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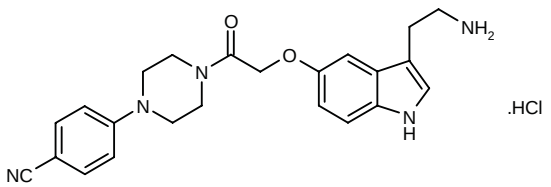
F-11356

5-HT$_{1B/1D}$ Receptor Agonist

Antimigraine

4-[4-[2-[3-(2-Aminoethyl)-1*H*-indol-5-yloxy]acetyl]piperazin-1-yl]benzonitrile hydrochloride



$C_{23}H_{25}N_5O_2.ClH$ Mol wt: 439.9444

CAS: 170911-68-9
CAS: 170912-52-4 (as free base)
CAS: 200615-15-2 (as monomesylate)

EN: 266330

Introduction

Migraine affects about 10% of the population worldwide, mainly women (1). The discovery of the involvement of serotonin (5-HT) in the mechanisms of headache and associated symptoms of migraine (2) has constituted a major advance in the understanding of this pathology, leading to the development of new drugs that activate 5-HT$_1$ receptors (3). Serotonin is involved in numerous disorders (*e.g.*, depression, anxiety) (4) and interacts with various distinct membrane receptors. These receptors have been classified into seven classes (termed 5-HT$_{1-7}$) based upon their pharmacological, structural and signaling properties. The 5-HT$_1$ receptors have been further subdivided into 5-HT$_{1A}$, 5-HT$_{1B}$ (formerly called 5-HT$_{1D\beta}$), 5-HT$_{1D}$ (formerly called 5-HT$_{1D\alpha}$), 5-ht$_{1e}$ and 5-ht$_{1f}$ subtypes (5, 6).

Sumatriptan (Fig. 1) (7) was the first compound to become available as an antimigraine medicine with a mechanism of action based on the selective activation of 5-HT$_{1B/1D}$ (previously 5-HT$_1$-like) receptors. Older compounds such as ergotamine and dihydroergotamine are also likely to exhibit antimigraine actions through 5-HT$_{1B/1D}$ receptor activation. However, these compounds are not selective, have a number of limiting side effects (8) and are characterized by low efficacy and poor oral bioavailability. Therefore, despite the disadvantages of side effects, low oral bioavailability and headache recurrence (9), sumatriptan was the first compound to clinically demonstrate effectiveness of selective 5-HT$_{1B/1D}$ receptor activation for the acute treatment of migraine (10).

The precise physiological mechanisms by which sumatriptan alleviates migraine are still not fully elucidated, but three distinct pharmacological actions upon the vasculature and neurons have been identified thus far. Vasoconstriction of cranial blood vessels (11, 12), inhibition of neurogenic inflammation involving reduced vasodilator sensory neuropeptide release from peripheral (dural) trigeminal nerve terminals (13) and/or inhibition of firing of trigeminal neurons (14, 15) have been proposed. It is now generally accepted that the vascular action of sumatriptan is mediated by the 5-HT$_{1B}$ receptor subtype (22, 23); the respective roles of 5-HT$_{1D}$ and 5-ht$_{1f}$ receptors remain less clear. However, several lines of evidence suggest that 5-HT$_{1D}$ and 5-ht$_{1f}$ receptors may inhibit sensory neurotransmitter release (CGRP, substance P) from trigeminal neurons (13, 24).

New 5-HT Receptor Agonists as Antimigraine Drugs

Encouraged by the clinical usefulness of sumatriptan, many new compounds with a similar mechanism of action have recently been developed. Like sumatriptan, these compounds are tryptamine derivatives which differ from each other by changes in the nature of the 5-substituent (zolmitriptan (16), rizatriptan (17)) and/or are conformationally restricted analogs at the amino-ethyl side chain level (naratriptan (18), eletriptan (19)) (Fig. 1). Despite these structural modifications, and probably because of the shared core structure, these compounds display similar therapeutic efficacy in clinical trials and have an improved oral bioavailability (9, 20).

These second generation compounds, which can be defined as “sumatriptan-like” drugs, have an in vitro pharmacological profile that is comparable to sumatriptan in terms of selectivity, potency and efficacy. They bind to both human 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors with similar affinity and, to a lesser extent, to human 5-ht$_{1f}$ sites (Table I).

Michel Perez*, Serge Halazy, Petrus J. Pauwels, Francis C. Colpaert, Gareth W. John. Centre de Recherche Pierre Fabre, 17 Avenue Jean Moulin, 81106 Castres Cedex, France. *Correspondence.

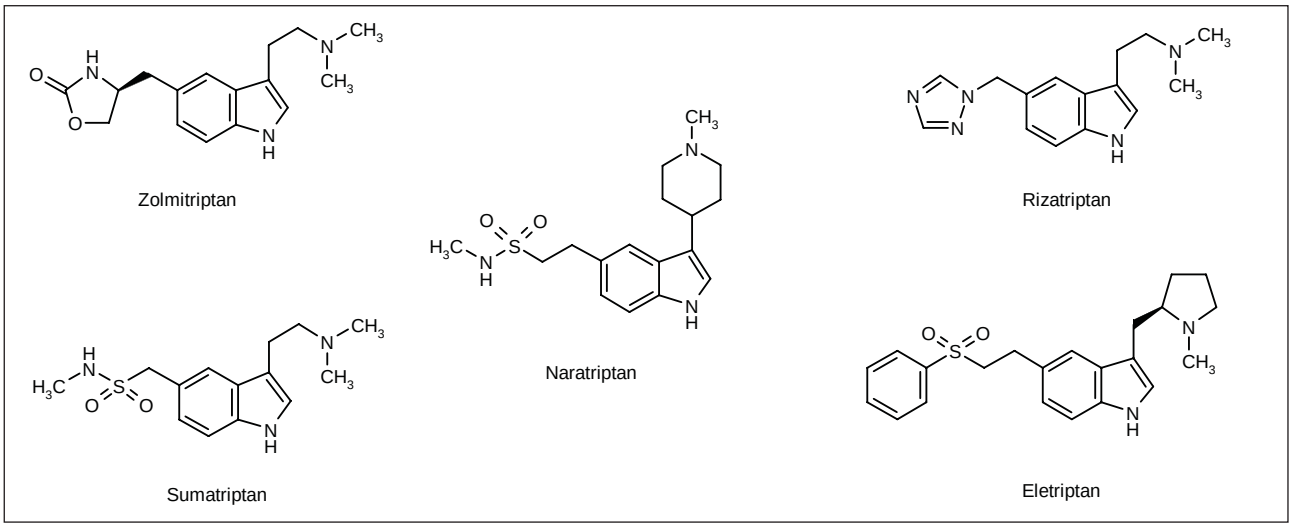


Fig. 1. Structures of nonselective 5-$HT_{1B/1D}$ receptor agonists.

Table I: In vitro *profile of 5-HT receptor agonists.*

	Receptor binding affinities[a] K_i (nM)			Intrinsic activity[b] h 5-HT_{1B}	
	h 5-HT_{1B}	h 5-HT_{1D}	h 5-ht_{1f}	EC_{50} (nM)	E_{max} (%)
Sumatriptan	3.2	2.1	16.6	234	96.4
Zolmitriptan	0.8	0.2	28.8	60.2	99.3
Rizatriptan	7.9	2.5	138	234	74.5
Naratriptan	0.5	0.7	4.0	22.9	79.8
Eletriptan	15.1	1.5	19.0	60.2	83.3
Alniditan	2.5	2.5	1230	16.5	81.3
F-11356	0.1	0.1	3400	1.8	100.2

[a]Binding data were obtained with [^{3}H] 5-CT for h 5-HT_{1B} and 5-HT_{1D} receptor in Cos-7 cells instead of C6 glioma cells as described (33) and with [^{3}H] 5-HT in Cos-7 (36). [b]Intrinsic activity was determined using a [^{35}S]GTPγS binding assay (36).

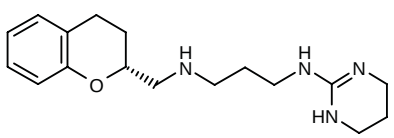
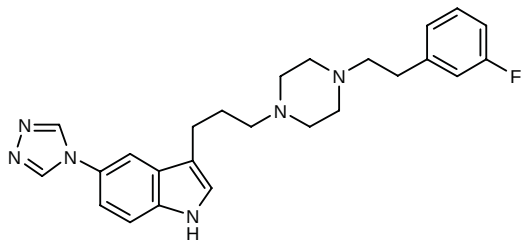


Fig. 2. Structure of alniditan.

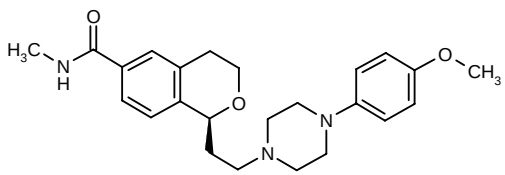
As mentioned above, the respective contribution of these receptors in the therapeutic activity of these compounds is not yet fully elucidated. The only compound which has poor 5-ht_{1f} affinity and reached clinical investigation, alniditan (Fig. 2), was discontinued in phase III. However, an early trial documented its clinical effectiveness in aborting migraine (25), indicating that the 5-ht_{1f} component is not a prerequisite for therapeutic efficacy.

Receptor mapping studies (26) have shown that the 5-HT_{1D} receptors are restricted to neuronal tissues, including the trigeminal ganglion, whereas 5-HT_{1B} receptors have a wider distribution that includes vascular tissues. Based on these observations, it has been proposed that selective 5-HT_{1D} receptor agonists may be devoid of vasoconstrictor actions while maintaining antimigraine activity. On this basis, selective 5-HT_{1D} receptor agonists have been designed (Fig. 3). Among them, L-775606 (Merck) has been selected as a development candidate in a series of propylpiperazinylindoles (27) with up to 200-fold selectivity for the 5-HT_{1D} over the 5-HT_{1B} receptor. Another compound, PNU-109291 from Pharmacia & Upjohn, was found serendipitously in a series of isochroman-6-carboxamides targeting dopamine D_4 receptors (28). This compound has a K_i of 0.9 nM for 5-HT_{1D} receptors and a 5-HT_{1B}/5-HT_{1D} affinity ratio of over 5000.

The fact that 5-$HT_{1B/1D}$ receptor agonists, such as sumatriptan, naratriptan, zolmitriptan and dihydroergotamine, display relatively high affinities for 5-ht_{1f} receptors (Table I) suggested that these compounds might exert their antimigraine action mainly or partly through this subtype. Furthermore, when agonist potencies for inhibiting neurogenic inflammation in the guinea pig model were compared with affinities for these receptor subtypes, the best correlation was with the 5-ht_{1f} subtype (29). The only



L-775606



PNU-109261

Fig. 3. Structures of selective 5-HT_{1D} receptor agonists.

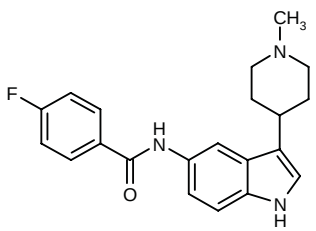


Fig. 4. Structure of LY-334370.

5-ht_{1f} receptor agonist which was undergoing clinical development, LY-334370 (Fig. 4), was very recently stopped in phase II because of toxicity seen in animal studies (company communication). In human trials, the compound reportedly had some effectiveness in aborting migraine but these preliminary results appear to be inconclusive.

F-11356

We have postulated that the main reason for the relatively limited improvement, in terms of clinical effectiveness by oral administration, of the newest triptans compared to sumatriptan is due to the moderate intrinsic activity produced by these compounds at 5-$HT_{1B/1D}$ receptors (*i.e.*, these ligands are partial agonists relative to 5-HT) (21). With the aim of identifying compounds having much greater intrinsic activity at 5-$HT_{1B/1D}$ receptors in different models, we focused our chemical approach on serotonin derivatives, since 5-HT is superior to tryptamine in terms of efficacy at these receptors. In order to obtain new 5-$HT_{1B/1D}$ receptor agonists with greater intrinsic activity than the triptan series, we assumed that 5-*O* substituted serotonin derivatives should activate 5-$HT_{1B/1D}$ receptors more effectively than previously reported tryptamine derivatives. Moreover, from a synthetic point of view, these derivatives are easily prepared from serotonin, which is a considerable advantage compared to 5-C-alkylated tryptamine derivatives. Thus, we prepared a series of 5-*O* substituted serotonin derivatives with the aim of preserving the high efficacy of serotonin while improving selectivity over other 5-HT receptor subtypes. As part of our synthetic program we considered the introduction of an arylpiperazide moiety as a 5-*O* substituent on serotonin (30, 31). F-11356 was selected from this series of compounds because of its exceptionally high efficacy at 5-$HT_{1B/1D}$ receptors *in vitro* and in pharmacological models of migraine *in vivo*.

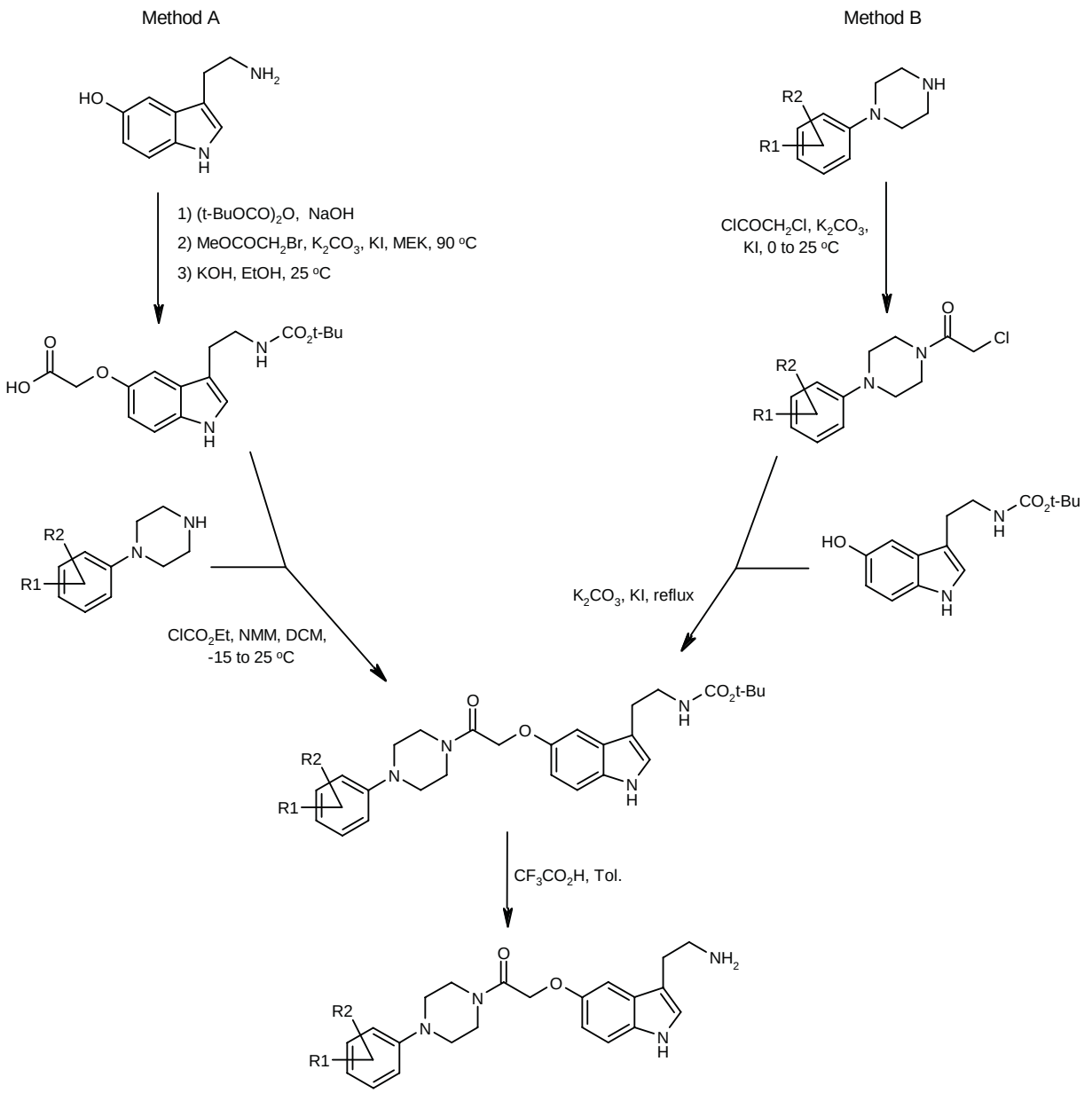
Chemistry

As shown in Scheme 1, F-11356 and its analogs are easily synthesized from serotonin following two synthetic pathways. The first method involves the preparation of {3-[2-*N*-*tert*-butoxycarbonyl)-amino-ethyl]-1*H*-indol-5-yloxy]-acetic acid, which is obtained by protection of serotonin with BOC_2O/NaOH, followed by *O*-alkylation with methyl bromoacetate and saponification of the methyl ester with KOH. The overall yield for the three steps was 81%. A coupling reaction between this acid and a phenyl piperazine derivative afforded the N-BOC-protected desired products which, upon subsequent treatment with trifluoroacetic anhydride, gave the free amines. In the second method, the phenylpiperazine derivatives were first treated with chloroacetylchloride and then the intermediates were allowed to react with N-BOC-serotonin to give the N-BOC-protected desired products. At this stage, and before the final deprotection, the R group can be modified to afford other analogs.

Structure-activity relationship

The main chemical modulation of our series of 4-aryl-1-(tryptamine-5-*O*-carboxymethyl)-piperazides concerned the substitution of the terminal phenyl ring. As shown in Table II, the binding affinities of the compounds were measured at recombinant h 5-HT_{1B}, 5-HT_{1D} and 5-HT_{1A} receptors. All the compounds were found to be equipotent at both 5-HT_{1B} and 5-HT_{1D} receptors with K_i values in the range of 0.1-22 nM. Following earlier studies (31), we postulated that a deep pocket is available in the binding domain of 5-$HT_{1B/1D}$ receptors. This was confirmed since compounds with a bulky substituent at the *para* position of the phenyl ring (R_1 = 4-(C_6H_5-CONH), 4-(4-F-C_6H_4-SO_2NH)) kept a good binding affinity. In contrast, the binding selectivity over h 5-HT_{1A} receptors was extremely sensitive to the nature of the substituents, especially at the *para* position.

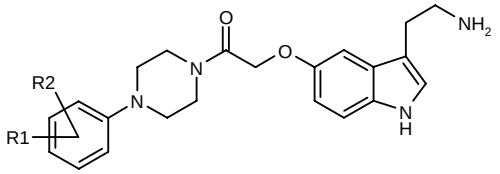
Scheme 1: Synthesis of F-11356 and Analogs



Intrinsic activity of the compounds was determined from their ability to inhibit forskolin-stimulated cAMP formation mediated by h 5-HT_{1B} receptors in C6 glioma cells (32). Most of the compounds behaved as full agonists with EC_{50} values in the range of 0.2-32 nM, in accordance with their binding affinities.

In this series, F-11356 was one of the compounds which displayed the highest affinity for both h 5-HT_{1B} and 5-HT_{1D} receptors, high selectivity over 5-HT_{1A} receptors and, most importantly, high intrinsic activity. Other chemical modulations were subsequently focused directly on the structure of F-11356. First, the length and the nature of the linker between the serotonin and the cyanophenyl piperazine moieties were studied (Table III). Interestingly, the binding affinity at both h 5-HT_{1B} and 5-HT_{1D} receptors was not affected by the length and only slightly affected by the nature of the linker. This result once again confirmed the deep topology of the binding domain as discussed above. However, the intrinsic activity was significantly affected by a 7C-linker (X = $CO(CH_2)_6$), suggesting a limitation in this series.

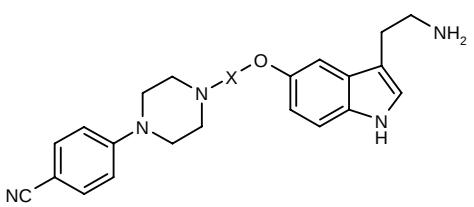
Table II: Modulation of the R groups on the terminal aromatic ring.



R_1	R_2	5-HT_{1D}	K_i (nM)[a] 5-HT_{1B}	5-HT_{1A}	EC_{50} (nM)[b] 5-HT_{1B}
4-CN	H	0.1	0.1	19.5	0.2
4-NH_2	H	2.92	1.64	607	-
4-(4-F-C_6H_4-SO_2NH)	H	0.35	0.46	14.2	3.8
4-(C_6H_5-CONH)	H	1.4	1.3	34.2	2.6
H	2-CH_3	2.08	0.8	8	1.3
4-NH_2	2-OCH_3	5.2	5.0	100	15
4-CN	2-Cl	0.3	0.3	13.0	0.2
4-CN	2-C_2H_5	10.0	22.0	71.0	32

[a]Conditions for receptor binding assays see Table I. [b]Inhibition of the forskolin-stimulated cAMP formation mediated by h 5-HT_{1B} receptors in C6 glioma cells (32).

Table III: Modulation of the linker between the serotonin and the cyanophenyl piperazine moieties.



X	5-HT_{1D}	K_i (nM)* 5-HT_{1B}	5-HT_{1A}	EC_{50} (nM)* 5-HT_{1B}
$COCH_2$ (F-11356)	0.1	0.1	19.5	0.2
$CSCH_2$	0.5	0.6	12.0	0.1
$CO(CH_2)_3$	1.2	1.6	36.0	0.9
$CO(CH_2)_4$	1.2	0.5	16.0	0.65
$CO(CH_2)_5$	0.5	0.2	20.0	0.65
$CO(CH_2)_6$	0.6	0.5	26.0	3.0
$(CH_2)_5$	0.6	0.2	17.0	0.14
$SO_2(CH_2)_3$	4.0	3.2	33.0	2.2
$CONH(CH_2)_3$	4.0	5.0	43.0	ND

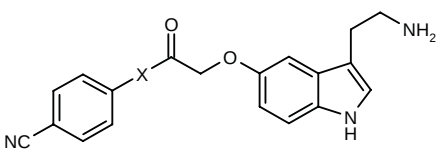
*See Table II.

A second chemical modulation concerned the replacement of the piperazine ring by other diamino rings (Table IV). The data showed a strong influence of the steric hindrance on the piperazine ring, especially on the intrinsic activity value for the h 5-HT_{1B} receptor.

The last modulation concerned the terminal ethylamino side chain (Table V). While the mono *N*-methylation had no effect on the profile, *N,N*-dimethylation decreased both the binding affinity and the intrinsic activity. A piperidine ring, as found in naratriptan, was also evaluated without success.

As depicted in the tables, none of the chemical modifications improved the affinity, efficacy, potency at h 5-HT_{1B} receptors or selectivity against h 5-HT_{1A} receptors compared to F-11356 (33).

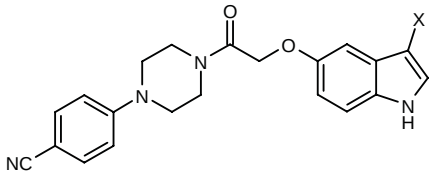
Table IV: Modulation of the piperazine ring.



X	5-HT_{1D}	K_i (nM)* 5-HT_{1B}	5-HT_{1A}	EC_{50} (nM)* 5-HT_{1B}
	0.1	0.1	19.5	0.2
	0.5	0.4	21.0	0.65
	15.0	14.0	78.0	3.5
	0.8	0.7	14.0	0.55
	2.0	6.0	46.0	45.0
	3.2	6.0	28.0	30.0

*See Table II.

Table V: Modulation of the terminal ethylamino side chain.



X	K_i (nM)* 5-HT_{1D}	5-HT_{1B}	5-HT_{1A}	EC_{50} (nM)* 5-HT_{1B}
$CH_2CH_2NH_2$	0.1	0.1	19.5	0.2
$CH_2CH_2NHCH_3$	0.2	0.3	20.0	0.1
$CH_2CH_2N(CH_3)_2$	0.7	0.8	93.0	2.8
	26.0	8.0	107.0	ND

*See Table II.

Pharmacological Profile of F-11356

In vitro

F-11356 has subnanomolar affinity for cloned human and nonhuman 5-HT_{1B} and 5-HT_{1D} receptors with K_i values ranging from 0.1-4.3 nM. F-11356 does not distinguish between 5-HT_{1B} and 5-HT_{1D} receptors, having equivalent affinity at these sites (Fig. 5). F-11356 has approximately 200 times less binding affinity for the h 5-HT_{1A} receptor (K_i = 19.5 nM) and over 500 times less affinity for other 5-HT receptors, including the h 5-ht_{1f} subtype, diverse neurotransmitter receptors, uptake sites and ion channel binding sites (Fig. 5).

F-11356 behaves as a potent agonist in cellular assays in which it inhibited forskolin-induced cAMP formation mediated by cloned human and nonhuman stably transfected 5-HT_{1B} and 5-HT_{1D} receptors; the mean EC_{50} values ranged from 0.20-1.86 nM. In C6 glioma cells stably transfected with h 5-HT_{1B} or h 5-HT_{1D} receptors, F-11356 stimulated specific [^{35}S]-GTPγS binding with similar efficacy but with greater potency compared to the native agonist, 5-HT at both 5-HT_{1B} and 5-HT_{1D} receptors (21). Most importantly, efficacy of F-11356 in this system was markedly superior to that of naratriptan, rizatriptan, sumatriptan, zolmitriptan and dihydroergotamine (21).

F-11356 was equipotent to 5-HT (pD_2 = 7.1 *vs.* 7.2) and more potent than the above tryptamine derivatives in contracting rabbit isolated saphenous vein. In guinea pig isolated trigeminal ganglion neurons, F-11356 was more potent (pD_2 = 7.3 *vs*. 6.7) and induced greater increases in outward hyperpolarizing Ca^{2+}-dependent K^+ current than sumatriptan (Fig. 6). Thus, in functional models relevant to both the vascular and neurogenic hypotheses in migraine, F-11356 is a highly effective and potent 5-$HT_{1B/1D}$ receptor agonist with an activity profile, particularly in terms of intrinsic activity (*i.e.*, magnitude of responses), superior to that of the tryptamine derivatives investigated (21).

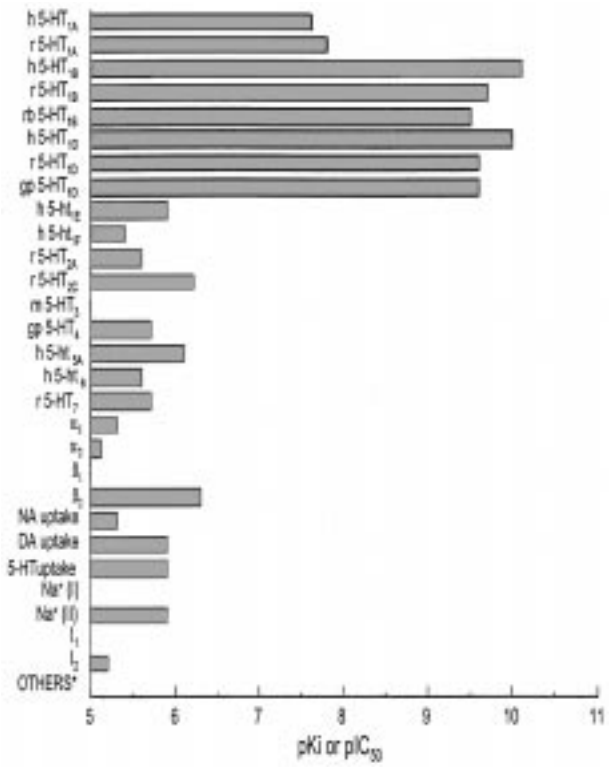


Fig. 5. Highly selective binding affinities of F-11356 for human and nonhuman 5-HT_{1B} and 5-HT_{1D} receptors studied at serotonergic and other major binding sites. *Others indicates pK_i or pIC_{50} values of 5 or lower at dopamine D_1 and D_2, histamine H_1 and H_2, muscarinic, NK 1, 2 and 3, NPY, nicotinic, opiate, PAF, VIP, adenosine A_1 and A_2, angiotensin AT_1 and AT_2, bradykinin B_1 and B_2, CGRP, $GABA_A$ and NMDA receptors, MAO A and B, L- and N-type Ca^{2+} channels, Ca^{2+} and ATP-dependent K^+ channels; α and β refer to α- and β-adrenoceptors; Na^+ (I) and (II) refer to binding sites I and II of sodium channels; I_1 and I_2 refer to imidazole sites; gp, h, m, r and rb, respectively, refer to guinea pig, human, mouse, rat and rabbit. For further details see ref. 21.

In vivo

In anesthetized pigs, F-11356 produced a more potent and greater carotid vasoconstriction than naratriptan and sumatriptan, thus demonstrating the compound's high efficacy at 5-$HT_{1B/1D}$ receptors *in vivo*. Furthermore, increases in mean arterial pressure were similar to those observed with sumatriptan and naratriptan (Fig. 7). As a consequence, the cerebrovascular selectivity exhibited by F-11356 is far superior to that of these compounds.

The potency (ED_{50} value) of F-11356 in reducing carotid blood flow was 0.53 μg/kg i.v. ED_{50} values could not be determined for naratriptan and sumatriptan, since carotid blood flow was not significantly decreased by sumatriptan and was significantly reduced by naratriptan only at the dose of 40 μg/kg i.v. F-11356-induced carotid vasoconstriction was abolished by GR-127935, a mixed 5-$HT_{1B/1D}$ receptor antagonist, confirming mediation by 5-$HT_{1B/1D}$ receptors (21).

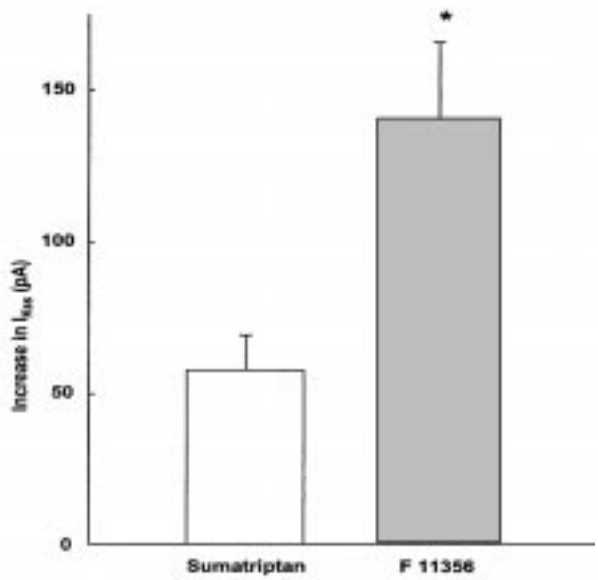


Fig. 6. Increases in outward steady-state (ss) hyperpolarizing K^+ current (I_K) evoked by F-11356 and sumatriptan (both 1 μM) in guinea pig isolated trigeminal ganglion cells using the whole-cell patch clamp technique. Note greater amplitude of responses elicited by F-11356. Data are means ± SEM; *$p < 0.05$ compared to sumatriptan. For further details see refs. 21 and 35.

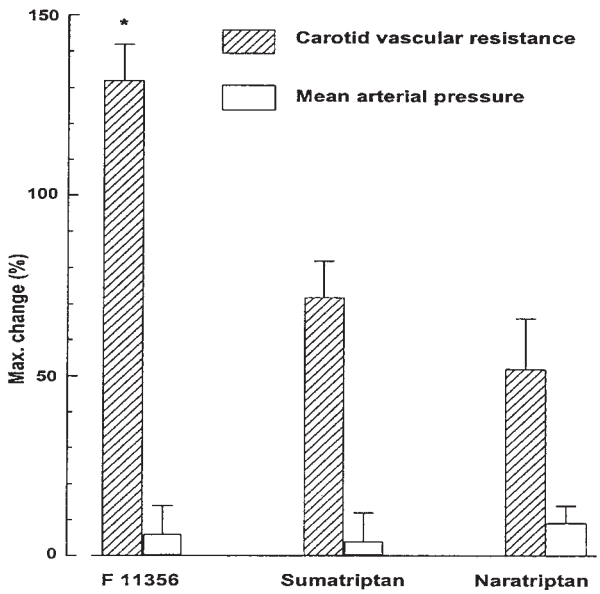


Fig. 7. Maximal increases in carotid vascular resistance and mean arterial pressure evoked by F-11356, sumatriptan and naratriptan in anesthetized domestic pigs. Drugs were administered as cumulative intravenous infusions of 0.63 μg/kg-2.5 mg/kg for sumatriptan and naratriptan (n = 7) and of 0.01-40 μg/kg for F-11356 (n = 7) over 15 min per dose. Data are means ± SEM; *$p < 0.05$ compared to sumatriptan and naratriptan. Note similar increases in arterial pressure induced by the 3 drugs (p = NS), whereas F-11356 produced approximately twice the increase in carotid vascular resistance compared to sumatriptan and naratriptan. Thus, F-11356 has greater carotid vascular selectivity over sumatriptan and naratriptan. See ref. 21 for further details.

In conscious dogs, orally administered F-11356 (from 0.63 mg/kg) produced long-lasting (> 12 h) decreases in carotid blood flow without affecting heart rate. Decreases in carotid blood flow were observed within 30 min following drug administration. F-11356 was well tolerated and no clinical signs were observed. In contrast, sumatriptan (up to 10 mg/kg p.o.) and naratriptan (up to 0.63 mg/kg p.o.) failed to significantly reduce carotid blood flow and produced noticeable clinical signs that included mydriasis, vocalization, exophthalmos, tachycardia and increased respiratory rate. The oral activity of F-11356 was confirmed in guinea pigs, in which hypothermic responses were produced (ED_{50} 1.6 mg/kg p.o. compared to 8.3, 9.9 and 12.3 mg/kg p.o. for zolmitriptan, naratriptan and rizatriptan, respectively). Sumatriptan failed to induce hypothermia at doses up to 40 mg/kg p.o. (21).

Summary

F-11356 is a selective, highly potent agonist at human and nonhuman 5-$HT_{1B/1D}$ receptors which differs from the sumatriptan-like drugs by exerting high intrinsic activity at these receptors in both vascular and neuronal models of migraine. Since dihydroergotamine, sumatriptan and the newer tryptamine derivatives (*e.g.*, naratriptan, rizatriptan, zolmitriptan, eletriptan) behave as partial agonists at 5-$HT_{1B/1D}$ receptors (34), F-11356, because of its high efficacy at these receptors, has the potential to provide superior acute therapeutic relief from migraine compared to the other drugs. Furthermore, because of its high cerebrovascular selectivity, its good efficacy should further enhance functional (clinical) selectivity. Finally, due to its long duration of action and excellent tolerability in animals, F-11356 should provide a very attractive alternative to currently available treatments.This new approach to the treatment of migraine remains to be tested clinically.

Manufacturer

Pierre Fabre Medicament (FR).

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