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SB-207266

Introduction

SB-207266, N-[(1-butyl-4-piperidinyl)methyl]-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide hydrochloride, is a potent and selective 5-HT₄ receptor antagonist in Phase III clinical trials for the treatment of irritable bowel syndrome. 5-HT₄ receptors are present in a number of different tissues both in the central nervous system and in the periphery. In the periphery, 5-HT₄ receptors are especially abundant in the gastrointestinal tract and activation of these receptors is associated with an increase in gastrointestinal motility and secretions, components associated with irritable bowel syndrome. There are no effective remedies for irritable bowel syndrome available at present. A selective 5-HT₄ antagonist is therefore of interest in treating this disease.

Synthesis and SAR

SB-207266 was one of ten indole-3-esters and indole-3-amides that were synthesized and evaluated for their receptor binding profiles and functional effects using several in vitro and in vivo assays [194582]. The ten compounds produced in the study consisted of five indole esters and five indole amides; both sets of five compounds reprised the same substitution patterns on the indole ring. Thus, the amides and esters each contained the following substitution patterns: unsubstituted, 2-methoxyindole, oxazolo-, oxazino-, and oxazepino-[3,2-a]indoles. To synthesize SB-207266, (1-butyl-4-piperidinyl)methylamine [1] was first coupled to indol-3-oyl chloride in the presence of triethylamine in methylene chloride to generate the indole amide. The [3,2-a]oxazino moiety was introduced into the indole nucleus by reaction of the indole amide with N-chlorosuccinimide in chloroform, followed by treatment of the solution with 3-bromopropan-1-ol. The resulting halo ether was then cyclized with potassium carbonate in acetone to give SB-207266 [194582]. No synthetic yields were reported.

The ten compounds were tested for their abilities to inhibit 5-HT-induced contractions of the guinea pig distal colon longitudinal muscle myenteric plexus preparation (LMMP). The results showed that the indole esters were consistently more potent than the corresponding indole amide derivatives [194582]. The potency of the amide-based compounds was increased by the introduction of an ether substituent into the indole nucleus, with the oxazino-[3,2-a]indole derivative (SB-207266) displaying the highest potency in this assay with an IC₅₀ of 0.63 nM. This drug was about 10-fold more potent than the oxazepine compound and about 25-fold more potent than the oxazole homologue. The unsubstituted indole amide had an IC₅₀ of about 200 nM. Oxazolo-, oxazino-, and oxazepino-substituents on the indole ring also increased potency in the indole-3-ester series of compounds, but due to the biological lability of esters compared to amides, it was anticipated that the indole ester series would have limited bioavailability.

Pharmacology

SB-207266 was assayed by Schild analysis in a concentration range of 0.1-100 nM; the agonist response was 5-HT-induced contractions of the guinea pig distal colon LMMP. The apparent pA₂ for SB-207266 was 10.6 ± 0.1 (= 25 pM) in this assay [194582]. Two other reports from the same laboratory reiterated this value [237234, 213694] and presented more detailed pharmacology. SB-207266 was devoid of any intrinsic activity when it was tested alone. The

partial serotonergic agonist activity of (endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-3-ethyl-2-oxo-1H-benzimidazole-1-carboxamide hydrochloride (BIMU 1) on the LMMP was antagonized by SB-207266 at all doses tested (0.1-10 nM) in one report [237234] and in a dose-dependent manner in another report [213694] with complete antagonism observed at 10 nM. SB-207266 at concentrations up to 1 μ M had no effect on the cholinergically-mediated contractions induced by the nicotinic agonist 1,1-dimethyl-4-phenyl-piperazinium iodide [194582, 213694]. The antagonist effect of SB-207266 was fully reversible, as responses to 5-HT were restored to control levels after drug washout [194582, 213694]. SB-207266 was profiled for its receptor binding [194582, 237234]. At 5-HT_{1A}, 5-HT_{1D}, and 5-HT_{1E} receptors, SB-207266 had a $K_i > 10 \mu$ M. At 5-HT_{2A}, 5-HT_{2C}, 5-HT₃, D₂, D₃, and H₁ receptors, SB-207266 had a $K_i > 1 \mu$ M. The K_i for the 5-HT₄ receptor, defined as the ability to displace [¹²⁵I]-SB-207710 [2] binding in piglet hippocampal membranes, was reported to be 0.5 nM [194582]. SB-207266 was evaluated in conscious dogs for its ability to block 5-HT₄ receptor-mediated contractile activity in a Heidenhain gastric pouch preparation [194582, 213694, 237234]. Intravenous administration of SB-207266 in a range of 0.1-100 μ g/kg produced no effect on basal motility [213694]. At 100 μ g/kg iv., SB-207266 abolished the contractile effect induced by 5 or 10 μ g/kg 5-HT within 15 min and this blockade persisted over the entire 105 min time course of the experiment [194582, 213694, 237234]. The 5-HT response was attenuated but not completely abolished by doses of 0.1, 1, 3, and 10 μ g/kg SB-207266; the 3 and 10 μ g/kg doses both reduced the 5-HT response by over 85% at 45 min [213694]. Based on these data, the dose producing 50% inhibition of the 5-HT response at 15 min was calculated to be 1.3 μ g/kg intravenously [213694, 237234]. In oral dosing studies, a 30 μ g/kg dose of SB-207266 produced similar effects, reducing the contractile response to 5-HT to about 5% of control at the 135 min time point, but the onset of action was delayed for about 45 min compared to the intravenous dosing protocol. The dose producing 50% inhibition of the 5-HT response at 45 min was calculated to be 9.6 μ g/kg [213694, 237234]. The ability of SB-207266 to antagonize the 5-HT-evoked contractile response was examined in tissue isolated from human colon and ileum [261216]. In both colonic and ileac circular muscle strips, SB-207266 caused a surmountable, rightward shift in the 5-HT dose-response curve. A pK_b value for 1 nM SB-207266 was reported as 10.7 in colonic tissue and 9.8 in ileac tissue [261216]. In addition to effects in gastrointestinal tissue, SB-207266 has actions on 5-HT₄ receptors found in the central nervous system. SB-207266 was studied in three rat models of anxiety: the social interaction, the elevated X-maze, and the Geller-Seifter tests [260037, 261217]. At 0.001 mg/kg sc. [260037] and also at 0.01 and 0.1 mg/kg sc. [260037, 261217], SB-207266 approximately doubled the amount of time spent in social interaction (grooming, following, sniffing, crawling over or under, boxing, biting) compared to saline treated controls; the positive control chlordiazepoxide at 5 mg/kg slightly more than doubled this parameter. The dose-response effect of SB-207266 was somewhat bell-shaped; higher doses tended to produce less of an increase in interactive behavior, and the 10 mg/kg dose was similar to saline controls [260037]. The same increase in social interaction was observed when SB-207266 was administered orally at 1 or 10 mg/kg and these doses were similar in effect to 5 mg/kg chlordiazepoxide administered p.o. but 0.1 mg/kg SB-207266 p.o. had no effect [261217]. There was a small, nonsignificant trend to decreased locomotion at the higher doses of SB-207266 when it was administered sc., but there was no effect on locomotion when the drug was administered p.o., nor was there an effect on locomotion at lower, behaviorally effective doses sc. [260037]. In the elevated X-maze, SB-207266 appeared to increase the amount of time spent on the open arm by about 50% and 68% at 0.1 and 1 mg/kg, respectively, but these increases were not statistically significant [260037, 261217]. The chlordiazepoxide positive control (5 mg/kg) increased open arm time by more than 2-fold. SB-207266 had no effect on punished responding in the Geller-Seifter assay at 0.1 or 1 mg/kg sc., but there was an 8.2% increase ($p < 0.05$) in unpunished responding at 1 mg/kg [260037].

Metabolism

None reported.

Toxicity

None reported.

Clinical Development

Currently in Phase II-III trials [247533, 236237]; Phase II trials in Japan [248285]. Initial Phase II results are reported to be "exceptional" [247533].

Side-effects and Contraindications

None reported, but potential central nervous system effects of SB-207266 merit consideration. Potential effects in cardiac muscle tissue.

Current Opinion

Irritable bowel syndrome is a pathological condition characterized by pain and alternating periods of constipation and diarrhea. It has been estimated that the market value for an effective medication for irritable bowel syndrome is over one billion dollars [247533], thus, there is considerable economic incentive to develop an effective pharmacological therapy. There are no consistently effective remedies available for this condition and there is a high (~ 60-70%) placebo effect. Nevertheless, it is known that stimulation of 5-HT₄ receptors in the gut produces abdominal cramps, prokinetic, and prosecretory effects and a selective antagonist at this receptor site may be useful in treating this disease. SB-207266 is a highly potent, selective, and orally active 5-HT₄ antagonist and is therefore of great interest as the first potential drug for the treatment of irritable bowel disorder. Preliminary preclinical and clinical results are encouraging. The chemical structure of SB-207266, incorporating an amide linkage, makes the drug resistant to metabolism and likely contributes to its high potency in vivo. This feature is an advantage over other 5-HT₄ antagonists such as SB-204070 [1], GR-113808 [3], or SDZ 205-557 [4] which all contain a metabolically-labile ester linkage. There is evidence for central nervous system effects of SB-207266 in animal models [260037, 261217]; the possibility of behavioral side-effects in humans should therefore be thoroughly investigated. In addition, clinical studies must be conducted with the utmost attention to rigorous experimental design to control for the high placebo effect associated with irritable bowel syndrome.

Annotations

Reference number 1

Gaster, L.M.; Jennings, A.J.; Joiner, G.F.; King, F.D.; Mulholland, K.R.; Rahman, S.K.; Starr, S.; Wyman, P.A.; Wardle, K.A.; Ellis, E.S.; Sanger, G.J. *J. MED. CHEM.*, 36, 4121-4123 (1993). Synthesis of (1-butyl-4-piperidinyl)methylamine (chemical precursor to SB-207266) and SB-204070.

Reference number 2

Brown, A.M.; Young, T.J.; Patch, T.L.; Cheung, C.W.; Kaumann, A.J.; Gaster, L.M.; King, F.D. *BR. J. PHARMACOL.*, 112, 105P (1994). Synthesis of [125I]-SB-207710.

Reference number 3

Grossman, C.J.; Kilpatrick, G.J.; Bunce, K. T. *BR. J. PHARMACOL.*, 109, 618-624 (1993). Report of [3H]GR-113808 as a 5-HT₄ antagonist.

Reference number 4

Buchheit, K.-H.; Gamse, R.; Pfannkuche, H.-J. NAUNYN-SCHMIEDEBERG'S ARCH. PHARMACOL., 345, 387-393 (1992). Characterization of SDZ 205-557 as 5-HT4 antagonist.

Reference number 194582

Synthesis, SAR of SB-207266.

Reference number 213694

Pharmacological study of SB-207266 in vitro and in vivo.

Reference number 236237

SmithKline Beecham report of new drugs under development.

Reference number 237234

Abstract; pharmacological study of SB-207266 in vitro and in vivo

Reference number 247533

IDdb meeting report, comments by Dr. F. King about market value for irritable bowel syndrome treatment. Positive results reported for Phase II study of SB-207266.

Reference number 248285

Phase II trial of SB-207266 reported in Japan.

Reference number 260037

Central nervous system (anxiolytic-like) effects of SB-207266 reported.

Reference number 261216

SB-207266 is a 5-HT4 antagonist in isolated human intestinal tissue.

Reference 261217

Abstract; anxiolytic-like effect of SB-207266 reported.

CLASSIFICATIONS

CHEMISTRY CLASSIFICATIONS

Study Type	Results	Reference
Synthesis	Synthesis of (1-butyl-4-piperidinyl)methylamine (chemical precursor to SB-207266)	1
Synthesis	Synthesis of [125I]-SB-207710.	2
Synthesis	Synthesis of [3H]GR-113808 as a 5-HT4 antagonist ligand	3
Synthesis/SAR	Synthesis and SAR of SB-207266 and nine other related compounds reported. Ester-based indole derivatives are more potent than amide-based derivatives in vitro	194582

BIOLOGY CLASSIFICATIONS

In vitro classifications

Effect studied	Experimental model	Result	Reference
Receptor binding	Radioligand competition	SDZ 205-557 is a 5-HT4 antagonist	4
Antagonism of 5-HT-induced contractions	Isolated guinea pig distal colon longitudinal muscle myenteric plexus	IC50 of 0.63 nM for SB-207266	194582
Receptor binding	Radioligand competition in cloned receptor subtypes	Ki = 0.5 nM for SB-207266 at 5-HT4 receptors; no significant binding at 5-HT1A, 5-HT1D, 5-HT1E, 5-HT2A, 5-HT2C, 5-HT3, D2, D3, H1 receptors	194582
Antagonism of 5-HT-induced contractions	Isolated human ileum and colon circular muscle strips	pKb value for 1 nM SB-207266 is 10.7 in colonic tissue and 9.8 in ileac tissue	261216

In vivo classifications

Effect studied	Experimental model	Result	Reference
Antagonism of 5-HT-induced contractions	Conscious dog Heidenhain pouch	IC50 = 1.3 ug/kg iv.; 9.6 ug/kg p.o.	213694
Antagonism of 5-HT-induced contractions	Conscious dog Heidenhain pouch	IC50 = 1.3 ug/kg iv.; 9.6 ug/kg p.o.	237234
Anxiolysis	Rat: social interaction, elevated X-maze, Geller-Seifter assay	SB-207266 at 0.01 and 0.1 mg/kg sc. or 1 and 10 mg/kg p.o. doubled the social interaction parameter; no significant effect in X-maze, 8.2% increase in unpunished responding at 1 mg/kg in Geller-Seifter test	260037
Anxiolysis	Rat: social interaction, elevated X-maze, Geller-Seifter assay	SB-207266 at 0.01 and 0.1 mg/kg sc. or 1 and 10 mg/kg p.o. doubled the social interaction parameter, no effect in X-maze or Geller-Seifter tests	261217