]

A solution of indole-5-carboxylic acid (**6**) (300 mg, 1.86 mmol) in dry THF (10 mL) was treated under a nitrogen atmosphere with *N*,*N*′-carbonyldiimidazole (302 mg, 1.86 mmol), and the mixture was stirred at room temperature until the gas development was finished. After addition of morpholinium chloride (460 mg, 3.72 mmol) and triethylamine (0.52 mL, 3.75 mmol), the reaction mixture was stirred at room temperature for 10 h, treated with water, and extracted exhaustively with diethyl ether. The combined organic layers were dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by silica gel chromatography (hexane/ethyl acetate, 1:1) to give **14** as a solid (340 mg, 79%); mp 128 °C. ^{1}H NMR ($CDCl_3$): δ 3.71 (br, 8H), 6.57–6.59 (m, 1H), 7.25–7.27 (m, 2H), 7.38 (dd, 1H), 7.72–7.73 (m, 1H), 8.50 (br, 1H). MS (EI) *m*/*z* (%): 230 (21) $[M]^+$, 144 (100).

5.9. (Morpholin-4-yl)-1-oxiranylmethylindol-5-ylmethanone (15)

A mixture of powdered KOH (85%; 182 mg, 2.76 mmol), compound **14** (310 mg, 1.35 mmol), tetrabutylammonium bromide (42 mg, 0.13 mmol), and epichlorohydrin (3 mL) was stirred under a nitrogen atmosphere at room temperature for 1 h, diluted with a small amount of CH_2Cl_2, and subjected to chromatography on silica gel (hexane/ethyl acetate, 2:3) to give **15** as an oil (368 mg, 95%). ^{1}H NMR ($CDCl_3$): δ 2.44 (dd, 1H), 2.81 (dd, 1H), 3.27–3.29 (m, 1H), 3.70 (br, 8H), 4.18 (dd, 1H), 4.49 (dd, 1H), 6.56 (dd, 1H), 7.20 (d, 1H), 7.30 (dd, 1H), 7.40 (d, 1H), 7.71 (d, 1H). MS (EI) *m*/*z* (%): 286 (70) $[M]^+$, 200 (100).

5.10. {1-[2-Hydroxy-3-(4-octylphenoxy)propyl]indol-5-yl}morpholin-4-ylmethanone (16)

Compound **15** (300 mg, 1.05 mmol), 4-octylphenol (216 mg, 1.05 mmol), and 4-dimethylaminopyridine (20 mg) were mixed thoroughly, and heated at 95 °C for 1.5 h stirring up the mixture several times. The cooled reaction mixture was dissolved in CH_2Cl_2 and subjected to chromatography on silica gel (hexane/ethyl acetate, 2:3) to give **16** as an oil (331 mg, 64%). ^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H), 1.24–1.29 (m, 10H), 1.56 (quint, 2H), 2.54 (t, 2H), 2.61 (d, 1H), 3.69 (br, 8H), 3.82 (dd, 1H), 3.90 (dd, 1H), 4.31–4.35 (m, 2H), 4.40–4.44 (m, 1H), 6.55 (d, 1H), 6.79 (d, 2H), 7.08 (d, 2H), 7.20–7.26 (m, 2H), 7.38 (d, 1H), 7.70 (m, 1H). MS (EI) *m*/*z* (%): 492 (61) $[M]^+$, 406 (100).

5.11. 1-[5-(Morpholine-4-carbonyl)indol-1-yl]-3-(4-octylphenoxy)propan-2-one (17)

A solution of **16** (270 mg, 0.55 mmol) in dry CH_2Cl_2 (5 mL) was treated with Dess–Martin periodinane

reagent (349 mg, 0.82 mmol), and stirred under a nitrogen atmosphere at room temperature for 3 h. A solution of sodium thiosulfate (1.0 g) in saturated sodium bicarbonate solution (20 mL) was added. After stirring for 10 min, the reaction mixture was extracted exhaustively with diethyl ether. The combined organic layers were dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by silica gel chromatography (hexane/ethyl acetate, 2:3) to give **17** as an oil (217 mg, 80%). ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H), 1.27–1.30 (m, 10H), 1.58 (quin, 2H), 2.57 (t, 2H), 3.70 (br, 8H), 4.63 (s, 2H), 5.21 (s, 2H), 6.63 (d, 1H), 6.83 (d, 2H), 7.09–7.15 (m, 4H), 7.26–7.28 (m, 1H), 7.72 (d, 1H). MS (EI) *m*/*z* (%): 490 (21) $[M]^+$, 286 (100).

5.12. 1-[3-(4-Octylphenoxy)-2-oxopropyl]indole-5-sulfonamide (22)

Compound **22** was prepared by coupling indole-5-sulfonamide[14] (**19**) with 2-(4-octylphenoxymethyl)oxirane at 60 °C for 6 h, followed by oxidation of the obtained intermediate with Dess–Martin periodinane reagent applying procedures similar to those described above for the synthesis of **10** and **17**. The crude product was purified by silica gel chromatography (hexane/ethyl acetate, 1:1), followed by RP-HPLC (acetonitrile/H_2O, 85:15). The eluates were concentrated under reduced pressure until most of the acetonitrile was distilled off. The remaining solvent was removed by freeze-drying yielding **22** as a solid; mp 180 °C (decomp.). ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H), 1.26–1.30 (m, 10H), 1.60 (quint, 2H), 2.58 (t, 2H), 4.67 (s, 2H), 4.71 (s, 2H), 5.29 (s, 2H), 6.71 (d, 1H), 6.86 (d, 2H), 7.16–7.18 (m, 4H), 7.73 (dd, 1H), 8.28 (d, 1H). MS (EI) *m*/*z* (%): 456 (35) $[M]^+$, 107 (100).

5.13. *N*-Methyl-1-[3-(4-octylphenoxy)-2-oxopropyl]indole-5-sulfonamide (23)

Compound **23** was prepared by coupling *N*-methylindole-5-sulfonamide[15] (**20**) with 2-(4-octylphenoxymethyl)oxirane at room temperature for 24 h, followed by oxidation of the obtained intermediate with DMSO/acetic anhydride applying procedures similar to those described above for the synthesis of **10** and **12**. The crude product was purified by silica gel chromatography ((1) hexane/ethyl acetate/triethylamine, 1:1:0.02; (2) hexane/ethyl acetate/formic acid, 1:1:0.02). The product fractions were washed with 10% aqueous $NaHCO_3$ solution, concentrated, and the residue was cleaned up by RP-HPLC as described for the purification of **22** to give **23** as a solid; mp 130 °C. ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H), 1.27–1.36 (m, 10H), 1.59 (quint, 2H), 2.58 (t, 2H), 2.64 (d, 3H), 4.28 (m, 1H), 4.68 (s, 2H), 5.28 (s, 2H), 6.71 (d, 1H), 6.86 (d, 2H), 7.15–7.25 (m, 4H), 7.65 (dd, 1H), 8.21 (d, 1H). MS (EI) *m*/*z* (%): 470 (35) $[M]^+$, 265 (100).

5.14. *N*,*N*-Dimethyl-1-[3-(4-octylphenoxy)-2-oxopropyl]indole-5-sulfonamide (24)

Compound **24** was prepared by coupling *N*,*N*-dimethylindole-5-sulfonamide[16] (**21**) with 2-(4-octylphenoxymethyl)oxirane at room temperature for 24 h, followed by oxidation of the obtained intermediate with DMSO/acetic anhydride applying procedures similar to those described above for the synthesis of **10** and **12**. Purification by silica gel chromatography (hexane/ethyl acetate, 7:3) gave **24** as a solid; mp 133 °C. ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H), 1.27–1.32 (m, 10H), 1.58 (quint, 2H), 2.58 (t, 2H), 2.70 (s, 6H), 4.68 (s, 2H), 5.28 (s, 2H), 6.73 (d, 1H), 6.86 (d, 2H), 7.15–7.19 (m, 4H), 7.59 (dd, 1H), 8.12 (d, 1H). MS (EI) *m*/*z* (%): 484 (30) $[M]^+$, 438 (100).

5.15. 5-{1-[3-(4-Octylphenoxy)-2-oxopropyl]indol-5-ylmethylidene}thiazolidine-2,4-dione (26)

A solution of 1-[2-hydroxy-3-(4-octylphenoxy)propyl]indole-5-carbaldehyde[8] (**25**) (270 mg, 0.66 mmol) in toluene (10 mL) was treated with thiazolidine-2,4-dione (78 mg, 0.66 mmol) and catalytic amounts of acetic acid and piperidine. The mixture was refluxed for 4 h, cooled, poured into water, and extracted exhaustively with ethyl acetate. The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure until crystallization occurred. The solid was sucked off and recrystallized from hexane/ethyl acetate (2:3) to yield the thiazolidine-2,4-dione derivative of **25** (180 mg, 54%). An aliquot of this compound (150 mg, 0.30 mmol) was oxidized in a similar way as described above for the synthesis of **17**. The crude product was purified by silica gel chromatography ((1) hexane/ethyl acetate, 2:3; (2) ethyl acetate) to yield **26** as a solid (111 mg); mp 203–205 °C (decomp.). ^{1}H NMR (DMSO-d_6): δ 0.88 (t, 3H), 1.27–1.29 (m, 10H), 1.56 (m, 2H), 2.54 (m, 2H), 5.02 (s, 2H), 5.46 (s, 2H), 6.66 (d, 1H), 6.92 (d, 2H), 7.15 (d, 2H), 7.39 (dd,1H), 7.43 (d, 1H), 7.54 (d, 1H), 7.88 (m, 2H), 12.50 (br, 1H). MS (EI) *m*/*z* (%): 504 (59) $[M]^+$, 257 (100).

5.16. 5-(3-Benzyl-1,2,4-oxadiazol-5-yl)indole (28)

To a solution of *N*-hydroxy-2-phenylacetamidine[17] (1.68 g, 11.2 mmol) in dry THF (20 mL) was added under a nitrogen atmosphere NaH (60% in mineral oil; 438 mg, 11.2 mmol). The mixture was stirred at room temperature for 1 h and then treated with a solution of methyl indole-5-carboxylate (**27**) (980 mg, 5.6 mmol) in dry THF (20 mL). The resulting mixture was heated under reflux for 2 h, cooled, poured into water, and extracted exhaustively with diethyl ether. The combined organic layers were dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by silica gel chromatography (hexane/ethyl acetate, 4:1) to give **28** as a solid (1.0 g, 65%); mp 135 °C. ^{1}H NMR ($CDCl_3$): δ 4.17 (s, 2H), 6.63–6.64 (m, 1H), 7.23–7.42 (m, 7H), 7.92 (dd, 1H), 8.45 (m, 1H), 8.66 (br, 1H). MS (EI) *m*/*z* (%): 275 (46) $[M]^+$, 144 (100).

5.17. 5-(3-Ethyl-1,2,4-oxadiazol-5-yl)indole (29)

N-Hydroxypropionamidine[18] was reacted with methyl indole-5-carboxylate following the procedure for the synthesis of **28**. Purification by silica gel chromatography (hexane/ethyl acetate, 7:3) gave **29** as a solid in

54% yield; mp 159 °C. ^{1}H NMR ($CDCl_3$): δ 1.41 (t, 3H), 2.84 (q, 2H), 6.68 (m, 1H), 7.30–7.32 (m, 1H), 7.50 (d, 1H), 7.97 (dd, 1H), 8.47 (br, 1H), 8.48 (m, 1H). MS (EI) *m*/*z* (%): 213 (70) $[M]^+$, 144 (100).

5.18. 1-[5-(3-Benzyl-1,2,4-oxadiazol-5-yl)indol-1-yl]-3-(4-octylphenoxy)propan-2-one (30)

Compound **30** was prepared by coupling **28** with 2-(4-octylphenoxymethyl)oxirane at 60 °C for 16 h, followed by oxidation of the obtained intermediate with DMSO/acetic anhydride applying procedures similar to those described above for the synthesis of **10** and **12**. The crude product was purified by flash chromatography on silica gel (hexane/ethyl acetate, 4:1) to give **30** as a solid; mp 148 °C. ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H), 1.26–1.32 (m, 10H), 1.55–1.60 (m, 2H), 2.57 (t, 2H), 4.15 (s, 2H), 4.66 (s, 2H), 5.24 (s, 2H), 6.70 (dd, 1H), 6.85 (d, 2H), 7.11 (d, 1H), 7.14–7.17 (m, 3H), 7.25–7.28 (m, 1H), 7.32–7.36 (m, 2H), 7.40–7.42 (m, 2H), 7.93 (dd, 1H), 8.45 (d, 1H). MS (EI) *m*/*z* (%): 535 (25) $[M]^+$, 330 (100).

5.19. 1-[5-(3-Ethyl-1,2,4-oxadiazol-5-yl)indol-1-yl]-3-(4-octylphenoxy)propan-2-one (31)

Compound **31** was prepared by coupling **29** with 2-(4-octylphenoxymethyl)oxirane at 60 °C for 3 h, followed by oxidation of the obtained intermediate with DMSO/acetic anhydride applying procedures similar to those described above for the synthesis of **10** and **12**. The crude product was purified by silica gel chromatography (hexane/ethyl acetate, 4:1) and recrystallized from hexane/ethyl acetate (7:3) to give **31** as a solid; mp 112 °C. ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H), 1.27–1.32 (m, 10H), 1.40 (t, 3H), 1.57–1.61 (m, 2H), 2.58 (t, 2H), 2.84 (q, 2H), 4.67 (s, 2H), 5.25 (s, 2H), 6.71 (d, 1H), 6.85 (d, 2H), 7.12 (d, 1H), 7.15–7.19 (m, 3H), 7.95 (dd, 1H), 8.46 (d, 1H). MS (EI) *m*/*z* (%): 473 (55) $[M]^+$, 268 (100).

5.20. 1-Oxiranylmethylindole-5-carbonitrile (33)

A mixture of powdered KOH (85%; 440 mg, 7.84 mmol), indole-5-carbonitrile (**32**) (500 mg, 3.52 mmol), tetrabutylammonium bromide (113 mg, 0.35 mmol), and epichlorohydrin (5 mL) was stirred under a nitrogen atmosphere at room temperature for 1 h, diluted with a small amount of CH_2Cl_2, and subjected to chromatography on silica gel ((1) hexane/ethyl acetate, 9:1; (2) hexane/ethyl acetate, 7:3) to give **33** as a solid (630 mg, 90%); mp 92–93 °C. ^{1}H NMR ($CDCl_3$): δ 2.45 (dd, 1H), 2.83–2.85 (m, 1H), 3.27–3.30 (m, 1H), 4.15 (dd, 1H), 4.54 (dd, 1H), 6.61 (d, 1H), 7.26–7.27 (m, 1H), 7.44–7.45 (m, 2H), 7.97 (s, 1H). MS (EI) *m*/*z* (%) 198 (75) $[M]^+$, 142 (100).

5.21. 1-[2-Hydroxy-3-(4-octylphenoxy)propyl]indole-5-carbonitrile (34)

Compound **33** (600 mg, 3.03 mmol), 4-octylphenol (625 mg, 3.03 mmol), and 4-dimethylaminopyridine (20 mg) were dissolved in CH_2Cl_2 (4 mL). The solvent was distilled off, and the residue heated under a nitrogen atmosphere at 60 °C for 2 h. The cooled reaction mixture was dissolved in a small amount of CH_2Cl_2 and subjected to chromatography on silica gel ((1) hexane/ethyl acetate, 9:1; (2) hexane/ethyl acetate, 4:1) to give **34** as an oil (1.04 g, 85%). ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H), 1.27–1.30 (m, 10H), 1.58 (m, 2H), 2.55 (t, 2H), 3.85 (dd, 1H), 3.92 (dd, 1H), 4.33–4.35 (m, 2H), 4.43–4.47 (m, 1H), 6.60 (d, 1H), 6.80 (d, 2H), 7.11 (d, 2H), 7.29 (d, 1H), 7.39 (d, 1H), 7.45 (d, 1H), 7.94 (s, 1H). MS (EI) *m*/*z* (%): 404 (100) $[M^+]$.

5.22. 3-{1-[2-Hydroxy-3-(4-octylphenoxy)propyl]indol-5-yl}-4,5- dihydro-1,2,4-oxadiazol-5-one (35)

A solution of **34** (290 mg, 0.72 mmol) in methanol (5 mL) was treated with a mixture of solutions of hydroxylammonium chloride (50 mg, 0.72 mmol) in methanol (3 mL) and NaOH (29 mg, 0.72 mmol) in water (3 mL). The resulting mixture was heated under reflux for 24 h. Then, another portion of a mixture of hydroxylammonium chloride (50 mg, 0.72 mmol) in methanol (3 mL) and NaOH (29 mg, 0.72 mmol) in water (3 mL) was added, and the reaction mixture was heated under reflux for another 24 h. The solvent was removed under reduced pressure, and the residue chromatographed on silica gel eluting with ethyl acetate to yield crude carboxamidine of **34** (280 mg). Without further purification, a solution of an aliquot of this intermediate (200 mg) in dry ethanol was treated with a sodium ethanolate solution, prepared from sodium (21 mg, 0.91 mmol) and dry ethanol (5 mL). When gas development had ceased, diethyl carbonate (0.22 mL, 1.83 mmol) was added, and the reaction mixture was heated under reflux overnight. After cooling to room temperature, the mixture was poured into water and extracted exhaustively with diethyl ether. The combined organic layers were dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by silica gel chromatography (hexane/ethyl acetate, 2:3) to give **35** as a solid (80 mg). ^{1}H NMR (DMSO-d_6): δ 0.88 (t, 3H), 1.26–1.28 (m, 10H), 1.54 (m, 2H), 2.50–2.53 (m, 2H), 3.86–3.88 (m, 2H), 4.18–4.19 (m, 1H), 4.32 (dd, 1H), 4.47 (dd, 1H), 5.46 (d, 1H), 6.62 (d, 1H), 6.87 (d, 2H), 7.11 (d, 2H), 7.53 (d, 1H), 7.57 (dd, 1H), 7.71 (d, 1H), 8.07 (m, 1H).

5.23. 3-{1-[3-(4-Octylphenoxy)-2-oxopropyl]indol-5-yl}-4,5-dihydro-1,2,4-oxadiazol-5-one (36)

Compound **35** was oxidized in a similar way as described above for the synthesis of **17**. The crude product was purified by silica gel chromatography (hexane/ethyl acetate, 2:3) to yield **36** as a solid; mp 201–203 °C. ^{1}H NMR (DMSO-d_6): δ 0.88 (t, 3H), 1.26–1.28 (m, 10H), 1.54 (m, 2H), 2.52–2.54 (m, 2H), 5.02 (s, 2H), 5.48 (s, 2H), 6.66 (d, 1H), 6.91 (d, 2H), 7.13 (d, 2H), 7.45 (d, 1H), 7.58 (m, 2H), 8.08 (s, 1H), 12.81 (s, 1H). MS (EI) *m*/*z* (%): 461 (29) $[M]^+$, 107 (100).

5.24. 1-(4-Octylphenoxy)-3-[5-(1*H*-tetrazol-5-yl)indol-1-yl]propan-2-ol (37)

A mixture of **34** (250 mg, 0.62 mmol), trimethylsilyl azide (0.12 mL, 0.93 mmol), and tetrabutylammonium

fluoride hydrate (81 mg, 0.31 mmol) was heated under a nitrogen atmosphere at 120 °C for 12 h. The reaction mixture was purified by silica gel chromatography ((1) hexane/ethyl acetate, 2:3; (2) ethyl acetate) to give **37** as a solid (160 mg, 58%). ^{1}H NMR (DMSO-d_6): δ 0.88 (t, 3H), 1.27–1.28 (m, 10H), 1.54 (m, 2H), 2.51–2.54 (m, 2H), 3.90 (d, 2H), 4.20–4.21 (m, 1H), 4.33 (dd, 1H), 4.48 (dd, 1H), 5.47 (d, 1H), 6.65 (d, 1H), 6.89 (d, 2H), 7.12 (d, 2H), 7.53 (d, 1H), 7.74 (d, 1H), 7.81 (d, 1H), 8.29 (s, 1H). MS (EI) *m*/*z* (%): 447 (76) $[M]^+$, 403 (100).

5.25. 1-(4-Octylphenoxy)-3-[5-(1*H*-tetrazol-5-yl)indol-1-yl]propan-2-one (38)

Compound **37** was oxidized in a similar way as described above for the synthesis of **17**. The crude product was purified by silica gel chromatography (hexane/ethyl acetate, 2:3) to yield **38** as a solid; mp 170–172 °C (decomp.). ^{1}H NMR (DMSO-d_6): δ 0.87 (t, 3H), 1.26–1.28 (m, 10H), 1.54 (m, 2H), 2.52–2.54 (m, 2H), 5.00 (s, 2H), 5.37 (s, 2H), 6.52 (d, 1H), 6.90 (d, 2H), 7.13 (d, 2H), 7.27 (d, 1H), 7.36 (d, 1H), 7.82 (dd, 1H), 8.16 (m, 1H). MS (ESI) *m*/*z* (%): 444 $[M-H]^+$.

5.25.1. Assay of cPLA$_2\alpha$ inhibition. The inhibition of cPLA$_2\alpha$ isolated from human platelets was performed as previously described.[19] Briefly, sonicated covesicles 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 substrate. 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 with solid phase extraction.

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