Drugs of the Future 1999, 24(10): 1078-1083

CCC: 0377-8282/99

Tonabersat

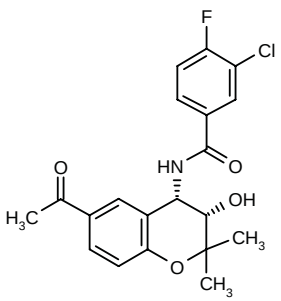
Antimigraine

Prop INN

SB-220453

(–)-(3*S*,4*S*)-*cis*-*N*-(6-Acetyl-3-hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-4-yl)-3-chloro-4-fluorobenzamide

(–)-*cis*-6-acetyl-4(*S*)-(3-chloro-4-fluorobenzamido)-3,4-dihydro-2,2-dimethyl-2*H*-benzo[*b*]pyran-3(*S*)-ol



$C_{20}H_{19}ClFNO_4$ Mol wt: 391.8300

CAS: 175013-84-0

EN: 231735

Synthesis

The cyclization of 4-hydroxyacetophenone (I) with 3-chloro-3-methyl-1-butyne (II) gives 6-acetyl-2,2-dimethyl-2*H*-1-benzopyran (III), which is enantioselectively epoxidated by means of Mn^{+3} salen catalysts, yielding the chiral epoxide (IV). The cleavage of the epoxide ring of (IV) with ammonia in ethanol affords the (3*R*,4*S*)-*trans*-aminoalcohol (V) (1,2). The acylation of (V) with 3-chloro-4-fluorobenzoyl chloride (VI) and triethylamine yields the (3*R*,4*S*)-*trans*-amide (VII) (3). The cyclization of (VII) by means of diethylaminosulfur trifluoride (DAST) in dichloromethane affords the (3a*S*-*cis*)-oxazoline (VIII), which is finally treated with 5N H_2SO_4 (4). Scheme 1.

Description

White crystals, m.p. 151-3 °C.

Introduction

Migraine, an unpleasant, highly prevalent, often severely painful and frequently disabling neurological disorder, affects 26 million Americans. Migraine costs American employers about $13 billion a year because of missed work days and impaired work function (5). Pharmacologic therapy of migraine consists of symptomatic treatment of acute attack (also referred to as abortive therapy), and prophylactic therapy to reduce the frequency and severity of headaches. Acute pharmacologic therapy includes analgesics and drugs targeted against the pathophysiology of migraine itself, such as 5-HT_{1D} agonists and the ergot alkaloids. Antiemetic therapy is a component of acute migraine management because of the frequent coexistence of nausea and vomiting. Prophylactic treatment of migraine includes β-blockers, central α-agonists, calcium channel blockers, 5-HT receptor antagonists, tricyclic antidepressants and anticonvulsants. Drugs under active development for the treatment of migraine are shown in Table I.

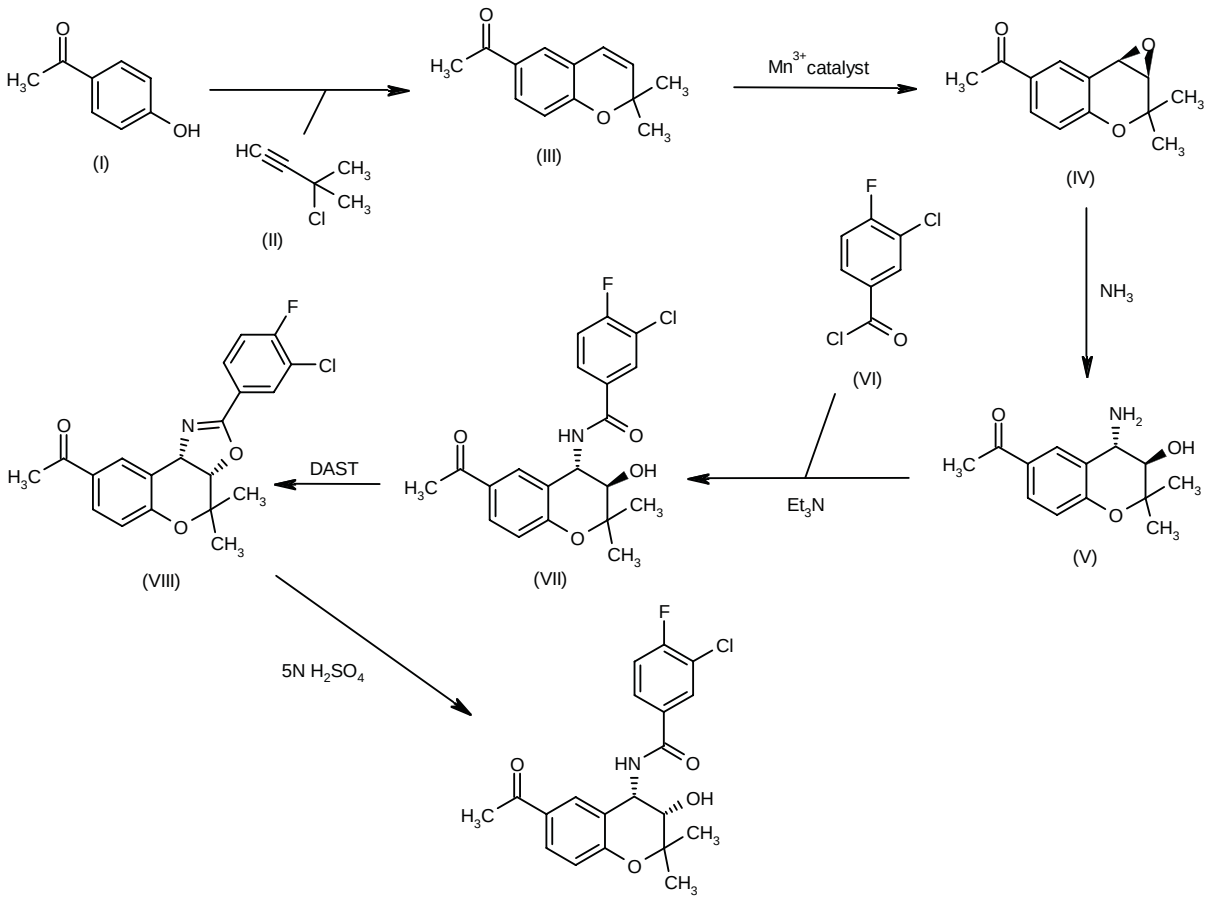
Several new pharmacological approaches to the treatment of migraine have been studied. In addition to 5-HT_{1B} and 5-HT_{1D} receptors, the novel 5-HT_{1F} receptor has been used as a target for the design of antimigraine drugs. LY-334370, a 5-HT_{1F} agonist in development by Lilly and Synaptic, was discontinued before beginning phase III trials due to the results from animal toxicology studies (6, 7).

Tachykinin NK_1 receptor antagonists have been reported to have a variety of potential clinical uses, including treatment of migraine. However, in a randomized, double-blind, placebo-controlled clinical trial, GR-205171 (Glaxo Wellcome), a highly potent and CNS-penetrating NK1 antagonist, was found not to be effective in the treatment of acute migraine. These results contradict previous findings that indicated a potentially important role for substance P in the pathophysiology of migraine (8).

The leukotrienes have been implicated in primary headache, but the efficacy of leukotriene antagonists, currently used for the prophylaxis of asthma, in the treatment of migraine has not been investigated. A prospective, open-label study of the leukotriene antagonist montelukast sodium (Singulair®; Merck & Co.) in 17 patients with migraine following a 2-month run-in period was carried out. A reduction in the frequency and intensity of

X. Rabasseda, P. Leeson, J. Castañer. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

Scheme 1: Synthesis of Tonabersat



migraine attacks was observed. These preliminary positive findings indicated the need for controlled trials of leukotriene antagonists for the treatment of migraine, cluster headache and pediatric migraine (9).

Encouraging results have been obtained with pericranial botulinum toxin (Botox®; Allergan) in the prophylactic management of migraine headache (10), and the vanilloid receptor agonist and neuronal calcium channel blocker zucapsaicin (civamide) is under development for the prophylactic therapy of migraine (11).

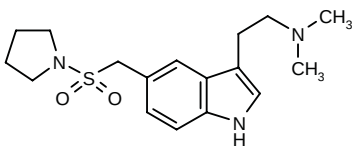
New formulations of available 5-$HT_{1B/1D}$ agonists have been launched. CIMA's fast-dissolving OraSolv® version of AstraZeneca's Zomig® (zolmitriptan) has received its first approval from the regulatory authorities in Sweden, the reference member state for European approval. This formulation, launched as Zomig® rapimelt, incorporates microencapsulated zolmitriptan into a tablet that melts within seconds on the tongue and enables patients to treat their migraine in situations where a drink of water may not be available (12-14). Another formulation that dissolves in the tongue within seconds and can be taken without liquids was launched in September in Canada as Maxalt™ (rizatriptan) wafer (15).

Yamanouchi's Shaklee Pharma Division has entered into a feasibility and option agreement with Glaxo Wellcome to enable the development and commercialization of prescription products for migraine therapy utilizing its Wowtab® quick-dissolving, without-water tablet technology. Glaxo Wellcome compounds targeted for commercialization as a Wowtab® dosage form include the currently marketed compounds, as well as investigational compounds that have potential as future therapies for migraine (16).

Baclofen, a $GABA_B$ agonist launched in 1971 to reduce spasticity, has proved to be an effective and well tolerated drug for the prevention of migraine in an open study (17). In addition, the GABA receptor modulator ganaxolone is being developed in phase II clinical trials by CoCensys for migraine prophylaxis. Ganaxolone belongs to the epalon family of neuroactive steroids which have the ability to suppress neurogenic

Table I: Antimigraine drugs recently launched and under development (Prous Science Ensemble database).

Acute pharmacologic therapy	**Company**	**Status**
5-HT$_{1B/1D}$ agonists		
1. Almotriptan[1]	Almirall	Preregistered
2. IS-159[1]	The Medicines Co.	Phase II
3. ALX-0646*,[1]	Allelix Biopharmaceuticals; Janssen	Phase I
4. F-11356[1]	Pierre Fabre	Preclinical
New formulations		
5. Zolmitriptan (Zomig rapimelt)[2]	AstraZeneca	Launched-1999
6. Rizatriptan (Moxalt wafer)[2]	Merck Frosst	Launched-1999
*Distinct mechanism of action***		
7. Tonabersat	SmithKline Beecham	Phase II
Prophylactic therapy		
Calcium channel blockers		
8. Zucapsaicin (civamide)[3]	Winston Laboratories	Phase II
9. Dotarizine[1]	Ferrer	Preregistered
10. Lomerizine HCl (Terranas)[1]	Nippon Organon	Launched-1999
GABA receptor modulators		
11. Baclofen	Tel Aviv Univ.	Phase II/III
12. Ganaxolone[1]	CoCensys	Phase II
Anticonvulsant		
13. Topiramate[1]	R.W. Johnson	Phase III
14. *Botulinum toxin type A* (Botox)[4]	Allergan	Phase II
Leukotriene antagonist		
15. Montelukast sodium (Singulair)[1]	Merck & Co.	Phase II
Histamine H$_3$ agonist		
16. Sch-50971[1]	Schering-Plough	Preclinical



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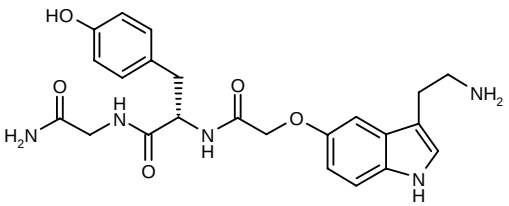

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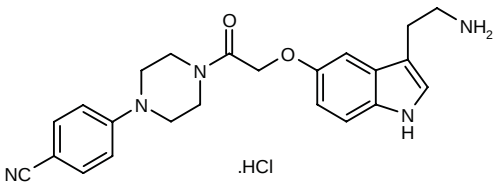

.HCl

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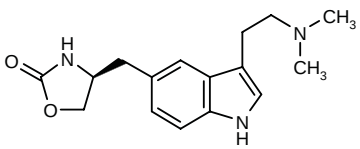

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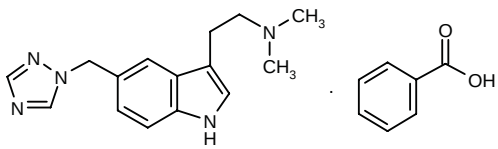

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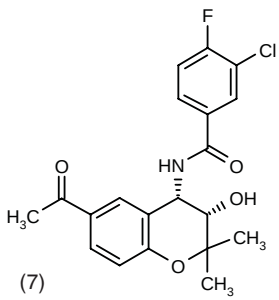

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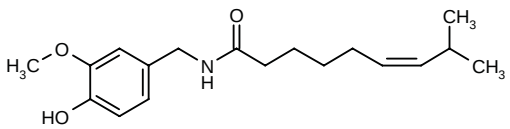

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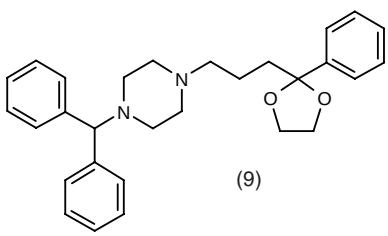
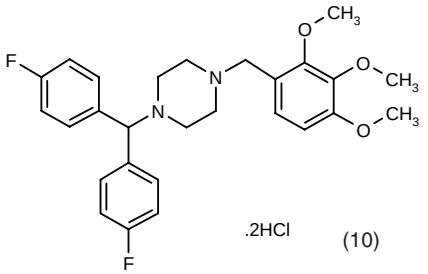


(9)

Route of administration: [1]oral; [2]buccal; [3]intranasal; [4]pericranial. *Structure not yet detected. **Not yet understood. (Continued)

Table I: Antimigraine drugs under development and recently launched.



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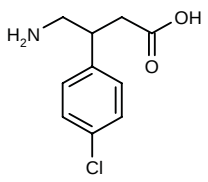

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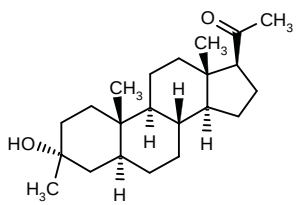

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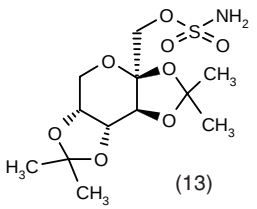

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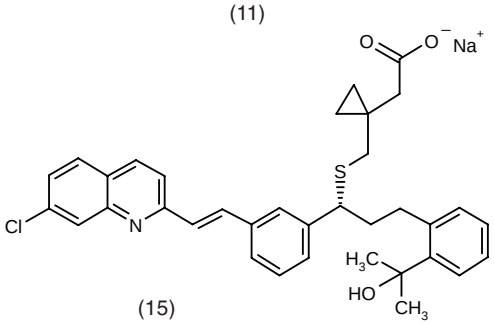

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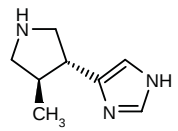


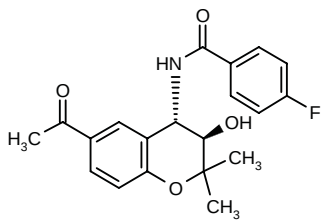
(16)

inflammation in the brain lining, which is believed to be associated with migraine headaches (18, 19).

The potential use of histamine H3 agonists for the treatment of migraine is also under investigation. The preclinical profile of an orally active, potent and selective agonist of H_3 receptors, Sch-50971, has shown its potential as a novel antimigraine agent (20, 21).

A series of (3*R*,4*S*)-benzopyrans reported by scientists at SmithKline Beecham were particularly active in increasing the seizure threshold in rodent maximal electroshock models. These models have been used to predict anticonvulsant activity. One compound in the series, SB-204269 (carabersat) [I], was identified as a candidate for clinical evaluation for the treatment of epilepsy (1, 22). Compounds of this type have been shown to interact at a unique binding site in the brain of several species, including man which was revealed by high affinity for [^{3}H]-SB-204269 (23).

Optimization of novel *cis*- and *trans*-4-(substituted-amido)benzopyran-3-ol derivatives has led to the identification of tonabersat (SB-220435) with an *in vivo* preclinical CNS profile predictive of potential antimigraine activity. SB-220435 has a completely distinct mechanism of action when compared to other antimigraine drugs, and has been selected as a pioneer agent for further development (24).



[I]

Pharmacological Actions

SB-204269 was found to bind to a novel binding site within the brain and to exert anticonvulsant activity in rodent maximal electroshock models. In *in vivo* tests, SB-220453 displaced [^{3}H]-SB-204269 from its binding site in rat brain membranes with a pK_i value of 7.9, being more potent than SB-204269 (pK_i = 7.3) (24). Data from studies in human brain showed a pK_i value for SB-220453 of 7.4, whereas sumatriptan, valproate, domperidone and dihydroergotamine had no appreciable affinity (pK_i < 5) (25).

Both SB-220453 and SB-204269 increased seizure threshold in the rodent maximal electroshock test when given orally at 10 mg/kg, the new compound being more potent in mice at 1 h postdose. SB-220453 (3 mg/kg p.o.) showed similar or greater potency but had a longer duration of action than SB-204269 (10 mg/kg p.o.) in rats (24).

Thus, SB-220453 potently inhibited abnormal levels of neuronal excitability in seizure models. The drug (19 mg/kg i.p.) was also shown to inhibit neurogenic plasma protein extravasation following trigeminal nerve stimulation in cats to a similar degree as sumatriptan (an antimigraine 5-$HT_{1D/1B}$ receptor agonist) (24). SB-220453 had no effect on resting pial artery hemodynamics (25, 26).

SB-220453 also reduced potassium-induced spreading depression in rat cortex (24, 26). This effect was related to an inhibition of nitric oxide release as a response to potassium stimulation, which may represent a novel antimigraine mechanism of action. In fact, in untreated cats, the application of potassium to the cortical surface produced repeated episodes of changes in cell potential that were associated with nitric oxide release. SB-220453

dose-dependently inhibited both the spreading depression and the associated nitric oxide release with no effects on basal hemodynamics (27).

While the CNS effects of SB-220453 are suggestive of potential antimigraine activity, the mechanism is different from that of sumatriptan. In contrast to this standard antimigraine compound, SB-220453 did not have vasoconstrictive effects in human isolated arteries (28). In experimental animals, SB-220453 induced no effects on heart rate, arterial blood pressure, carotid blood flow or resistance (25).

Clinical Studies

SB-220453 is undergoing phase II clinical evaluation as an antimigraine agent (29).

Manufacturer

SmithKline Beecham plc (GB).

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