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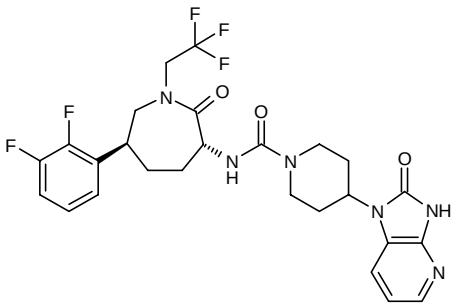
MK-0974

Calcitonin Gene-Related Peptide (CGRP) Antagonist
Antimigraine Agent

N-[6(*S*)-(2,3-Difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)perhydroazepin-3(*R*)-yl]-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide

InChI=1/C26H27F5N6O3/c27-18-4-1-3-17(21(18)28)15-6-7-19(23(38)36(13-15)14-26(29,30)31)33-24(39)35-11-8-16(9-12-35)37-20-5-2-10-32-22(20)34-25(37)40/h1-5,10,15-16,19H,6-9,11-14H2,(H,33,39)(H,32,34,40)/t15-,19-/m1/s1



$C_{26}H_{27}F_5N_6O_3$
Mol wt: 566.5232

CAS: 781649-09-0

CAS: 781649-31-8 (racemate)

CAS: 784157-00-2 (hydrochloride)

CAS: 915312-27-5 (potassium salt)

EN: 387102

Abstract

Calcitonin gene-related peptide (CGRP) has been suggested to play a key role in migraine pathophysiology. MK-0974, an oral CGRP receptor antagonist, is being developed by Merck for the treatment of acute migraine attacks. In preclinical studies, MK-0974 demonstrated high affinity and selectivity for the human CGRP receptor. The agent has favorable pharmacokinetic parameters in animals, including rats, dogs and rhesus monkeys, and humans. MK-0974 was generally well tolerated in clinical studies, and adverse events did not increase with dose. Compared to placebo, MK-0974 significantly improved mean migraine pain relief and pain freedom 2 h after dosing, and the effects on pain freedom were sustained for 24 h. The dose of 300 mg was identified as the most promising.

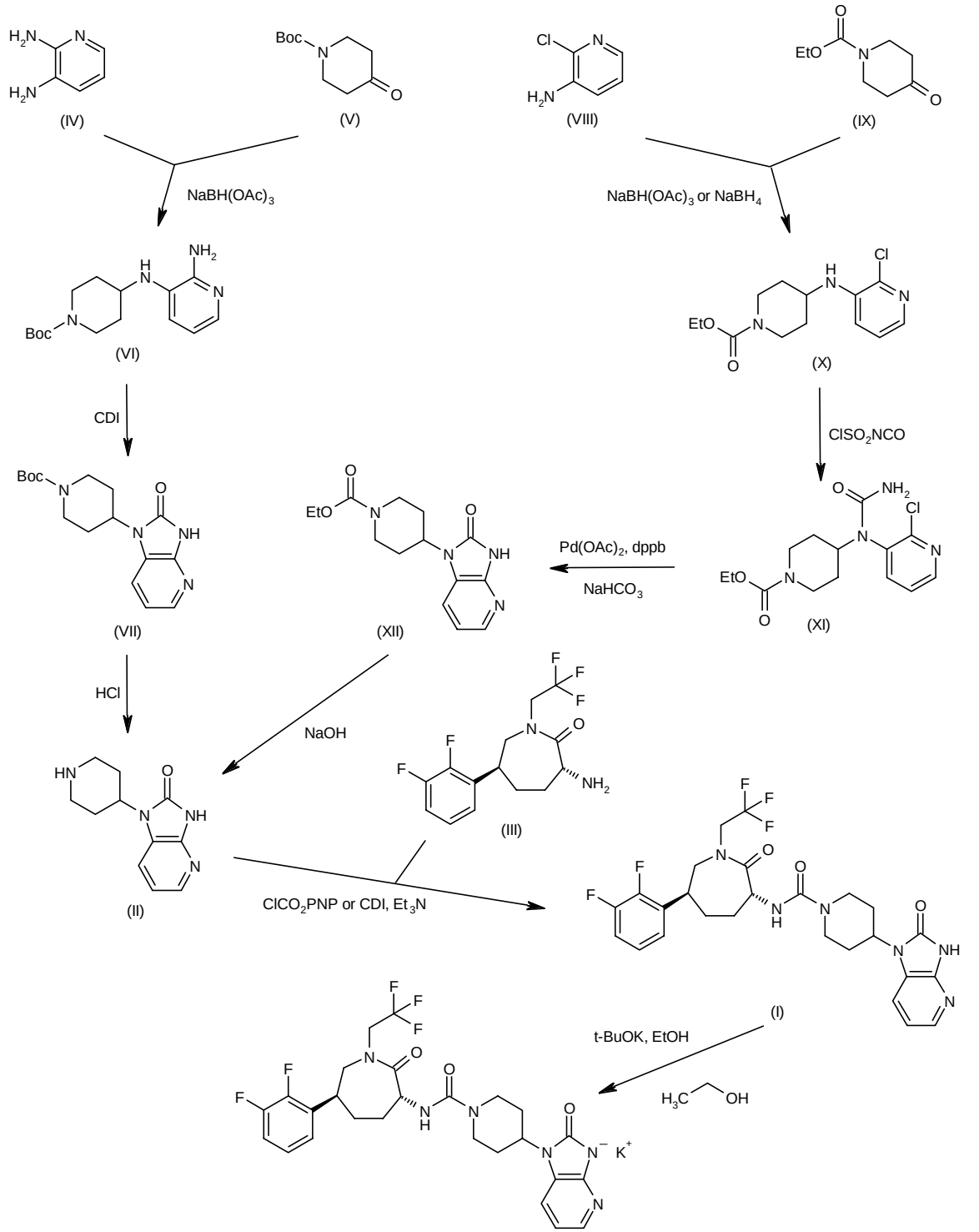
Synthesis

MK-0974 (I) can be prepared by condensation of 2-oxo-1-(4-piperidinyl)-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridine (II) with aminoazepinone (III) using either *p*-nitrophenyl chloroformate (1) or carbonyl diimidazole (CDI) (2-5) in the presence of Et_3N. Treatment of (I) with potassium *tert*-butoxide in ethanol gives the corresponding potassium salt ethanolate (2-5). The intermediate imidazopyridine (II) can be prepared by two related methods. Reductive alkylation of 2,3-diaminopyridine (IV) with 1-Boc-4-piperidone (V) in the presence of $NaBH(OAc)_3$ in CH_2Cl_2 gives the piperidinylamino pyridine (VI), which on treatment with CDI in CH_3CN yields the pyridoimidazolone derivative (VII). Acidic Boc group cleavage in (VII) then provides the target intermediate (II) (1). In a related method, 3-amino-2-chloropyridine (VIII) is reductively alkylated with 1-(ethoxycarbonyl)-4-piperidone (IX) using either $NaBH(OAc)_3$ or $NaBH_4$ in the presence of trifluoroacetic acid to provide (X), which is converted to the *N*-carbamoyl derivative (XI) upon treatment with chlorosulfonyl isocyanate. Then, cyclization of (XI) by means of palladium diacetate and bis(diphenylphosphino)butane leads to the protected imidazopyridinone (XII), from which the *N*-carbethoxy group is removed by hydrolysis under alkaline conditions to furnish intermediate (II) (2-5). Scheme 1.

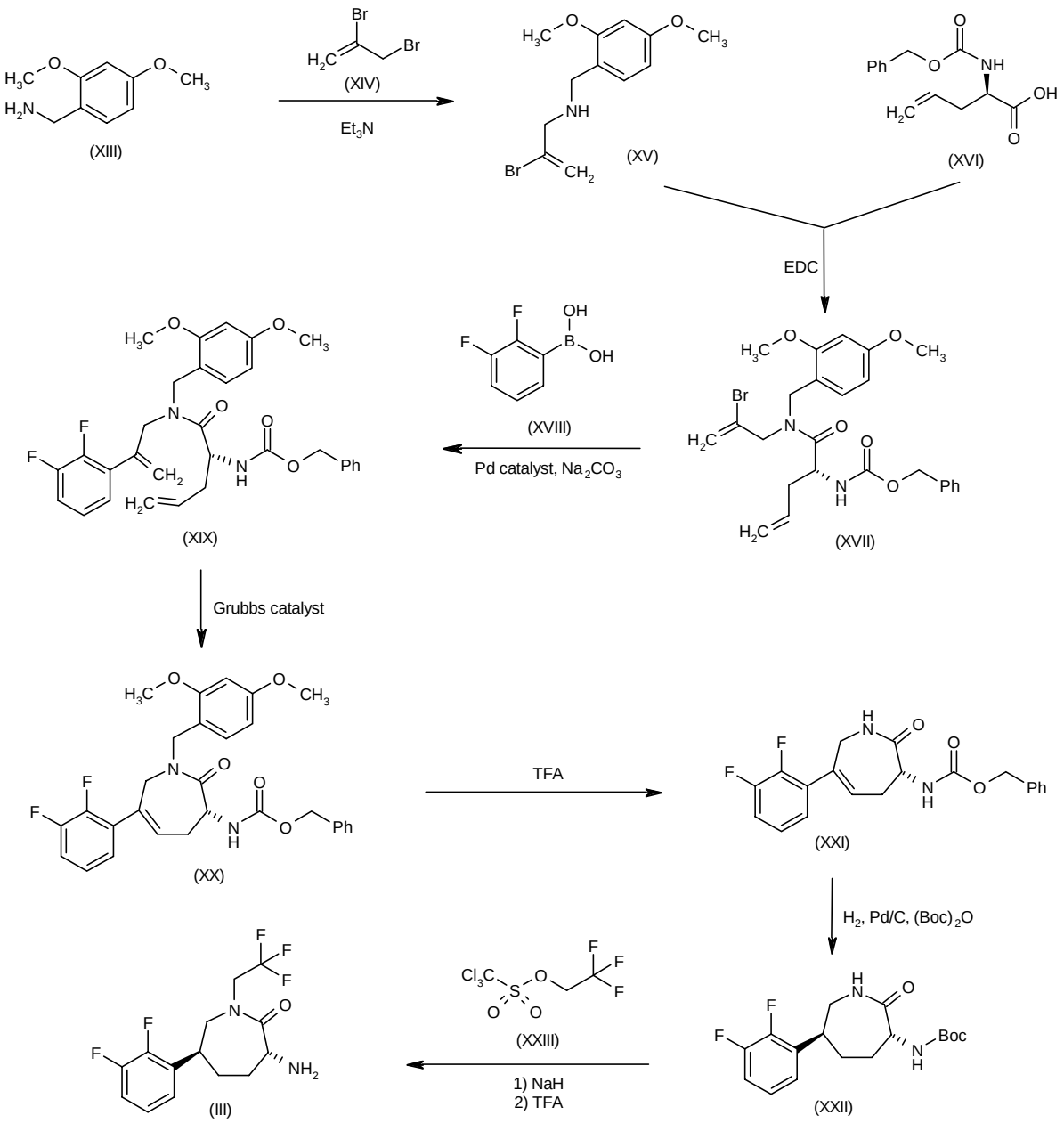
The aminoazepinone building block (III) can be prepared as follows. 2,4-Dimethoxybenzylamine (XIII) is alkylated with 2,3-dibromopropene (XIV) in the presence of Et_3N to yield amine (XV), which is condensed with 2(*R*)-(benzyloxycarbonylamino)-4-pentenoic acid (XVI) by means of EDC in CH_2Cl_2 giving amide (XVII). Subsequent coupling of vinyl bromide (XVII) with 2,3-difluorophenylboronic acid (XVIII) in the presence of 1,1'-

Y. Wang. IBC, 8106 Runnymeade Dr., Frederick, MD 21702, USA. N. Serradell, E. Rosa, J. Bolós. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

Scheme 1: Synthesis of MK-0974



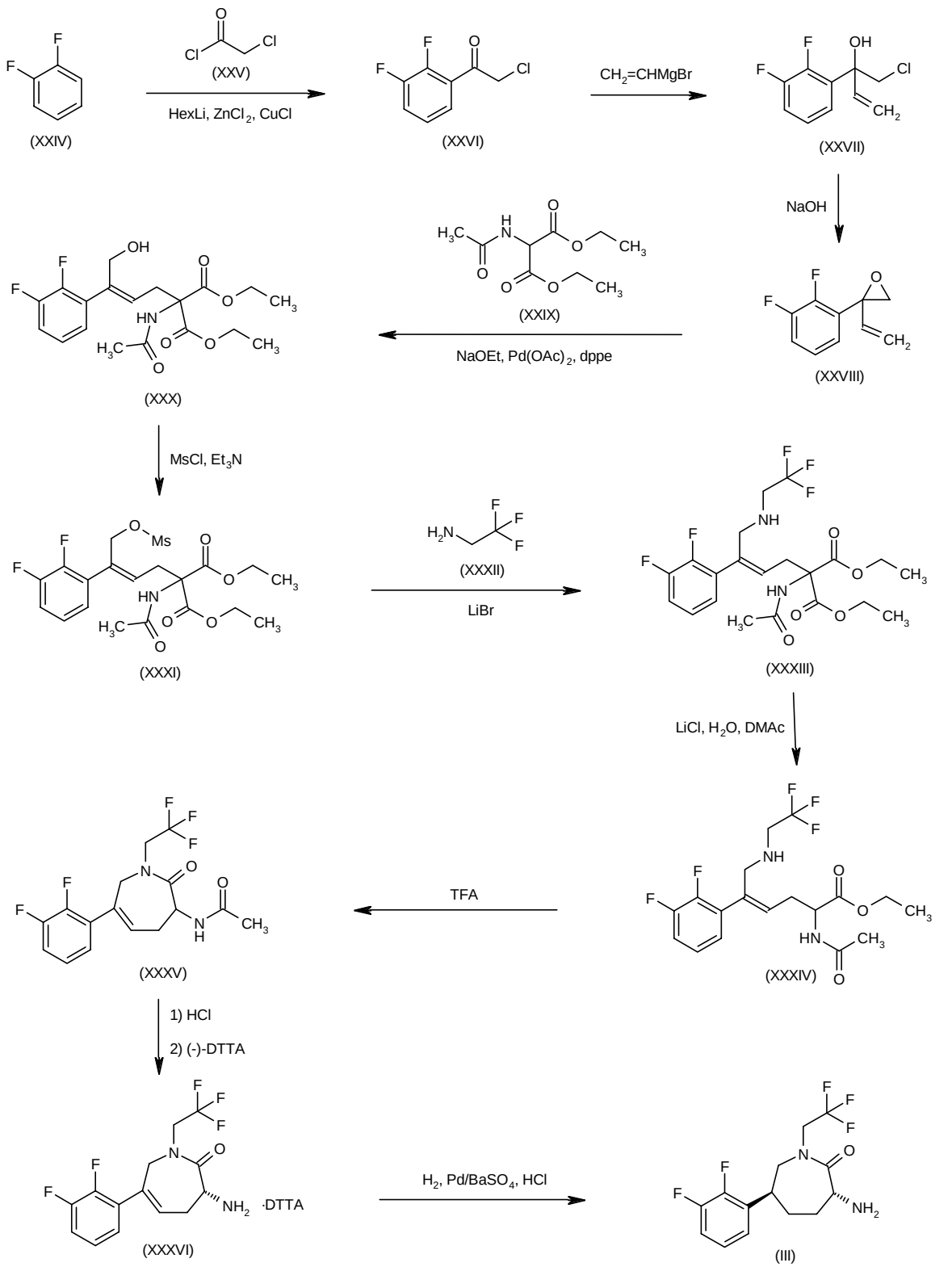
Scheme 2: Synthesis of Intermediate (III)



bis(diphenylphosphino)ferrocenedichloropalladium(II)·CH_2Cl_2 and Na_2CO_3 in DMF gives (XIX). Ring-closing olefin metathesis in diene (XIX) utilizing a second-generation Grubbs catalyst generates the azepinone derivative (XX), from which the dimethoxybenzyl group is removed by means of trifluoroacetic acid in CH_2Cl_2 to provide compound (XXI). Hydrogenation of olefin (XXI) and simultaneous Cbz group cleavage in the presence of Pd/C and Boc_2O leads to the Boc-protected aminoperhydroazepinone (XXII). After alkylation of lactam (XXII) with the 2,2,2-trifluoroethyl sulfonate (XXIII) and NaH in DMF, the *N*-Boc group is removed using trifluoroacetic acid to furnish the target amine (III) (1). Scheme 2.

In an alternative route to intermediate (III), *ortho*-metalation of 1,2-difluorobenzene (XXIV) with *n*-hexyllithium in THF followed by sequential addition of $ZnCl_2$, CuCl and

Scheme 3: Synthesis of Intermediate (III)



then chloroacetyl chloride (XXV) gives 2-chloro-2',3'-difluoroacetophenone (XXVI). Subsequent condensation of chloroketone (XXVI) with vinylmagnesium bromide followed by cyclization of the resulting chlorohydrin (XXVII) under alkaline conditions yields epoxide (XXVIII). This is then coupled with diethyl acetamidomalonate (XXIX) in the presence of $Pd(OAc)_2$ and 1,2-bis(diphenylphosphino)ethane (dppe) to generate the allyl alcohol adduct (XXX), which after conversion to the corresponding mesylate (XXXI) is reacted with 2,2,2-trifluoroethylamine (XXXII) in dimethylacetamide to furnish the allylic amine (XXXIII). Decarbethoxylation of malonate (XXXIII) by heating with LiCl in moist dimethylacetamide provides the *N*-acetyl aminoester (XXXIV). Then, cyclization of (XXXIV) by means of trifluoroacetic acid in hot toluene gives the azepinone derivative (XXXV). After acidic hydrolysis of acetamide (XXXV), the resulting racemic amine is resolved utilizing (–)-*O,O'*-di-*p*-toluoyl-L-tartaric acid (DTTA) in the presence of a trace amount of 5-nitrosalicylaldehyde to provide the (*S*)-amine ditoluoyltartrate salt (XXXVI). Finally, liberation of the tartrate salt (XXXVI) with HCl in isopropanol and simultaneous hydrogenation of the azepine double bond in the presence of $Pd/BaSO_4$ provides the *trans*-perhydroazepinone (III) (2-5). Scheme 3.

Background

Migraine, a chronic neurovascular disorder, is the most common type of headache seen in primary care. According to a survey conducted on approximately 20,000 people in the U.S.A., 17.6% of women and 5.7% of men experience at least one episode of migraine headache a year. The socioeconomic burden associated with migraine is dramatic. However, migraine is often undertreated (6, 7).

Currently available therapies for the treatment of migraine are classified as pain-relieving medications, also known as acute or abortive treatment, and preventive medications. Table I summarizes currently available medications for migraine pain relief. The US Headache Consortium recommends $5\text{-}HT_{1B/1D}$ receptor agonists, including triptans, as first-line therapy for patients with migraine who experience moderate to severe disability. However, not all migraines respond to triptans. Commonly used preventive medications include β-blockers and calcium channel blockers, antidepressants, cyproheptadine and botulinum toxin type A (Botox®), but only four drugs have been approved by the FDA for this indication (divalproex sodium, propranolol, timolol maleate and topiramate). Preventive medications can reduce the frequency, severity and length of migraines but cannot, in general, eliminate headaches completely and are often associated with serious side effects (7, 8).

The mechanism of migraine headache is not fully understood, but calcitonin gene-related peptide (CGRP), a naturally occurring 37-amino-acid peptide, has been suggested to play a key role in migraine pathophysiology. During a migraine attack, CGRP levels in the cranial circulation are markedly increased and increasing evidence indicates that CGRP receptor antagonists could alleviate migraine by returning dilated intracranial arteries to normal without leading to active vasoconstriction. Moreover, triptans are known to exert their beneficial effects in migraine in part via normalization of CGRP levels (9, 10). Thus, increasing evidence suggests that the CGRP receptor may be a potential therapeutic target for the treatment of migraine. BIBN-4096BS (olcegepant), the first potent and selective small-molecule CGRP antagonist developed at Boehringer Ingelheim, demonstrated encouraging effects in acute migraine. In clinical trials, BIBN-4096BS effectively inhibited the dilatation of dural arteries induced by CGRP (9-12), but development of the compound was discontinued due to formulation problems.

Recently, Merck & Co. developed a series of nonpeptide, small-molecule CGRP receptor antagonists. MK-0974, an oral CGRP receptor antagonist, was chosen as a lead compound for the treatment of acute migraine attacks (13-15). MK-0974 is currently in phase III development.

Preclinical Pharmacology

The receptor affinity of MK-0974 was determined using standard competitive receptor binding assays. MK-0974 demonstrated high affinity for the human CGRP receptor, with a K_i of 0.77-0.78 nM. MK-0974 also demonstrated high selectivity for the CGRP receptor, with little or no affinity for the closely related human adrenomedullin receptors RAMP2 (K_i > 100 μM) and RAMP3 (K_i = 29 μM). High binding affinity for primate CGRP receptors (K_i = 1.2 nM) was also observed, whereas the affinity for receptors from other species, such as dogs and rats (K_i = 1204 and 1192 nM, respectively), was markedly reduced. In functional assays, it potently and competitively inhibited α-CGRP-stimulated cAMP production in cells (IC_{50} = 2.2 nM, K_B = 1.1-1.8 nM). In the rhesus dermal vasodilatation assay, MK-0974 led to concentration-dependent inhibition of capsaicin-induced vasodilatation, with EC_{50} and EC_{90} values of 127 and 994 nM, respectively (15-17).

Pharmacokinetics and Metabolism

The pharmacokinetics of MK-0974 were tested in rats, dogs and rhesus monkeys. The clearance and half-life of i.v. MK-0974 in rhesus monkeys were 7.0 ml/min/kg and 2.8 h, respectively, and the respective values in rats were 9.4 ml/min/kg and 1.6 h; clearance in dogs was 17 ml/min/kg. The oral bioavailability of the compound in rats and dogs was 20% and 35%, respectively (15).

The pharmacokinetics of MK-0974 during a migraine attack and between migraine attacks were investigated in a randomized, double-blind, placebo-controlled clinical trial in 23 migraineurs. A total of 15 patients received 300 mg MK-0974 p.o. and 8 patients received placebo. In the first period, patients received study drug within 2 h after the onset of a moderate to severe migraine attack and at

Table I: Pain-relieving medications for migraine.

Medication	Application	Limitations
Triptans such as rizatriptan, zolmitriptan, sumatriptan, naratriptan, almotriptan, frovatriptan and eletriptan	First-line therapy for migraine	Lack of efficacy, cost, side effects
Nonsteroidal antiinflammatory drugs (NSAIDs) such as ibuprofen and aspirin	For mild migraines	Not effective alone for severe migraines; may lead to ulcers, gastrointestinal bleeding and rebound headaches if used for long periods of time
Ergots such as ergotamine and dihydroergotamine	Commonly used before triptans were introduced	Less effective than triptans
Anti-nausea medications such as metoclopramide and prochlorperazine	Combined with other medications	Must be combined with other medications
Butalbital combinations such as sedative butalbital with aspirin, acetaminophen, caffeine or codeine	For migraine attacks	Rebound headaches
Opiates	For migraineurs who cannot take triptans or ergots	Habit-forming

least 4 h after their last meal; in the second period, patients received study drug after at least a 4-h fast and at a similar time of day as in the first study period. C_{max}, AUC_{0-4h} and $AUC_{0-\infty}$ were comparable during and between migraine attacks, with geometric mean values of 0.71 and 1.11 μM, 0.77 and 1.14 μM.h and 0.91 and 1.25 μM.h, respectively. Similar t_{max} and mean apparent $t_{1/2}$ were also observed during (1.5 and 8.5 h, respectively) and between migraine attacks (1.0 and 10.6 h, respectively) (18, 19).

Clinical Studies

Inhibition by MK-0974 of the capsaicin-induced increase in dermal blood flow was studied in a crossover study conducted in 12 healthy male subjects. In each period, the subjects received a single oral dose of MK-0974 (300 or 800 mg) or placebo followed by two topical doses of 300 and 1000 μg capsaicin/20 μl water-ethanol mixture applied at two sites on the volar surface of the left and right forearms. MK-0974 at both doses induced robust inhibition of the capsaicin-induced increase in dermal blood flow (78-100% for 300 mg and 90-98% for 800 mg at 4 h after administration) (20-22).

The safety and efficacy of MK-0974 in relieving migraine pain were studied in a randomized, double-blind, placebo- and active-controlled, dose-ranging phase II trial. MK-0974 at oral doses of 25, 50, 100, 200, 300, 400 and 600 mg was used to treat moderate to severe migraine attack in patients diagnosed with migraine with or without aura. Rizatriptan (10 mg) and placebo were also used in the trial for comparison. The four lowest doses of MK-0974 (25, 50, 100 and 200 mg) were discontinued because of insufficient efficacy. For the remaining treatment groups (300, 400 and 600 mg), the proportion of patients reporting pain relief at 2 h after dosing was 68.1% on 300 mg MK-0974 (n=38), 48.2% on 400 mg MK-0974 (n=45), 67.5% on 600 mg MK-0974 (n=40), 69.5% on rizatriptan (n=34) and 46.3% on placebo (n=115). Compared to placebo, MK-0974 significantly (p = 0.015) improved mean migraine pain relief 2 h after dosing. A similar pattern was seen for pain freedom at 2 h and sustained pain freedom was observed at 24 h; the proportion of patients achieving pain freedom at 2 h was 45.2% for 300 mg MK-0974, 24.3% for 400 mg MK-0974, 32.1% for 600 mg MK-0974, 33.4% for rizatriptan and 14.3% for placebo, and sustained pain freedom at 24 h was observed in 39.6% for 300 mg MK-0974, 22.0% for 400 mg MK-0974, 32.0% for 600 mg MK-0974, 18.4% for rizatriptan and 11.0% for placebo (23-25). MK-0974 was generally well tolerated in both healthy volunteers and migraineurs and adverse events did not increase with dose (18, 19, 23-25).

Phase II and III clinical trials are ongoing or planned to evaluate the efficacy and safety of MK-0974 in acute migraine (26-29).

Source

Merck & Co., Inc. (US).

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