Carbocyclic[*g*]indole Inhibitors of Human Nonpancreatic s-PLA_2

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A vinyl azide cyclization method was used to synthesize three different carbocyclic[*g*]indole scaffolds as inhibitors of human nonpancreatic secretory phospholipase A_2. Each scaffold demonstrated potent enzyme activity in a chromogenic assay system, with select examples also demonstrating potent activity in a secondary DOC/PC assay. Compound **11**, representative of the cyclopent[*g*]indole series, gave an IC_{50} of 10 nM for the inhibition of hnps-PLA_2 in the chromogenic assay.

Introduction

Excess levels of human nonpancreatic secretory phospholipase A_2 (hnps-PLA_2) have been associated with a number of disease states including arthritis, septic shock, and atherosclerosis.[1] While a number of different inhibitors of hnps-PLA_2 have been described,[2] the indole glyoxamide series exemplified by LY315920 (**1**) has been the most thoroughly explored.[3−5] In this study we present the chemistry and SAR evaluation of a series of carbocyclic[*g*]indole compounds representing a new advance in the construction of potent sPLA_2 inhibitors.

Chemistry

For each 6,7-fused carbocyclic ring system examined, a different synthetic approach was required. Scheme 1 illustrates the route to 1,6,7,8-tetrahydrocyclopent[*g*]-indole compounds **10** and **11** and is representative of the strategy used for the remaining ring systems. In the event, 2,3-dihydro-6-methoxy-1*H*-indene (**2**) was formylated via a Vilsmeir procedure to provide aldehyde **3**, which was subsequently condensed with ethyl azidoacetate giving α,*β*-unsaturated ester **4**. Ring closure to produce the 2-carbethoxy-substituted indole **5** was achieved through thermal cyclization,[6] although in the case of the 6,7,8,9-tetrahydro-1*H*-benz[*g*]indole examples (compounds **21**−**24**), rhodium(II) acetate dimer was added to facilitate the reaction. As indicated for compounds **10** and **11**, targets requiring a 2-methyl substituent were secured beginning with alkylation at the 1-position, which was accompanied by partial hydrolysis of the ester. Treatment of the intermediate mixture with base provided acid **6**, which was then reduced with lithium aluminum hydride to primary alcohol **7**. Further reduction via hydrogenolysis gave the 2-methyl intermediate **8**.

For examples requiring an ethyl group at the 2-position (e.g., compounds **18/19**), the intermediate acid **6** was treated with methyllithium to form the corresponding acetyl derivative, which was reduced to the secondary alcohol with sodium borohydride, then further reduced with palladium and hydrogen. In the case of compounds **23/24**, Tebbe Reagent, followed by hydrolysis in situ, was used to secure the acetyl intermediate, which was then reduced with palladium and 1,4-cyclohexadiene (see Supporting Information). Completion of the final examples was similar to Scheme 1, where methyl ether **8** was demethylated, alkylated to give oxoacetic ester **9**, and treated with oxalyl chloride and ammonia to provide ester **10**. Simple hydrolysis with aqueous hydroxide gave final acid **11**. In the case of *N*-acylsulfonamide compound **20**, conversion was effected via the treatment of **11** with benzenesulfonamide in the presence of EDC and a suitable base.

Discussion

Compounds were originally examined as inhibitors of hnps-PLA_2 in a chromogenic assay system utilizing a synthetic substrate [1,2-bis(heptanoylthio)-1,2-dideoxy-*rac*-glycero-3-phosphorylcholine] as previously described.[4a] Mole fractions for each measurement are also presented since the molar IC_{50} values are dependent on the lipid concentration in the assay (Table 1).[4c] In general, it was found that compounds containing saturated rings fused to the 6,7-position of the indole ring proved to be very potent at inhibiting the enzyme (compounds **11**, **22**, and **24**). As previously noted in the original indole SAR,[4c] the ethyl group at the 2-position was interchangeable with methyl (compare compound pairs **1/19** and **22/24**). Adding a fluorine atom to the benzyl ring was tolerated at the ortho and meta positions (compounds **13** and **15**), but less so at the para position (**17**), where an approximately 8-fold drop in potency was observed. *N*-Acylsulfonamide **20** was equipotent with the corresponding carboxylic acid **11**, indicating that the space around the acid binding site is sterically tolerant. An exchange of unsaturation between the benzyl aromatic and carbocyclic rings of **22** produced the benzo-fused example **26**, which was accomplished without loss of activity. As observed with the original indole series, the precursor esters for all of the carbocyclic[*g*]indoles tested were approximately 10-fold less potent.

As a check on the results obtained in the chromogenic assay, some of the more potent compounds were tested

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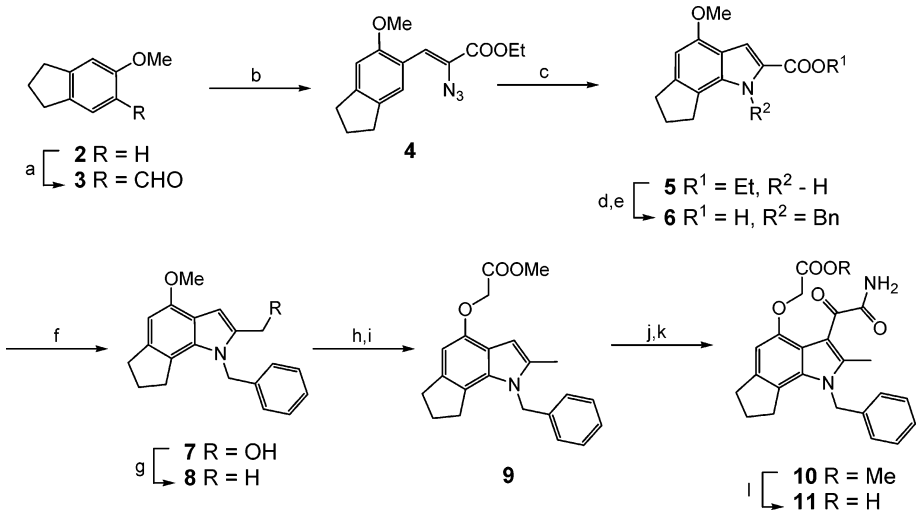
Scheme 1[a]



[a] Reagents: (a) $POCl_3$, DMF; (b) N_3CH_2COOEt, NaOEt; (c) toluene, heat; (d) BnBr, NaH; (e) aq. NaOH; (f) $LiAlH_4$, THF; (g) H_2, Pd(C), THF, EtOAc, $CHCl_3$; (h) BBr_3, $CHCl_3$; (i) methyl bromoacetate, Cs_2CO_3; (j) oxalyl chloride; (k) NH_3; (l) LiOH, THF, MeOH, H_2O.

in the deoxycholate/phosphatidylcholine (DOC/PC) mixed micelle assay, which uses higher levels of lipid (4 mM vs 1.23 mM for the chromogenic assay) and less enzyme (3 nM vs 16 nM for the chromogenic assay). Generally, the DOC/PC mole fractions (Table 2) were found to be approximately 8-fold lower than values observed for the chromogenic assay, even though the IC_{50} values were nearly the same. Comparison of mole fraction values may be more indicative of absolute enzyme inhibitory activity since they are independent of the lipid concentration in each assay.

Finally, compound **19** was evaluated in an ex vivo model in transgenic mice expressing human $sPLA_2$ protein.[7] Animals were dosed with compound, and serum enzyme activity at 1 and 2 h was evaluated in the DOC/PC mixed micelle assay. At an oral dose of 0.3 mg/kg, compound **19** gave 83% inhibition of the enzyme at the 1-h time point and 61% inhibition at the 2-h time point. This compares favorably with compound **1**, which gave values of 65% and 55%, respectively, in this assay.[3b]

The present group of carbocyclic[*g*]indoles has proven to have in vitro potency comparable to the hnps-PLA_2 indole series represented by compound **1.** Compounds of this potency may be useful in delineating the role of hnps-PLA_2 in the treatment of human disease.

Experimental Section

For general experimental parameters see Supporting Information.

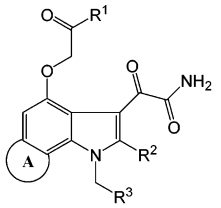
Representative Procedure for the Preparation of Carbocyclic[*g*]indole $sPLA_2$ Inhibitors: Synthesis of 2-[[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-benzyl-1,6,7,8-tetrahydrocyclopent[*g*]indol-4-yl]oxy]acetic Acid (11). Preparation of 2,3-Dihydro-6-methoxy-1*H*-indene-5-carboxaldehyde (3). Phosphorus oxychloride (67.1 mL, 0.710 mol) was added to *N*,*N*-dimethylformamide (60 mL) at 0 °C. After stirring for 0.5 h, 2,3-dihydro-6-methoxy-1*H*-indene (**2**; 50.0 g, 0.338 mol) was added and the resulting mixture heated carefully at 80 °C for 4 h. The mixture was cooled to room temperature, poured over crushed ice, and stirred for 18 h. The resulting precipitate was collected via vacuum filtration. Recrystallization (absolute ethanol) provided 43.5 g (73%) of the title product as yellow plates: mp 73−74 °C.

Preparation of 3-(2,3-Dihydro-6-methoxy-1*H*-inden-5-yl)-2-azido-2-propenoic Acid Ethyl Ester (4). Sodium (13.8 g, 0.600 mol) was dissolved in absolute ethanol (400 mL). After cooling to −10 °C, a mixture of 2,3-dihydro-6-methoxy-1*H*-indene-5-carboxaldehyde (**3**; 26.5 g, 0.150 mol) and ethyl azidoacetate (72.0 g, 0.558 mol) in diethyl ether (100 mL) was added dropwise in such a manner that the temperature did not rise above −10 °C. The mixture was allowed to warm to 20 °C over 3 h. After gas evolution had ceased, the mixture was poured into water (700 mL). The mixture was extracted thrice with diethyl ether, and the combined organic fractions were washed with water and saturated sodium chloride solution, dried (sodium sulfate), filtered, and concentrated in vacuo. The resulting oil was cooled to −10 °C for 24 h and resulted in the formation of a solid. This material was slurried in hexanes and collected via vacuum filtration (15.6 g). The filtrate was concentrated in vacuo and purifed via chromatography (silica gel, 5% ethyl acetate/95% hexane) to provide an additional 7.3 g (53% total yield) of the title product as a yellow crystalline material (single isomer, geometry not determined): mp 64−66 °C. ^{1}H NMR ($CDCl_3$) δ 8.05 (s, 1H), 7.41 (s, 1H), 6.79 (s, 1H), 4.38 (q, J = 7.3 Hz, 2H), 3.84 (s, 3H), 2.89 (q, J = 7.3 Hz, 4H), 2.07 (quintet, J = 7.3 Hz, 2H), 1.38 (t, J = 7.3 Hz, 3H); MS FD+ *m/e* 287 (p); IR ($CHCl_3$, cm^{-1}) 2961, 2122, 1704, 1081. Anal. Calcd for $C_{15}H_{17}N_3O_3$: C, 62.71; H, 5.96; N, 14.62. Found: C, 62.46; H, 5.99; N, 14.40.

Preparation of 2-Carboethoxy-4-methoxy-1,6,7,8-tetrahydrocyclopent[*g*]indole (5). A mixture of 3-(2,3-dihydro-6-methoxy-1*H*-inden-5-yl)-2-azido-2-propenoic acid ethyl ester (**4**; 7.28 g, 25.3 mmol) in toluene (200 mL) was refluxed for 6 h. Upon cooling to room temperature, a crystalline precipitate formed that was collected via vacuum filtration and washed with hexanes to provide 3.38 g (52%) of the title product as white needles: mp 185−187 °C. ^{1}H NMR ($CDCl_3$) δ 8.97 (bs, 1H, N*H*), 7.36 (d, J = 2.2 Hz, 1H), 6.46 (s, 1H), 4.41 (q, J = 7.0 Hz, 2H), 3.93 (s, 3H), 3.03 (q, J = 6.6 Hz, 4H), 2.22 (quintet, J = 7.3 Hz, 2H), 1.42 (t, J = 7.3 Hz, 3H); MS ES+ *m/e* 260 (p + 1); IR ($CHCl_3$, cm^{-1}) 3400, 1698, 1258. Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.71; H, 6.62; N, 5.45.

Preparation of 1-Benzyl-2-carboxy-4-methoxy-1,6,7,8-tetrahydrocyclo-pent[*g*]indole (6). To a slurry of a 60% oil suspension of sodium hydride (7.00 g, 0.175 mol) in *N*,*N*-dimethylformamide (350 mL) was added 2-carbethoxy-4-methoxy-1,6,7,8-tetrahydrocyclopent[*g*]indole (**5**; 34.5 g, 0.133 mol) and the resulting mixture stirred for 15 min. Benzyl bromide (21.0 mL, 0.176 mol) was added and the mixture allowed to stir at room temperature for 48 h. The mixture was dissolved in approximately 300 mL of 1:1 methanol/tetra-

Table 1. Inhibitory Activity of Carbocyclic[*g*]indoles against Human Nonpancreatic Secretory Phospholipase A_2 (Chromogenic Assay)



cmpd	A	R^1	R^2	R^3	IC_{50} (μM)[a]	mole fraction[b]
1	--	OH	Et		0.013 ± 0.001	1.1×10^{-5}
10		OMe	Me		0.106 ± 0.035	8.6×10^{-5}
11		OH	Me		0.010 ± 0.001	8.1×10^{-6}
12		OMe	Me		0.073 ± 0.014	5.9×10^{-5}
13		OH	Me		0.009 ± 0.002	7.3×10^{-6}
14		OMe	Me		0.132 ± 0.027	1.1×10^{-4}
15		OH	Me		0.010 ± 0.006	8.1×10^{-6}
16		OMe	Me		0.806 ± 0.140	6.5×10^{-4}
17		OH	Me		0.082 ± 0.027	6.7×10^{-5}
18		OMe	Et		0.108 ± 0.015	8.8×10^{-5}
19		OH	Et		0.013 ± 0.001	1.1×10^{-5}
20		$NHSO_2Ph$	Me		0.007 ± 0.003	5.7×10^{-6}
21		OMe	Me		0.109 ± 0.045	8.9×10^{-5}
22		OH	Me		0.010 ± 0.002	8.1×10^{-6}
23		OMe	Et		0.100 ± 0.029	8.1×10^{-5}
24		OH	Et		0.011 ± 0.002	8.9×10^{-6}
25		OMe	Me		0.148 ± 0.016	1.2×10^{-4}
26		OH	Me		0.011 ± 0.004	8.9×10^{-6}

[a] Chromogenic assay system; mean values ± SEM for a minimum of three determinations. [b] Mole fraction is the IC_{50} concentration divided by the total lipid concentration (1230 μM).

Table 2. Inhibitory Activity of Selected Carbocyclic[*g*]indoles against Human Nonpancreatic Secretory Phospholipase A_2 (DOC/PC assay)

compd	IC_{50} (μM)[a]	mole fraction[b]
1	0.007[c]	1.8×10^{-6}
11	0.006	1.5×10^{-6}
19	0.007	1.8×10^{-6}
20	0.003	7.5×10^{-7}
22	0.016	4.0×10^{-6}
24	0.017	4.2×10^{-6}
26	0.004	1.0×10^{-6}

[a] DOC/PC assay system; single-point determination. [b] Mole fraction is the IC_{50} concentration divided by the total lipid concentration (4000 μM). [c] Data from ref 4c.

hydrofuran and treated with aqueous 5 N sodium hydroxide solution at 50 °C until nearly all of the precipitate had dissolved. The mixture was filtered and the filtrate adjusted to pH 2 with concentrated hydrochloric acid. The resulting precipitate was collected via vacuum filtration, washed with water, and dried under vacuum at 40 °C for 48 h to provide 37.5 g (87%) of the title product as a white solid: mp 248−250 °C (dec). ^{1}H NMR (DMSO-d_6) δ 12.68 (bs, 1H), 7.29 (s, 1H), 7.22 (m, 3H), 6.80 (d, J = 7.0 Hz, 2H), 6.52 (s, 1H), 5.94 (bs, 2H), 3.89 (s, 3H), 2.93 (m, 2H), 2.84 (t, J = 7.3 Hz, 2H), 1.94 (quintet, J = 7.3 Hz, 2H); MS ES+ *m/e* 322 (p + 1); IR (KBr, cm^{-1}) 3000, 1662, 1610, 1497. Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.59; H, 5.64; N, 4.38.

Preparation of 1-Benzyl-2-hydroxymethyl-4-methoxy-1,6,7,8-tetrahydrocyclopent[*g*]indole (7). A solution of 1-benzyl-2-carboxy-4-methoxy-1,6,7,8-tetrahydrocyclopent[*g*]-indole (**6**; 3.21 g, 10.0 mmol) in tetrahydrofuran (70 mL) was treated carefully with lithium aluminum hydride (0.58 g, 15 mmol) at room temperature for 18 h. Additional small portions of lithium aluminum hydride were added until the conversion of starting material was complete via TLC. The reaction was quenched by the addition of excess sodium sulfate decahydrate and the resulting suspension filtered. The filtrate was dried (sodium sulfate), filtered, and concentrated in vacuo to provide a quantitative yield of the title compound as white crystals. An analytical sample was obtained by recrystallization (ethyl acetate/hexanes): mp 135−140 °C. ^{1}H NMR ($CDCl_3$) δ 7.20−7.30 (m, 3H), 6.91 (d, J = 7 Hz, 2H), 6.64 (s, 1H), 6.54 (s, 1H), 5.62 (s, 2H), 4.63 (s, 2H), 3.97 (s, 3H), 3.03 (t, J = 7 Hz, 2H), 2.97 (t, J = 7 Hz, 2H), 2.20 (bs, 1H), 2.08 (quintet, J = 7 Hz, 2H); MS ES+ *m/e* 308 (p + 1); IR ($CHCl_3$, cm^{-1}) 2944, 1595, 1497. Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.52; H, 6.82; N, 4.61.

Preparation of 1-Benzyl-2-methyl-4-methoxy-1,6,7,8-tetrahydrocyclo-pent[*g*]indole (8). To a nitrogen-purged solution of 1-benzyl-2-hydroxymethyl-4-methoxy-1,6,7,8-tetrahydrocyclopent[*g*]indole (**7**; 2.0 g, 6.5 mmol) and chloroform (3 mL) in 1:1 tetrahydrofuran/absolute ethanol (200 mL) was added 10% palladium-on-carbon (400 mg). The resulting suspension was hydrogenated at 45−50 psi for 18 h. The mixture was filtered through Celite and concentrated in vacuo to provide a solid. Chromatography (silica gel, 7% ethyl acetate/93% hexanes) provided 0.50 g (26%) of the title compound as a white solid: mp 128−130 °C. ^{1}H NMR ($CDCl_3$) δ 7.24 (m, 3H), 6.88 (d, J = 7.0 Hz, 2H), 6.46 (s, 1H), 6.40 (bs, 1H), 5.42 (s, 2H), 3.93 (s, 3H), 3.00 (t, J = 7.3 Hz, 2H), 2.93 (t, J = 7.7 Hz, 2H), 2.28 (s, 3H), 2.05 (quintet, J = 7.3 Hz, 2H); MS ES+ *m/e* 292 (p + 1); IR (KBr, cm^{-1}) 2939, 1596, 1497, 1251. Anal. Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.14; H, 7.29; N, 4.83.

Preparation of 2-[(2-Methyl-1-benzyl-1,6,7,8-tetrahydrocyclopent[*g*]indol-4-yl)oxy]acetic Acid Methyl Ester (9). A solution of 1-benzyl-2-methyl-4-methoxy-1,6,7,8-tetrahydrocyclopent[*g*]indole (**8**; 2.2 g, 7.6 mmol) in chloroform (40 mL) was treated with boron tribromide (2.8 mL, 30 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 2.5 h. The mixture was poured into water and extracted with chloroform. The organic layer was washed once with water, once with saturated sodium chloride solution, dried (sodium sulfate), filtered, and concentrated in vacuo to provide an unstable blue oil. A solution of this material in *N,N*-dimethylformamide (35 mL) was treated with cesium carbonate (3.21 g, 9.10 mmol) and methyl bromoacetate (0.86 mL, 9.1 mmol) at room temperature. After stirring for 18 h, the mixture was poured into water and extracted with ethyl acetate. The organic layer was washed once with water and once with saturated sodium chloride solution, dried (sodium sulfate), filtered, and concentrated in vacuo. Chromatography (silica gel, 10% ethyl acetate/90% hexanes) provided 0.43 g (16%) of the title product as a white solid: mp 135−138 °C. ^{1}H NMR ($CDCl_3$) δ 7.22 (m, 3H), 6.88 (d, J = 7.0 Hz, 2H), 6.47 (s, 1H), 6.36 (s, 1H), 5.42 (s, 2H), 4.76 (s, 2H), 3.82 (s, 3H), 3.00 (t, J = 7.3 Hz, 2H), 2.90 (t, J = 7.3 Hz, 2H), 2.29 (s, 3H), 2.04 (quintet, J = 7.0 Hz, 2H); MS ES+ *m/e* 350 (p + 1).

Preparation of 2-[[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-benzyl-1,6,7,8-tetrahydrocyclo-pent[*g*]indol-4-yl]oxy]-acetic Acid Methyl Ester (10). A solution of 2-[(2-methyl-1-benzyl-1,6,7,8-tetrahydrocyclopent[*g*]indol-4-yl)oxy]acetic acid methyl ester (**9**; 0.38 g, 1.1 mmol) in methylene chloride (8 mL) was cooled to 0 °C and treated with oxalyl chloride (0.47

mL, 5.4 mmol). The resulting mixture was stirred for 1 h and concentrated in vacuo. The residue was dissolved in methylene chloride and concentrated in vacuo. The residue was again dissolved in methylene chloride (5 mL) and treated with a 1 M solution of ammonia in dioxane (10 mL). The mixture was stirred for 30 min and concentrated in vacuo. The resulting material was slurried in hot ethyl acetate, and the resulting solids were collected via vacuum filtration to provide 0.28 g (61%) of the title compound as a bright yellow solid: mp 226−228 °C. ^{1}H NMR (DMSO-d_6) δ 7.63 (bs, 1H), 7.30 (m, 4H), 6.92 (d, J = 7.3 Hz, 2H), 6.50 (s, 1H), 5.54 (s, 2H), 4.71 (s, 2H), 3.70 (s, 3H), 2.96 (t, J = 7.3 Hz, 2H), 2.82 (t, J = 7.3 Hz, 2H), 2.41 (s, 3H), 1.96 (quintet, J = 7.0 Hz, 2H); IR ($CHCl_3$, cm^{-1}) 3154, 1640, 1406. FAB+ MS exact mass calculated for $C_{24}H_{25}N_2O_5$: m/z = 421.1763 (p + 1). Found: 421.1768. Anal. Calcd for $C_{24}H_{24}N_2O_5$: C, 68.56; H, 5.75; N, 6.66. Found: C, 68.29; H, 5.85; N, 6.51.

Preparation of 2-[[3-(2-Amino-1,2-dioxoethyl)-2-methyl-1-benzyl-1,6,7,8-tetrahydrocyclopent[*g*]indol-4-yl]oxy]-acetic Acid (11). A solution of 2-[[3-(2-amino-1,2-dioxoethyl)-2-methyl-1-benzyl-1,6,7,8-tetrahydrocyclopent[*g*]indol-4-yl]oxy]-acetic acid methyl ester (**10**; 95 mg, 0.23 mmol) in a 1:1 mixture of methanol/tetrahydrofuran (1 mL) was treated with excess 1 M lithium hydroxide for 19 h at room temperature. The mixture was concentrated in vacuo, diluted with water, and acidified with 5 N hydrochloric acid. The resulting precipitate was collected via vacuum filtration and recrystallized (absolute ethanol) to provide 65 mg (71%) of the title product as yellow crystals: mp 255−257 °C. ^{1}H NMR (DMSO-d_6) δ 12.84 (bs, 1H, O*H*), 7.69 (bs, 1H), 7.33 (m, 4H), 6.92 (d, J = 7.0 Hz, 2H), 6.46 (s, 1H), 5.54 (s, 2H), 4.61 (s, 2H), 2.95 (t, J = 7.0 Hz, 2H), 2.82 (t, J = 7.3 Hz, 2H), 2.42 (s, 3H), 1.96 (quintet, J = 7.0 Hz, 2H); MS ES+ m/e 407 (p + 1). Anal. Calcd for $C_{23}H_{22}N_2O_5$: C, 67.97; H, 5.46; N, 6.89. Found: C, 68.07; H, 5.31; N, 7.22.

The following assays have been previously described: chromogenic assay;[4a] DOC/PC assay;[4c] transgenic human sPLA$_2$ mouse model.[3b]

Supporting Information Available: Detailed synthetic methods for the preparation of compounds in Table 1, including analytical and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Uhl, W.; Nevalainen, T. J.; Büchler, M. W., Eds. *Phospholipase A$_2$: Basic and Clinical Aspects in Inflammatory Diseases*; S. Karger, AG: Basel, 1997. (b) Kovanen, P. T.; Pentikäinen, M. O. Secretory Group II Phospholipase A$_2$: A Newly Recognized Acute-Phase Reactant With a Role in Atherogenesis. *Circ. Res.* **2000**, *86*, 610−612.

(2) Springer, D. M. An Update on Inhibitors of Human 14 kDa Type II s-PLA$_2$ in Development. *Curr. Pharm. Des.* **2001**, *7*, 181−198.

(3) (a) Schevitz, R. W.; Bach, N. J.; Carlson, D. G.; Chirgadze, N. W.; Clawson, D. K.; Dillard, R. D.; Draheim, S. E.; Hartley, L. W.; Jones, N. D.; Mihelich, E. D.; Olkowski, J. L.; Snyder, D. W.; Sommers, C.; Wery, J.-P. Structure-Based Design of the First Potent and Selective Inhibitor of Human Non-Pancreatic Secretory Phospholipase A$_2$. *Nat. Struct. Biol.* **1995**, *2*, 458−465. (b) Snyder, D. W.; Bach, N. J.; Dillard, R. D.; Draheim, S. E.; Carlson, D. G.; Fox, N.; Roehm, N. W.; Armstrong, C. T.; Chang, C. H.; Hartley, L. W.; Johnson, L. M.; Roman, C. R.; Smith, A. C.; Song, M.; Fleisch, J. H. Pharmacology of LY315920/S-5920, [[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]-acetate, a Potent and Selective Secretory Phospholipase A$_2$ Inhibitor: a New Class of Anti-inflammatory Drugs, SPI. *J. Pharmacol. Exp. Ther.* **1999**, *288*, 1117−1124.

(4) (a) Dillard, R. D.; Bach, N. J.; Draheim, S. E.; Berry, D. R.; Carlson, D. G.; Chirgadze, N. Y.; Clawson, D. K.; Hartley, L. W.; Johnson, L. M.; Jones, N. D.; McKinney, E. R.; Mihelich, E. D.; Olkowski, J. L.; Schevitz, R. W.; Smith, A. C.; Snyder, D. W.; Sommers, C. D.; Wery J.-P. Indole Inhibitors of Human Nonpancreatic Secretory Phospholipase A$_2$. 1. Indole-3-acetamides. *J. Med. Chem.* **1996**, *39*, 9(26), 5119−5136. (b) Dillard, R. D.; Bach, N. J.; Draheim, S. E.; Berry, D. R.; Carlson, D. G.; Chirgadze, N. Y.; Clawson, D. K.; Hartley, L. W.; Johnson, L. M.; Jones, N. D.; McKinney, E. R.; Mihelich, E. D.; Olkowski, J. L.; Schevitz, R. W.; Smith, A. C.; Snyder, D. W.; Sommers, C. D.; Wery J.-P. Indole Inhibitors of Human Nonpancreatic Secretory Phospholipase A$_2$. 2. Indole-3-acetamides With Additional Functionality. *J. Med. Chem.* **1996**, *39*(26), 5137−5158. (c) Dillard, R. D.; Bach, N. J.; Draheim, S. E.; Berry, D. R.; Carlson, D. G.; Chirgadze, N. Y.; Clawson, D. K.; Hartley, L. W.; Johnson, L. M.; Jones, N. D.; McKinney, E. R.; Mihelich, E. D.; Olkowski, J. L.; Schevitz, R. W.; Smith, A. C.; Snyder, D. W.; Sommers, C. D.; Wery J.-P. Indole Inhibitors of Human Nonpancreatic Secretory Phospholipase A$_2$. 3. Indole-3-glyoxamides. *J. Med. Chem.* **1996**, *39*, 9(26), 5159−5175.

(5) Bernard, P.; Pintore, M.; Berthon, J.-Y.; Chrétien, J. R. A Molecular Modeling and 3D QSAR Study of a Large Series of Indole Inhibitors of Human Non-Pancreatic Secretory Phospholipase A$_2$. *Eur. J. Med. Chem.* **2001**, *36*, 1−19.

(6) (a) Henn, L.; Hickey, D. M. B.; Moody, C. J.; Rees, C. W. Formation of Indoles, Isoquinolines, and Other Fused Pyridines from Azidoacetates. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2189−2196. (b) Adams, R. E.; Press: J. B.; Deegan, E. G. Synthesis of a 4-Hydroxy-1*H*-indole-2-carbonitrile via a Vinyl Nitrene Cyclization. *Synth. Commun.* **1991**, *12*, 675−681.

(7) Fox, N.; Song, M.; Schrementi, J.; Sharp, J. D.; White, D. L.; Snyder, D. W.; Hartley, L. W.; Carlson, D. G.; Bach, J. J., Dillard, R. D., Draheim, S. E.; Bobbitt, J. L.; Fisher, L.; Mihelich, E. D. Transgenic model for the discovery of novel human secretory nonpancreatic phospholipase A$_2$ inhibitors. *Eur. J. Pharmacol.* **1996**, *308*, 195−203.

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