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Tryptamine and homotryptamine-based sulfonamides as potent and selective inhibitors of 15-lipoxygenase

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Abstract—A series of inhibitors of mammalian 15-lipoxygenase based on tryptamine and homotryptamine scaffolds is described. Compounds with aryl substituents at C-2 of the indole core of tryptamine and homotryptamine sulfonamides (e.g., **37a**–**p**) proved to be potent inhibitors of the isolated enzyme. Selected compounds also demonstrated desirable inhibition selectivities over isozymes 5- and P-12-LO.

Mammalian lipoxygenases (LO's) are nonheme iron-containing enzymes responsible for the oxidation of polyunsaturated fatty acids and esters to hydroperoxy derivatives.[1] A heterogeneous family of enzymes distributed widely throughout the plant and animal kingdoms,[2] they are named according to the position at which a key substrate, arachidonic acid (AA) is oxidized. Of the mammalian lipoxygenases involved in the etiology of human disease, 5-lipoxygenase (5-LO) is now well established as a target for inhibiting the production of leukotrienes involved in the progression of inflammatory diseases, in particular asthma.[3] More recently, 15-lipoxygenase (15-LO) has emerged as an attractive target for therapeutic intervention.[4] 15-LO has been implicated in the progression of certain cancers[5] and chronic obstructive pulmonary disease (COPD).[6] Evidence for the inhibition of 15-LO in the treatment of vascular disease is, however, most compelling.[7] Both transgenic and knockout studies implicate a role for 15-LO in atherogenesis.[8] The enzyme is abundantly expressed in macrophages residing within the atherosclerotic lesion.[4] In addition, the immediate products of 15-LO oxidation of AA and linoleic acid (LA) have been shown to be pro-inflammatory[9] and prothrombotic.[10]

Previously reported inhibitors of 15-LO include PD-146176 (**1**, Fig. 1),[11] nordihydroguaiaretic acid (NDGA, **2**),[12] the sponge-derived terpenoids jaspaquinol (**3**) and jaspic acid (**4**),[13] and some naturally occurring flavonoids.[14] PD-146176 reportedly demonstrated efficacy in an animal model of atherosclerosis.[11] At least some of the inhibitory effects of these naturally-derived phenol-containing 15-LO inhibitors **2**–**4** is believed to be due to their anti-oxidant and/or radical scavenging properties.[12–15]

We set out to identify potent inhibitors of 15-LO with selectivity over the two other significant human lipoxygenases, 5-LO and platelet-derived 12-LO (P-12-LO). To reduce the potential for off-target pharmacology, the inhibitors would also need to be reversible, nonredox inhibitors of the enzyme. A virtual 4-point pharmacaphore screen[16] of our corporate compound collection utilizing **1** was carried out, and high-scoring compounds were assayed for their inhibition of isolated rabbit reticulocyte 15-LO in the presence of both AA and LA as substrates.[17] These efforts led to the identification of dansyl tryptamine **5** as a modestly potent 15-LO inhibitor with an IC_{50} of 4.1 μM with LA as substrate.

Keywords: 15-Lipoxygenase inhibitors; Arachadonic acid; Linoleic acid; Tryptamine; Homotryptamine; Sulfonamides.
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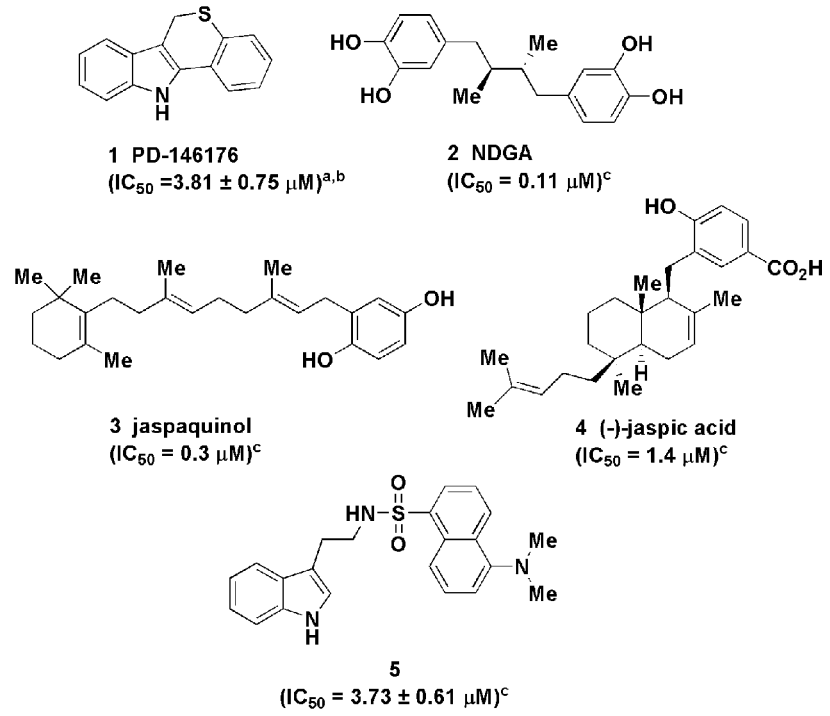


Figure 1. Some known inhibitors of 15-LO and dansyl tryptamine **5**. [a]Enzyme inhibition measured in the presence of LA as substrate. [b]Standard deviations are based on multiple test occasions ($n \geqslant 2$). [c]As reported in the literature.[12,13]

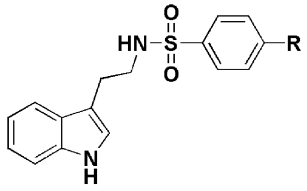
Replacement of the dansyl moiety of **5** with *para*-substituted phenyl sulfonamides (prepared by treatment of tryptamine with commercially available sulfonyl chlorides in dichloromethane in the presence of triethylamine) gave compounds of improved potency (Table 1). While introduction of a methyl or ethyl group (**6** and **7**) provided inactive compounds, chain elongation to *n*-propyl led to a compound (**8**) equipotent with dansyl tryptamine **5**. Potency continued to improve with chain extension, leading to the identification of the *n*-pentyl substituted phenyl sulfonamide **10** as the first submicromolar 15-LO inhibitor in this series.

The biaryl tryptamine sulfonamides **11**–**20** were prepared via Suzuki-coupling of the 4-bromophenyl sulfonamide derivative **21** with arylboronic acids, as shown in Scheme 1.

The biphenylsulfonamide derivative **11** was found to be equipotent with dansyl tryptamine **5**. A methyl walk on the pendant phenyl ring gave improvement in activity at all three positions (compounds **12**–**14**), particularly in competition with AA as substrate. *para*-Substitution of the distal phenyl ring in **11** with small alkyl groups led to improved activity against both AA and LA as substrates (**15**–**19**). The isopropyl and the 4-*tert*-butyl groups (compounds **16** and **19**, respectively) at this position were found to provide the most potency.

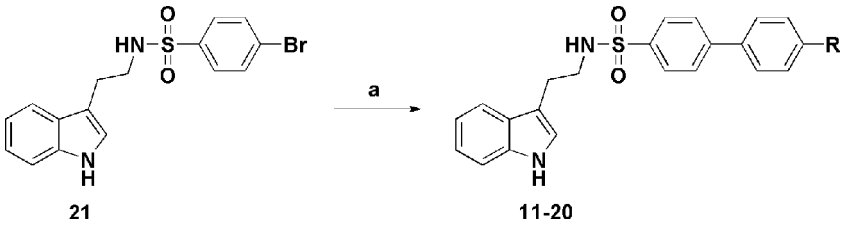
The linker region between indole and sulfonamide moieties was then studied (Fig. 2, Table 2). *N*-Methylation of the sulfonamide moiety of **10** gave **22**, which showed a complete loss of activity against 15-LO. The acidic acylsulfonamide analogue **23** and racemic sulfonyl pyrrolidine **24** also proved to be inactive (IC_{50} >10 μM). The α-methyl sulfonamide **25** led to a nearly fourfold

Table 1. 15-LO inhibitory activities of tryptamine sulfonamides



Compd	R	15-LO IC_{50} (μM)	
		LA[a]	AA[b]
6	CH_3	>10	>10
7	Et	>10	>10
8	*n*-Propyl	3.13 ± 0.05	3.2
9	*n*-Butyl	3.07 ± 2.22	4.0
10	*n*-Pentyl	0.42 ± 0.01	1.02 ± 0.13
11	Ph	3.40 ± 2.0	4.2
12	2-Me-Ph	0.92	0.46
13	3-Me-Ph	0.45	0.32 ± 0.07
14	4-Me-Ph	–[c]	0.47
15	4-Et-Ph	0.26	0.47
16	4-*i*-Pr-Ph	0.28 ± 0.02	0.14 ± 0.05
17	4-*n*-Butyl-Ph	0.53	0.20
18	4-*i*-Butyl-Ph	0.91	0.17
19	4-*t*-Bu-Ph	0.27	0.23
20	4-OMe-Ph	1.50	1.09

[a] Enzyme inhibition measured in the presence of linoleic acid as substrate.
[b] Enzyme inhibition measured in the presence of arachidonic acid as substrate.
[c] Not tested.



Scheme 1. Reagents and conditions: (a) $ArB(OH)_2$, Na_2CO_3, ethanol/toluene (1:1), $Pd(PPh_3)_4$ (65–85%).

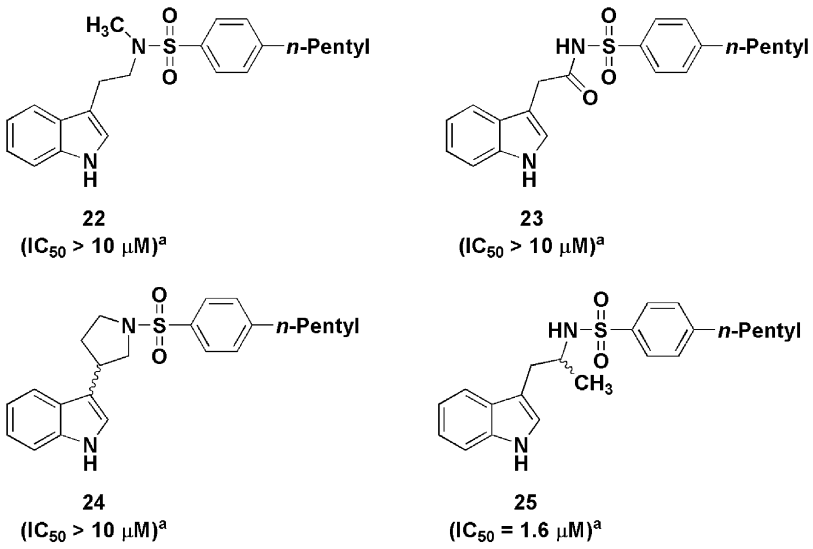
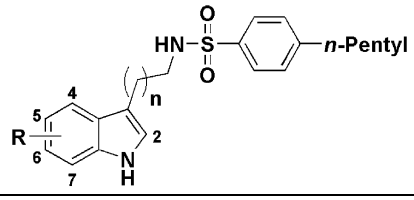


Figure 2. SAR of the linker group. [a]Enzyme inhibition measured in the presence of LA as substrate.

Table 2. 15-LO inhibitory activities of tryptamine and homotryptamine sulfonamides **26**–**34**



Compd	*n*	R	15-LO IC_{50} (μM)	
			LA[a]	AA[b]
26	2	H	0.047 ± 0.003	0.30 ± 0.11
10	1	H	0.42 ± 0.01	1.02 ± 0.13
27	3	H	0.11 ± 0.02	0.73 ± 0.09
28	1	7-CH_3	—[c]	3.3
29	1	5-CH_3	—	3.9
30	1	5-F	—	6.3
31	1	6-F	—	2.9
32	1	6-CO_2CH_3	0.236	0.472 ± 0.08
33	1	6-CO_2H	24	>30
34	1	5-(2-Pyrrolyl)	0.78 ± 0.13	—

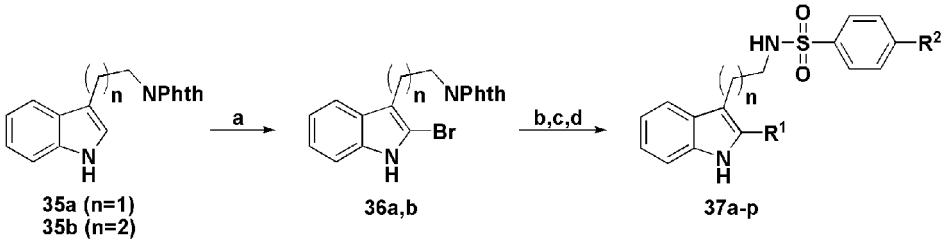
[a] Enzyme inhibition measured in the presence of linoleic acid as substrate.
[b] Enzyme inhibition measured in the presence of arachidonic acid as substrate.
[c] Not tested.

loss in potency relative to the unsubstituted tryptamine derivative **10**.

To identify the optimal chain length between the indole and the sulfonamide moieties, the homotryptamine sulfonamide derivative **26** was prepared (Table 2). This compound proved to be 10-fold more potent than the corresponding tryptamine derivative **10** with LA as substrate, and about fourfold more potent with AA as substrate. Further chain-length extension of the linker portion proved to be deleterious, the indolylbutyl phenylsulfonamide **27** losing two to threefold potency over **26**.

The effects of introduction of substituents to the benzene ring of the indole core were then studied. Little change in potency (with AA as substrate) was noted with the introduction of methyl groups to C-7 and C-5 of the indole core (**28** and **29**). Fluorine substituents at C-5 and C-6 (**30** and **31**) also failed to improve potency. Introduction of a carboxymethyl group to C-6 of the indole core (**32**) did provide a twofold improvement in potency over the parent tryptamine derivative **10**, while the corresponding carboxylic acid **33** proved to be virtually inactive.

An important advance was realized with the incorporation of substituents to C-2 of the indole core (Scheme 2, Table 3). Regioselective bromination of C-2 of phthalimide-protected tryptamine **35a** was carried out as previously described,[18] and was also found to be effective for the bromination of homotryptamine phthalimide[19] **35b**. Subsequent Suzuki couplings of bromides **36a**,**b** with



Scheme 2. Reagents and conditions: (a) pyridinium tribromide, THF, $CHCl_3$ (73%); (b) $R^1B(OH)_2$, LiCl, Na_2CO_3, ethanol/toluene (1:1), $Pd(PPh_3)_4$ (5 mol %) (30–75%); (c) NH_2NH_2, MeOH (80–95%); (d) *p*-(R^2)$PhSO_2Cl$, Et_3N, CH_2Cl_2 (95%).

Table 3. 15-LO inhibitory activities of C-2 substituted tryptamine and homotryptamine sulfonamides **37a–p**

Compd	*n*	R^1	R^2	15-LO IC_{50} (μM)	
				LA[a]	AA[b]
6	1	H	CH_3	>10	>10
37a	1	(4-OCH_3)Ph	CH_3	0.11	0.78
37b	1	(4-OCH_3)Ph	*n*-Butyl	0.11 ± 0.01	—[c]
37c	1	(4-OCH_3)Ph	*n*-Pentyl	0.037	0.164
37d	1	(4-OCH_3)Ph	CO_2H	>10	—[c]
37e	1	(4-OCH_3)Ph	Ph	0.027 ± 0.005	0.247
37f	1	Ph	*n*-Pentyl	0.062	0.14 ± 0.023
37g	1	(3-CH_3)Ph	*n*-Pentyl	0.025	0.058 ± 0.012
37h	1	(4-Cl)Ph	*n*-Pentyl	0.032	0.12 ± 0.040
37i	1	(4-OEt)Ph	*n*-Pentyl	0.011	0.039
37j	1	(4-CF_3)Ph	*n*-Pentyl	0.011	0.042
37k	1	(2,5-DiOMe)Ph	*n*-Pentyl	0.028 ± 0.001	0.132
37l	1	2-Benzofuranyl	*n*-Pentyl	0.006 ± 0.001	0.021 ± 0.001
37m	2	2-Benzofuranyl	*n*-Pentyl	0.010 ± 0.003	0.014
37n	2	2-Benzofuranyl	Ph	0.008 ± 0.001	0.017
37o	1	2-Dibenzofuranyl	*n*-Pentyl	0.010 ± 0.002	0.071 ± 0.032
37p	1	3-Quinolinyl	*n*-Pentyl	0.013	0.050

[a] Enzyme inhibition measured in the presence of linoleic acid as substrate.
[b] Enzyme inhibition measured in the presence of arachadonic acid as substrate.
[c] Not tested.

commercially available boronic acids followed by hydrazinolysis of the phthalimide functionality and sulfonylation of the resulting primary amines gave C-2 aryl-substituted tryptamine and homotryptamine sulfonamides **37a–p**.

While tosyl tryptamine **6** is inactive against 15-LO, introduction of a *p*-methoxy phenyl group to C-2 of the indole core gave a compound (**37a**) with greater than 100-fold improvement in potency. Chain elongation of the alkyl group at the *para*-position of the phenyl sulfonamide moiety to *n*-butyl (**37b**) gave no improvement in inhibition, while the *n*-pentyl analog **37c** provided only modest improvements in potency, obviating the need for a very large hydrophobic substituent at that position. Substitution with a carboxylic acid group provided an inactive compound (**37d**). The biphenyl sulfonamide **37e** proved to be of similar potency to *n*-pentyl substituted **37c**. Little effect on potency was noted with modification of the substituents about the phenyl ring at C-2 of the indole core (**37f–k**). More dramatic effects were observed with increasing bulk of the indole C-2 group. Thus, the 2-benzofuranyl tryptamine and homotryptamine derivatives **37l–m**[20] were both single digit nanomolar enzyme inhibitors (LA), with very similar potencies employing AA as substrate. The nearly equipotent activities of **37l–n** is noteworthy given the large difference in potencies for the C-2 unsubstituted tryptamine and homotryptamine derivatives **10** and **26**. Groups of similar or even large size to benzofuran (dibenzofuran **37o** and quinoline **37p**) were nearly equally tolerated as benzofuran with LA as substrate, and 4–5 fold less potent with AA as substrate.

Structure–activity relationships around the 2,2′-linked benzofuranyl tryptamine core of sulfonamide **37l** were then studied (Table 4). To this end, phthalimide **38** (Scheme 3) was prepared following the procedures described in Scheme 2. Methylation of the free indole nitrogen, followed by hydrazinolysis of the phthalimide and subsequent sulfonylation provided the *N*-methyl tryptamine derivative **39**. The amine resulting from hydrazinolysis of phthalimide **38** was also sulfonylated with tosyl chloride to give **40a**. Sulfonylation of the same intermediate amine with *p*-bromobenzene sulfonyl chloride gave bromide **40b**, which was subsequently coupled with 4-pyridyl boronic acid under standard Suzuki conditions to give the 4-pyridylphenyl sulfonamide **40c**. Amides **40d–j** were also prepared by sulfonylation with 4-(chlorosulfonyl)benzoic acid followed by condensation with various amines under standard conditions.

Table 4. 15-LO inhibitory activities of 2-(2′-benzofuranyl)tryptamine sulfonamides **37l**, **39**, **40a–j**

Compd	R	15-LO IC_{50} (μM)	
		LA[a]	AA[b]
37l	*n*-Pentyl	0.006	0.02
39	—	0.143 ± 0.029	1.42
40a	CH_3	0.010 ± 0.001	0.078
40b	Br	0.030 ± 0.002	0.161
40c	4-Pyridyl	0.047 ± 0.01	0.179 ± 0.113
40d	C(O)NHPh	0.015 ± 0.003	0.051
40e	C(O)NH(4-OCH_3)Ph	0.011 ± 0.001	0.026
40f	C(O)NH*n*-butyl	0.042 ± 0.008	0.112
40g	C(O)NHcyclohexyl	0.012 ± 0.001	0.034
40h	$C(O)NHNH_2$	0.089 ± 0.010	0.135 ± 0.045
40i	$C(O)N(CH_3)$-$(CH_2)_2OH$	0.440 ± 0.008	4.05
40j	$C(O)N(CH_3)$-$(CH_2)_2N(CH_3)_2$	0.076 ± 0.011	0.382

[a] Enzyme inhibition measured in the presence of linoleic acid as substrate.

[b] Enzyme inhibition measured in the presence of arachidonic acid as substrate.

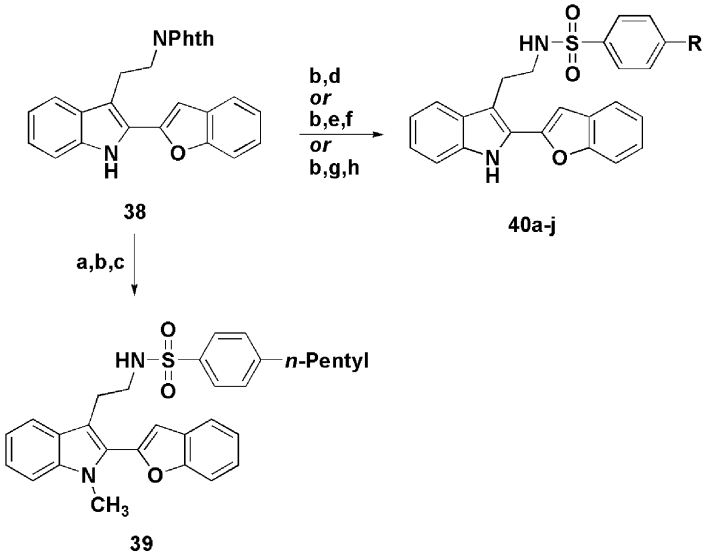
The *N*-methyl indole analog **39** proved to be significantly less potent than the corresponding unmethylated indole **37l**. The loss in potency may be attributed to size restrictions imposed by the enzyme and/or the need for a hydrogen bond donor at this position in the inhibitor. The tosyl benzofuranyl tryptamine **40a** maintained most of the potency of the *n*-pentyl benzene sulfonamide **37l**, offering the advantage of somewhat decreased lipophilicity. The 4-pyridyl substituent of **40c** gave no distinct advantage over the simple methyl group of **40a**, with a fivefold decrease in potency in competition with LA as substrate. Anilides **40d–e** and secondary amides **40f–g** also maintained good enzyme inhibitory activity. Efforts to improve the hydrophilicity (log *P*) of the benzofuranyl tryptamine leads with polar group-bearing side chains included acyl hydrazide **40h**, alcohol **40i**, and amine **40j**. The improved physicochemical properties of these compounds was accompanied by some compromise in inhibitory potency over the simply alkyl-substituted benzene sulfonamides **37l** and **40a**.

Several compounds were assayed for inhibition selectivities over the lipoxygenase isoforms 5- and P-12- LO (Table 5). Inhibitory activities of potent 15-LO inhibitors in these related enzymes were measured following the oxidation of AA as substrate. All compounds tested showed at least a 20-fold selectivity for 15-LO over 5-LO. The homotryptamine-derived 4-(*n*-pentyl)benzene sulfonamide **26** proved to be only modestly selective (three-fold) for 15-LO over P-12-LO. The incorporation of an aryl group to C-2 of the indole core of this series appears to have ameliorated this problem, with compounds **37c**,**f**,**h**,**l** and **40a**,**h** proving to be at least 60-fold selective for 15-LO over P-12-LO.

The identification of potent inhibitors of 15-LO may ultimately lead to therapies for indications in which the enzyme is believed to be involved. The work described here has demonstrated that highly potent inhibitors of 15-LO may be generated via simple tryptamine and homotryptamine precursors by introduction of aryl

Table 5. Selectivity data for selected compounds

Compd	IC_{50} (μM)	
	5-LO	P-12-LO
26	>10	1.07
37c	8.9	>10
37f	>3	>10
37h	>3	>10
37l	>3	>3
40a	>10	>10
40h	3.5	>10



Scheme 3. Reagents and conditions: (a) NaH, MeI, DMF (97%); (b) NH_2NH_2, MeOH (93–96%); (c) 4-*n*-pentylbenzenesulfonyl chloride, triethylamine, CH_2Cl_2 (95%); (d) *p*-toluenesufonyl chloride, triethylamine, CH_2Cl_2 (95%); (e) (4-Br)$PhSO_2Cl$, triethylamine, CH_2Cl_2 (95%); (f) 4-pyridylboronic acid, LiCl, Na_2CO_3, ethanol/toluene (1:1), $Pd(PPh_3)_4$ (5 mol %) (38%); (g) 4-(chlorosulfonyl)benzoic acid, triethylamine, CH_2Cl_2 (85%); (h) amine, HOAt/EDC, CH_3CN (55–75%).

and heteroaryl substituents to the indole C-2 position. Similarly, a wide range of substituents are tolerated on the aryl sulfonamide portion of the molecule, and provide a handle for modulating their physical properties. The unprecedented potency and lipoxygenase selectivity profiles of the tryptamine sulfonamides make them attractive leads for optimization of pharmacokinetic properties and assessment in models of 15-LO mediated diseases, such as atherosclerosis.

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17. 15-LO enzyme was obtained from phenylhydrazine-treated rabbits and purified according to the method of Rapoport et al. [*Eur. J. Biochem.* **1979**, *96*, 546]. Recombinant human 5-LO and 12-LO enzymes were from a commercial source (Caymen Chemical). The inhibitory activity of the compounds against purified 15-LO enzyme was determined using a standard colorimetric assay in which the lipid hydroperoxide product of either linoleic or arachidonic acid [13-hydroperoxyoctadecadienoic acid (13-HPODE) and 15-hydroperoxyeicosatetraenoic acid (15-HPETE), respectively] oxidizes Fe^{2+} under mildly acidic conditions Jiang et al. [*Lipids* **1991**, *26*, 853]. The Fe^{3+} forms a chromophore with xylenol orange that absorbs strongly at 560 nm. Inhibitory activity was compared to an uninhibited (maximal) reaction to yield % inhibition (compound concentration in which enzyme activity is reduced by 50% is termed the IC_{50}). The inhibitory activity of the compounds against 5-LO [*Biochemistry* **1995**, *34*, 13603] and 12-LO [*Methods Enzymol.* **1982**, *86*, 49] enzyme were determined by standard methods using a spectrophotometer to measure the rate of diene formation (A_{234}). Many of the IC_{50} values generated for 15-LO enzyme using the colorimetric assay were also verified in the spectrophotometric assay.
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20. N-(2-(2-(benzofuran-2-yl)-1*H*-indol-3-yl)ethyl)-4-pentylbenzenesulfonamide (**37l**). HPLC [YMC S5 ODS 4.6 × 40 mm, 4 mL/min, 90% water/methanol to 90% methanol/water, 0.2% phosphoric acid, 4 min gradient] t_R = 4.28 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80 (t, 3H, J = 7 Hz), 1.20–1.27 (m, 4H), 1.49 (m, 2H), 2.51 (dd, 2H, J = 15, 8 Hz), 3.22 (dd, 2H, J = 13, 6 Hz), 3.29 (dd, 2H, J = 13, 7 Hz), 6.93 (s, 1H), 7.04 (dd, 1H, J = 15, 8 Hz), 7.10 (d, 2H, J = 8 Hz), 7.15–7.26 (m, 3H), 7.31 (d, 1H, J = 8 Hz), 7.42 (d, 2H, J = 8 Hz), 7.53 (d, 1H, J = 7 Hz), 7.57 (d, 2H, J = 8 Hz), 8.54 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.36, 22.83, 25.97, 31.08, 31.76, 36.15, 43.33, 103.21, 111.24, 111.36, 111.54, 119.21, 120.77, 121.53, 123.81, 124.04, 125.05, 126.05, 127.38, 128.98, 129.35, 136.26, 137.36, 148.62, 148.82, 154.45. ESI-MS *m/e* Calcd for $C_{29}H_{30}N_2O_3S$ 486.2. Found 487.4 $[M+H]^+$.