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SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF SC-53228, A LEUKOTRIENE B_4 RECEPTOR ANTAGONIST WITH HIGH INTRINSIC POTENCY AND SELECTIVITY

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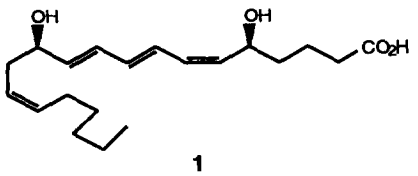
Abstract

The Structure Activity Relationship (SAR) studies leading to the identification of a novel high potency Leukotriene B_4 receptor antagonist SC-53228 are delineated. This compound shows excelled pharmacodynamic efficacy in animal models of inflammatory disease.

Leukotriene B_4 [(5S, 12R)-dihydroxy-6, 14-cis, 8, 10-trans-eicosatetraenoic acid], (LTB_4)[1], **1** has been shown to stimulate the aggregation and degranulation of human neutrophils[2], promote chemotaxis and chemokinesis of leukocytes and is a mediator of lysosomal enzyme release and superoxide generation[3]. It has been postulated as a primary pathologic mediator of a number of inflammatory diseases including psoriasis and inflammatory bowel disease.



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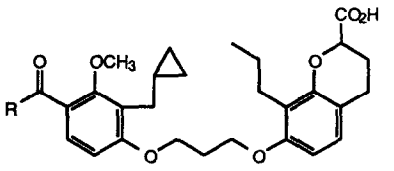
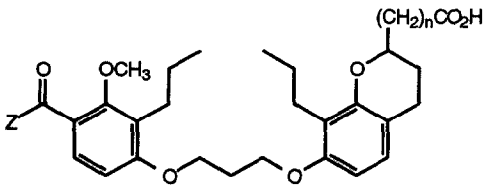
Our strategy at Searle over the last few years has been to identify novel Leukotriene B_4 receptor antagonists (LTB_4-RA) as potential therapeutic agents for the treatment of the above disease states. These studies showcased SC-41930 **2** as a prototype orally active LTB_4-RA which is currently undergoing Phase II clinical trials in man.



SC-41930 R = CH_3, **2**
SC-48928 R = NH_2, **3**

Our recent studies have been directed towards the production of a backup compound for our flagship antagonist. To this end, through an exhaustive series of SAR studies, we unearthed the primary amide SC-48928, **3** as a promising lead. This compound showed enhanced potency relative to **2** in our *in vitro* panel of biological assays [4] including receptor binding and neutrophil chemotaxis. A series of amide containing analogs were synthesized and both primary and secondary amides were noted to show acceptable pharmacologic profiles (Table 1).

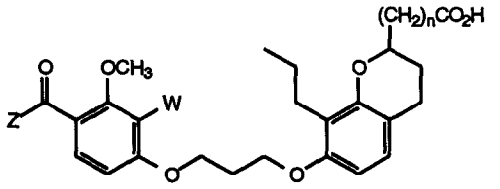


SC	Z	n	LTB_4 Receptor** Binding[a]	LTB_4 Induced** Chemotaxis[a]
41930	CH_3	0	1.0	1.0
48928	NH_2	0	2.4±0.3	2.7 (n=2)
50073	$NHCH_3$	0	0.85±0.05	1.3±0.66
52073	NH*i*Pr	0	0.1	0.11±0.00
52569	NMe2	0	0.15±0.05	<0.14±0.06
50135	N⬠	0	<0.1	<0.16±0.06

**Data expressed as potency relative to SC-41930.
IC_{50} receptor binding = 32 ± 2 nM;
IC_{50} chemotaxis = 1.79 ± 0.49 μM
a) Values are either individual determinations or mean ± SEM of 2 or more assays

Table 1

At this juncture, further SAR studies were conducted in which we incorporated pharmacophoric fragments into the basic SC-48928 structural framework that we knew from our previously reported studies[5] could lead to enhancements of intrinsic potency within the series (Table 2).



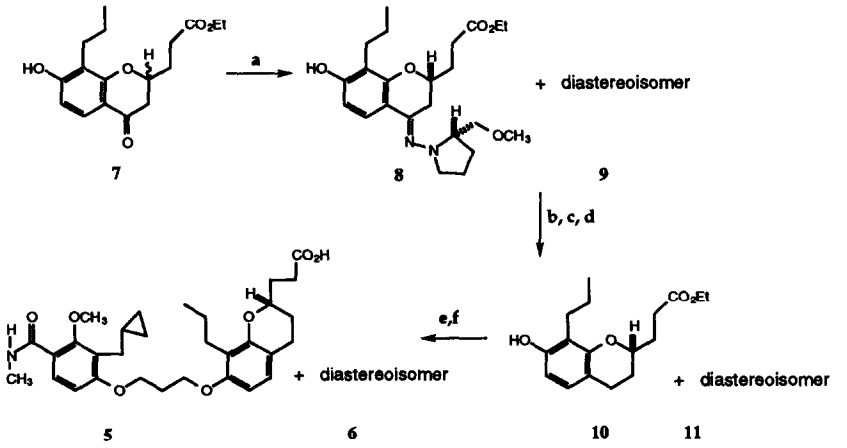
SC	Z	W	n	LTB_4 Receptor** Binding[a]	LTB_4 Induced** Chemotaxis[a]
41930 , 2	CH_3	propyl	0	1.0	1.0
50073	$NHCH_3$	propyl	0	0.85 ± 0.05	1.3 ± 0.66
50676	$NHCH_3$	cpMe	0	5.3 ± 0.8	13.0 ± 4.0
51146 , 4	$NHCH_3$	cpMe	2	10.9 ± 0.9	21.9 ± 6.0
53228 , 5 (S)	$NHCH_3$	cpMe	2	14.5 ± 1.6	24.4 ± 6.1
53229 , 6 (R)	$NHCH_3$	cpMe	2	8.5 ± 1.4	10.7 ± 0.3

**Data expressed as potency relative to SC-41930.
cp = Cyclopropyl
a) Values are either individual determinations or mean ± SEM of 2 or more assays.

Table 2

As can be seen from Table 2, SC-51146, **4**, emerged from these studies as a relatively optimized structural congener of **3** with respect to its *in vitro* pharmacology profile. **4** was subsequently resolved into its individual constitutive antipodes as shown in Scheme I.

Scheme I



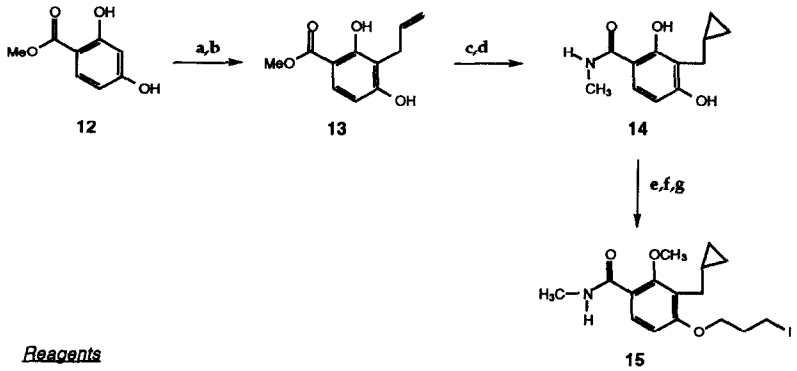
7 8 9 10 11 5 6

Reagents

a) SAMP, 60°C, 58%; b) CH_3I; c;) 2N HCl, EtOAc/pentane, 44% yield for 2 steps; d) 4% Pd/C, EtOAc, 60 psi, 60°C; e) 15, K_2CO_3, DMF, 25°C, 48%; f) 1N LiOH/MeOH, 100%.

The success of this process relied heavily on the use of homochiral RAMP/SAMP hydrazines developed by Enders[6]. Briefly, the known chromanone[7] **7** was treated with neat (S)-(-)1-amino-2-(methoxymethyl)pyrrolidine at 60°C and the diastereoisomeric pair of hydrazones **8** and **9** separated by flash chromatography (EtOAc/hexane,2:8). The individual ketones were regenerated by sequential methylation and acid hydrolysis. Catalytic hydrogenolysis of these ketones (4% Pd/C, EtOAc, 60 psi) provided the requisite chroman derivatives **10** and **11**. These were transformed to the desired end products by coupling with the key cyclopropane containing western fragment **15** which was constructed as shown in Scheme II. Allylation of commercially available methyl 2,4-dihydroxybenzoate **12** under standard conditions (allyl bromide, potassium carbonate, DMF) provided the 4-allyl ether as the predominant product along with a smaller quantity (~5%) of the 2-allyl ether. This mixture was subjected to thermally induced Claisen rearrangement (neat, 190°C) to access the requisite tetrasubstituted aromatic nucleus **13**. The yield for these two steps was ~55%. Cyclopropanation of the allyl group was best effected by the use of diazomethane under palladium acetate catalysis (quantitative yield)[8]. This diol ester was converted, uneventfully to the amide **14** with a 40% solution of methylamine in water containing catalytic sodium cyanide and the linker attached under standard conditions ($Cl(CH_2)_3Br$, DMF, K_2CO_3). This reaction proved to be non-selective and low yielding (~45% yield). Methylation (dimethyl sulfate, KOH, THF) followed by Finkelstein reaction (NaI, MEK) provided **15**. The synthesis of either SC-53228 (+)-**5** or SC-53229 (-)-**6**[9] was finally consummated by the coupling of fragments **15** and **10** or **11** in a 2-step process involving intermolecular alkylation (K_2CO_3,DMF) followed by lithium hydroxide mediated ester hydrolysis.

Scheme II



Reagents

a)  (1 equiv), K_2CO_3 (2.1 equivs.) acetone, reflux, 85%; b) 190°C, neat, 65%;
c) CH_2N_2, $Pd(OAc)_2$, Et_2O, 100%; d) 40% CH_3NH_2 in water, cat. NaCN, 50°C, 80%;
e)  , K_2CO_3, DMF, 39%; f) Me_2SO_4, KOH, THF, 100%; g) NaI, MEK, reflux, 83%.

Both antipodes of SC-51146 were found to be extremely potent binders to the LTB_4 receptor on human neutrophils and antagonists in our battery of functional assays. This data is also shown in Table 2.

Both **5** and **6** displayed little or no pharmacologic promiscuity in that they exhibited no significant activity in either LTD_4 receptor binding (at μM concentrations) or fMLP induced human neutrophil degranulation assays. In addition, neither compound was found to inhibit the 5-LO, LTA_4 hydrolase or porcine pancreatic PLA_2 enzyme also at μM concentrations.

Based on its overall *in vitro* profile, SC-53228 was compared to SC-41930 in several *in vivo* inflammation paradigms (Table 3)[10] and found to be more potent in all cases. In addition, in the intradermal chemotaxis assay it exhibited a markedly enhanced pharmacodynamic duration of action relative to SC-41930 when administered orally at a dose of 3 mg/kg (24 vs. 5.5 hours).

***In vivo* Bioassays**

	Guinea pig LTB_4 induced Intradermal Chemotaxis	TPA induced Ear inflammation in the mouse	
	Oral ED_{50}	Topical ED_{50}	Oral ED_{50}
SC-41930	1700 ± 200 μg/kg	1400 ± 180 μg	18 mg/kg
SC-53228	70 ± 20 μg/kg	200 ± 62 μg	<2.5 mg/kg
SC-53229	200 ± 40 μg/kg	1200 ± 175 μg	ND

Table 3

Based on the above data and encouraging initial pharmacokinetic, pharmacodynamic and toxicologic profiles[11] in the guinea pig, rat, dog and primate, SC-53228 has been selected for clinical development.

Acknowledgements

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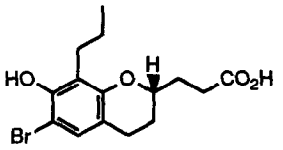
9. The absolute stereochemistry of SC-53228 was determined by X-ray crystallographic analysis of compound **16**, a derivative of intermediate **10**.



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