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DIMERIZATION OF SUMATRIPTAN AS AN EFFICIENT WAY TO DESIGN A POTENT, CENTRALLY AND ORALLY ACTIVE 5-HT$_{1B}$ AGONIST

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Abstract: A new bivalent ligand of formula **3** which results from the covalent coupling of two sumatriptan molecules with a p-xylyl spacer at the level of the sulfonamide nitrogen has been prepared and evaluated as a 5-HT$_{1B/1D}$ receptors agonist. In vitro experiments at 5-HT$_{1B}$ human cloned receptors (Ki = 0.64 nM; EC_{50} = 0.58 nM) and at the level of the contraction of the New Zealand white rabbit saphenous vein (pD_2 = 6.6) demonstrate the superior potency of dimer **3** as a 5-HT$_{1B}$ receptor agonist when compared to sumatriptan or zolmitriptan. Interestingly enough, the new bivalent agonist **3** was found to induce hypothermia in the guinea-pig upon oral administration suggesting good oral activity and access to the brain.

Migraine is a common neurological disorder that can severely affect quality of life and daily functioning. The pathophysiology of migraine is incompletely understood but evidence suggests that it may involve the dilation of cerebral blood vessels and excessive activity of the trigeminal system. Serotonin (5-HT) probably plays a key role in these processes[1,2] and the recent discovery that sumatriptan **1**, a prototypic 5-HT$_{1B/1D}$ agonist, is an effective drug for the treatment of acute attacks of migraine[3] has stimulated extensive research efforts in this area. The implication of 5-HT$_{1B/1D}$ receptor subtypes in migraine pathology has been confirmed by very recent results which show that other selective 5-HT$_{1B/1D}$ receptor agonists, such as zolmitriptan (**2**),[4] rizatriptan,[5] naratriptan[6] and eletriptan[7] are also clinically effective in the treatment of migraine headache.

Recent studies have shown that in addition to a well-established location on cranial blood vessels and the terminals of the sensory nerves innervating them, 5-HT$_{1B/1D}$ receptors are also present within the trigeminal nucleus caudalis where they serve to modulate cranial nociceptive input.[8,9] These central sites may represent an additional important target for drug action, one which is less accessible to sumatriptan which, under normal conditions, does not readily cross the blood-brain barrier. This implies that a 5-HT$_{1B/1D}$ receptor agonist with central as well as peripheral actions might exhibit improved efficacy against migraine headache. This has been the claim for the new anti-migraine drug zolmitriptan (**2**), a 5-HT$_{1B/1D}$ receptor agonist with a dual mechanism of action, having effects at both central (trigeminal nucleus caudalis) and peripheral (trigeminovascular system) targets.[10]

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A major challenge in developing new 5-$HT_{1B/1D}$ receptor agonists for the treatment of migraine lies in the design in molecules which would concomitantly demonstrate a good oral bioavailability, brain access and hopefully improved potency as 5-$HT_{1B/1D}$ receptor agonists in comparison to compounds currently in clinical development.

In this communication, we report about our progress toward that goal and describe the discovery, synthesis, and preliminary pharmacological profile of the new sumatriptan dimer **3**.

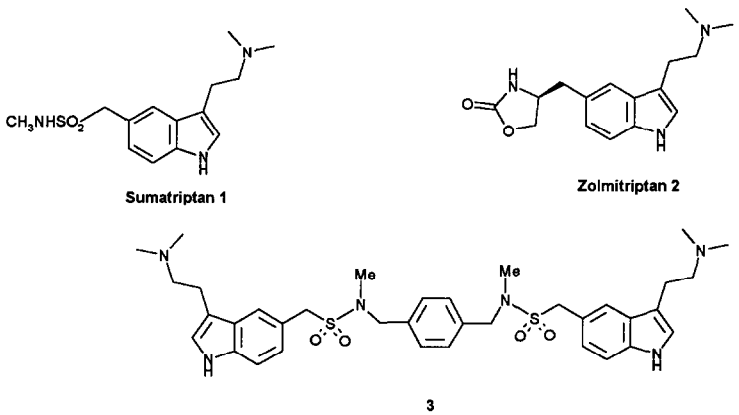
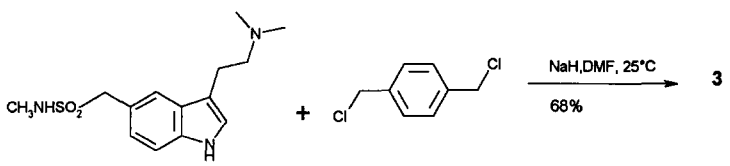


Figure 1

We have recently reported[11] on the dimerization of serotonin as a very efficient method to design potent and selective (especially when compared to serotonin itself) 5-$HT_{1B/1D}$ receptor agonists. Based on these observations, the bivalent ligand approach was selected as a method of choice to improve sumatriptan's pharmacological profile. Sumatriptan dimer **3** was identified as the ideal prototype since previous investigations had shown that dimerization at position 5 of the tryptamine residue is of primary importance[11,12] and that the p-xylyl group should serve as the optimal linker between the two pharmacophores. As a consequence, we have prepared compound **3** which results from the dimerization of sumatriptan at the nitrogen atom of the sulfonamide residue with the help of a p-xylyl spacer. The synthesis of **3** (scheme 1) can be achieved in one step by condensing 2 equivalents of sumatriptan **1** with a,a'-dichloro-p-xylene in the presence of NaH in DMF. (68% yield).[13]



The binding affinities of compounds **1-3** have been measured at cloned human 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1A} receptors.[14,15] As shown in table 1, compound **3** binds at human 5-HT_{1B} and 5-HT_{1D} receptors with much higher

affinity than sumatriptan **1** and also with much higher affinity than **2** at 5-HT_{1B} receptors. Furthermore, despite higher affinity for human 5-HT_{1A} receptors, compound **3** has roughly the same selectivity index in favor of 5-HT_{1B} receptors (5-HT_{1B}/5-HT_{1A} selectivity index of 27 for compound **3** compared to 21 for sumatriptan and 29 for zolmitriptan). Moreover, data obtained at human cloned 5-HT_{1B} receptors stably transfected in CHO cell lines[14] by measuring inhibition of forskolin-stimulated c-AMP formation also demonstrate (table 1) that sumatriptan dimer **3** is more potent (EC_{50} = 0.58 nM) than sumatriptan itself (approximately 2 log units) (EC_{50} = 38.3 nM) but also more potent than zolmitriptan (EC_{50} = 15.7 nM). In summary, *in vitro* data obtained at human cloned receptors demonstrate that dimerization of the anti-migraine drug sumatriptan represents a very efficient way to design potent (Ki and EC_{50} < 1 nM) and selective 5-$HT_{1B/1D}$ receptor agonists. From this point of view, the *in vitro* results (table 1) obtained with compound **3** are in perfect agreement with results previously obtained with serotonin dimers.[11]

Table 1: Comparison of dimer 3 with sumatriptan 1 and zolmitriptan 2 at human 5-HT_{1B}, 5-HT_{1D} and 5-HT_{1A} receptors.

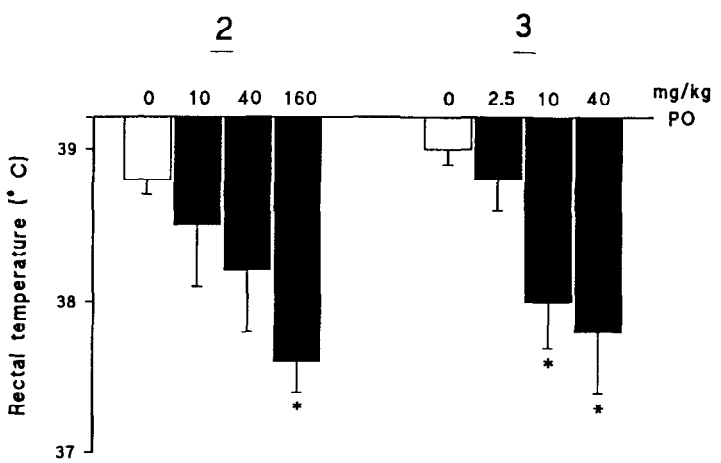
	Ki (nM)[a]			EC_{50} (nM)[a]
Compound	5-HT_{1A}	5-HT_{1B}	5-HT_{1D}	5-HT_{1B}
1	407.1	19.1	8.6	38.3
2	124	4.2	0.76	15.7
3	17.7 ± 8.1	0.64 ± 0.25	0.89 ± 0.33	0.58

[a] Ki and EC_{50} values are given as the mean of two or three independent determinations, each performed in duplicate, typically with individual values within ± 10-20 % of the mean. Binding experiments have been performed with [^{3}H]-5-CT at 5-$HT_{1B/1D}$ receptors and with [^{3}H]-8-OH-DPAT at 5-HT_{1A} sites.

The superior agonist potency of sumatriptan dimer **3** compared to sumatriptan and zolmitriptan has been confirmed in the rabbit saphenous vein contraction model.[16] This functional model, widely used to characterize 5-$HT_{1B/1D}$ receptor agonists or antagonists, is of particular interest when considering vasoconstriction as an important action relevant to the anti-migraine effect of sumatriptan. Thus, under previously reported experimental conditions,[16] compound **3** (pD_2 = 6.6) was found more potent in contracting the rabbit saphenous vein than sumatriptan (pD_2 =5.7) or zolmitriptan (pD_2 = 6.2), reaching a maximum contractile effect that does not differ statistically from those observed with 5-HT. Considering that these responses have been demonstrated[16] to be mediated by the 5-HT_{1B} receptor subtype, data obtained in this model further confirm the superior efficacy of dimer **3** as a 5-HT_{1B} agonist.

Among the different methods available to evaluate 5-$HT_{1B/1D}$ agonists *in vivo*, the induction of hypothermia by a 5-$HT_{1B/1D}$ receptor agonist is particularly attractive since this model provides an easy means of demonstrating *in vivo* an action at the level of the CNS and serves as a preliminary evaluation of oral bioavailability. Indeed, several 5-$HT_{1B/1D}$ receptor agonists such as GR-46611,[17] SKF 99101H[18] or arylpiperazide derivatives of serotonin[19,20] reliably produce hypothermia in the guinea-pig. Hypothermia is likely to be mediated through central mechanisms since sumatriptan, which displays poor brain penetration, is inactive upon systemic administration even at high doses (100 mg/kg, i.p.) whereas it is active after intracerebroventricular administration (40 µg/kg).[17] Recent investigations suggest that the hypothermic responses to 5-$HT_{1B/1D}$ agonists is probably mediated by 5-HT_{1B} receptor subtypes rather than 5-HT_{1D}.[21] We observed that sumatriptan dimer **3** (ED_{50} = 1.3 mg/kg) as well as zolmitriptan **2** (ED_{50} = 3.2 mg/kg) were able to induce hypothermia in the guinea-pig upon systemic administration (i.p.), while, under the same experimental conditions , sumatriptan **1** had no effect, as reported previously. These results support previous data strongly suggesting that zolmitriptan **2**, is better able to cross the blood-brain barrier,[22] and suggest that sumatriptan dimer **3**, in contrast to sumatriptan itself, is also able to access the brain. Interestingly enough, sumatriptan dimer **3** (as well as zolmitriptan **2**) was also found to induce hypothermia in the guinea-pig following oral administration (figure 2) indicating a good bioavailability for that compound. This observation is particularly relevant since sumatriptan **1** is characterized by a poor oral bioavailability. Results from figure 2 also confirm the superior potency and efficacy of dimer **3** compared to zolmitriptan **2** (compare induction of hypothermia at 10 and 40 mg/kg).

Figure 2: Effects of oral administration of 2 (left panel) and sumatriptan dimer 3 (right panel) on rectal temperature in guinea-pigs.



In conclusion , results obtained in the hypothermia model, together with the data obtained with human cloned 5-$HT_{1B/1D}$ receptors and in the rabbit saphenous vein model indicate that compound **3** is a new potent, selective, orally active 5-$HT_{1B/1D}$ agonist with central activity. The results with sumatriptan dimer **3** as reported here demonstrate that dimerization of a known drug or receptor ligand, can not only improve the potency of a drug (better Ki, pD_2 or EC_{50}) but, interestingly enough, can also provide a means of improving the quality of pharmacokinetic parameters such as CNS penetration and oral activity. These findings represent an example of the application of the bivalent ligand approach to the improvement of an existing drug. Work is in progress to further assess the therapeutic potential and safety profile of compound **3,** and to extend this concept to other 5-$HT_{1B/1D}$ agonists.

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13 **Preparation of C-[3-(2-dimethylaminoethyl)-1*H*-indol-5-yl]-N-(4-{[3-(2-dimethylamino-ethyl)-1*H*-indol-5-ylmethanesulfonyl]-methylaminomethyl}benzyl)-N-methyl methanesulfonamide hydrochloride (3):**

A solution of sumatriptan (534 mg; 1.8 mmol) in dry DMF (11 mL) was treated, at 0°C and under nitrogen, with NaH (60 % in oil) (80 mg; 2 mmol) and the mixture was stirred from 0°C to room temperature for 1 h. α,α'-dichloro-p-xylene (158 mg; 0.90 mmol) was then added and the mixture was stirred at room temperature for 4 h. The mixture was diluted with MeOH, treated with "wet" Na_2SO_4 to remove excess NaH, filtered and evaporated to dryness. The crude product was purified by chromatography (CH_2Cl_2/MeOH/NH_4OH, 90/9/1 then 85/14/1) to give the pure product (429 mg; 68.5 %) isolated as the hydrochloride salt. mp 140°C; ^1H NMR (DMSO-d6) δ 2.58 (s, 6H, N-Me); 2.83 (s, 12H; NMe2); 3.10-3.20 (m, 4H, CH_2); 3.20-3.30 (m, 4H, CH_2); 4.14 (br s, 4H, CH_2); 4.53 (br s, 4H, CH_2); 7.17 (d, 2H, J = 8.4 Hz, Ar); 7.25 (s, 4H, Ar); 7.28 (d, 2H, J = 1.9 Hz, Ar); 7.40 (d, 2H, J = 8.4Hz; Ar); 7.68 (s, 2H, Ar); 10.67 (br s, 2H, NH^+); 11.15 (d, 2H, J = 1.7Hz, NH)

Anal. ($C_{36}H_{50}Cl_2N_6O_4S_2$, 1.5$H_2O$) Calc. (%) C 54.57; H 6.76; N 10.48; Cl 9.05
Found (%) C 54.53; H 6.74; N 10.60; Cl 8.94

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