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LECTURE TEXT

Migraine drugs

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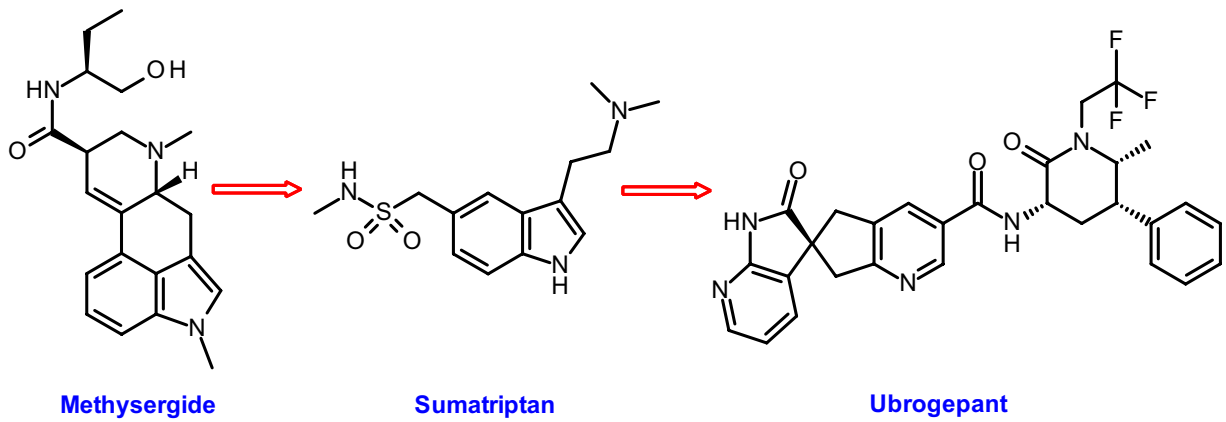
Abstract

According to recent studies, migraine affects more than 1 billion people worldwide, making it one of the world's most prevalent diseases. Although this highly debilitating illness has been known since ancient times, the first therapeutic drugs to treat migraine, ergotamine (Gynergen) and dihydroergotamine (Dihydergot), did not appear on the market until 1921 and 1946, respectively. Both drugs originated from Sandoz, the world's leading pharmaceutical company in ergot alkaloid research at the time. Historically, ergot alkaloids had been primarily used in obstetrics, but with methysergide (1-methyl-lysergic acid 1′-hydroxy-butyl-(2*S*)-amide), it became apparent that they also held some potential in migraine treatment. Methysergide was the first effective prophylactic drug developed specifically to prevent migraine attacks in 1959. On the basis of significantly improved knowledge of migraine pathophysiology and the discovery of serotonin and its receptors, Glaxo was able to launch sumatriptan in 1992. It was the first member from the class of triptans, which are selective 5-$HT_{1B/1D}$ receptor agonists. Recent innovations in acute and preventive migraine therapy include lasmiditan, a selective 5-HT_{1F} receptor agonist from Eli Lilly, the gepants, which are calcitonin gene-related peptide (CGRP) receptor antagonists discovered at Merck & Co and BMS, and anti-CGRP/receptor monoclonal antibodies from Amgen, Pfizer, Eli Lilly, and others.

Graphical abstract



Keywords Migraine · Ergotamine · Triptans · Ditans · Gepants · Fischer indole synthesis · Total synthesis · Biosynthesis

In memoriam: Bernd Janssen (1950–2022), my mentor and dear friend (B.S.).

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Infobox: Instructions for the reader

This review is not intended to be read in a linear fashion. If you are interested in a particular topic, please feel free to jump directly to the section of interest. The content ranges from
1. Introduction
2. Description of Migraine
3. Treatment of Migraine attacks
4. Chemical Syntheses of Migraine Drugs
5. Migraine and Natural Medicine

In this review, we emphasize on total and industrial syntheses. If your focus is on thepathophysiology or pharmacology of migraine, please consult also the relevant literature cited.

As you browse through this review, you will find numerous infoboxes that contain interesting and sometimes entertaining information, but they are not essential to the story and can be skipped.

In order to simplify retracing the numerous building blocks, the drawings of most chemical syntheses are in color. The color code is consistent within a total synthesis, but not between two different ones.

Fig. 1 The statue of William Dunbar at the Scottish National Portrait Gallery in Edinburgh (© Stephencdickson)

Introduction

History of migraine

William Dunbar (about 1460–1530) was a distinguished bard (Scottish: Markar) in the service of James IV of Scotland (1473–1513) (Fig. 1) [1]. In the first stanza of his brief Middle Scots poem "On his heid-ake" he bequeathed us a late medieval description of the headache phase of migraine, authentically featuring the debilitating effects on his own body: photophobia and pain [2–4]. In the second and third stanzas, Dunbar thoroughly captured the postdrome phase [5] (literally hangover or aftermath) of migraine, such as fatigue, dullness, and distress, and the inability to find the right words.

On his heid-ake	**On his headache** [6]
My heid did yak yester nicht, This day to mak that I na micht. So sair the magryme dois me menyie, Perseing my brow as ony ganyie, That scant I luik may on the licht.	My head did ache last night, so much that I cannot write poetry today. So painfully the migraine does disable me, piercing my brow just like any arrow, that I can scarcely look at the light.
And now, schir, laitlie eftir mes To dyt thocht I begow the to dres, The sentence lay full evill till find, Unsleipit in my heid behind, Dullit in dulnes and distres.	And now, Sire, shortly after mass, though I tried to begin to write, the sense of it lurked very hard to find, deep down sleepless in my head, dulled in dullness and distress.
Full oft at morrow I upryse Quhen that my curage sleipeing lyis. For mirth, for menstrallie and play, For din nor danceing nor deray, It will not walkin me no wise.	Very often in the morning I get up when my spirit lies sleeping. Neither for mirth, for minstrelsy and play, nor for noise nor dancing nor revelry, it will not awaken in me at all.

Actually, the first artifacts as well as human remains relating to headache and migraine are much older, originating in prehistoric times. As early as in the Neolithic era 9000 years ago, trepanation, the removal of a piece of bone from the skull, might have been an ultimate surgical treatment of this condition [7]. Sumerian cuneiform inscriptions and Egyptian papyri, e.g., the Ebers papyrus (c. 1550 BC) and the Hearst papyrus (2000 BC)) suggest that migraine might have been viewed as a spiritual entity rather than an ailment [8, 9]. Mesopotamians attributed migraine to Ti'u, the evil spirit of headache, and its appeasing with medicinal formulas or its release by trepanation were considered appropriate treatments (Fig. 2) [10] 11].

The brain itself does not feel pain, because it lacks pain receptors. However, in most other inner parts of the head nociceptors are found, including the eyes, ears, teeth, the lining of the mouth, the cranial and spinal nerves, the head and neck muscles, the extracranial arteries, the middle meningeal artery, the dural venous sinuses, the meninges, and parts of the brainstem [12].

Fig. 2 The painting "Extracting the stone of madness" by Hieronymus Bosch (circa 1450–1516) is displayed in the Museo del Prado in Madrid. It depicts a surgeon, wearing a funnel hat, performing a medieval trepanation (© public domain)

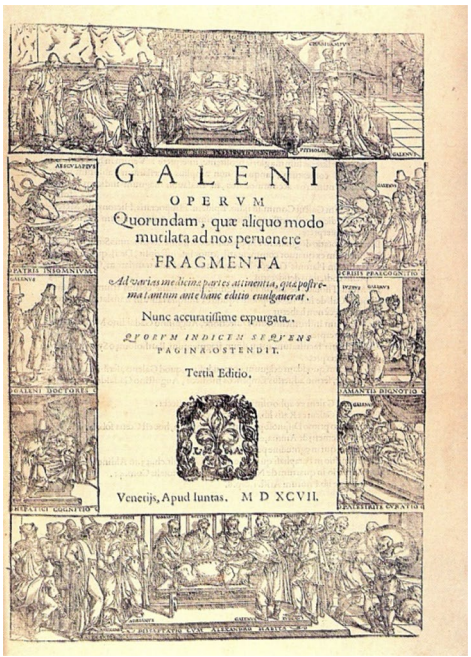


Fig. 3 The front cover of the "Opera" by Galen edited in Venice in 1597 (© public domain)

Hippocrates of Kos (460–377 BC) conceived all illnesses, including headache, as an imbalance of natural factors and conceptualized the treatment as a rebalancing of these disturbances. He was the first physician describing the visual symptoms resembling a migraine aura in *The seventh book of epidemics* about his patient called Phaenix:

Phaenix's complaint was of such a nature that flashes like lightning seemed to dart from his eye, and generally his right eye. Not long after, a violent pain seized his right temple, and then his whole head and neck. The back part of his head at the vertebrae swelled; and the tendons were upon the stretch and hard. Now if he attempted to move his head, or to open his teeth, a pain seized him from the violence of the stretch. Vomitings, whenever they happened, removed the pains now mentioned, or made them easier. Bleeding was also of service; and hellebore draughts brought away all sorts of humors, especially porraceous [13].

Aulus Cornelius Celsus (25 BD-50 AD) recognized in migraine a lifelong disorder, which might be triggered by numerous factors.

Aretaeus of Cappadocia (81–138 AD) was able to differentiate three types of headache, among those heterocrania, a paroxysmal headache on one side of the head, which frequently is accompanied by nausea, vomiting, and photophobia.

Galen of Pergamon (c. 129 to c. 199 AD), personal physician to the Roman emperor Marcus Aurelius (121–180 AD), coined the term hemicrania [from *hemikranion* (Gr.): half skull] for recurrent painful attacks affecting almost half of the head. He also supposed that the throbbing pain might be caused by arterial pulsation (Fig. 3).

Infobox: Transcutaneous electrical nerve stimulators for the treatment of migraine

Already in ancient times electricity was used experimentally to treat migraine. Prominent physicians, such as Scribonius Largus (c. 1 to c. 50 AD) [14], personal doctor to Claudius (10 BC to 54 AD), and a century after him, Galen of Pergamon [10], pioneer of galenics, suggested treating migraine by using an electric torpedo fish attached to the forehead of the patient (Fig. 4). In the eighteenth century, the sixth president of Pennsylvania Benjamin Franklin (1706–1790) proposed the use of electrostatic gadgets to relieve pain (Fig. 5). The development of modern devices for transcutaneous electrical nerve stimulation is credited to Guillaume-Benjamin-Amand Duchenne de Boulogne (1806–1875) and foremost to the US neurosurgeon Clyde Norman Shealy (Fig. 6). Some recent meta-analyses reveal the effectiveness of transcutaneous electrical nerve stimulation for the acute and prophylactic treatment of migraine. However, these studies also point out that future large and well-conducted studies are needed to improve the present data [15, 16].

Fig. 4 Common torpedo (*Torpedo torpedo*) of Corsica, France. The male torpedo fish can grow up to a length of 60 cm; females can reach 41 cm. They generate surges of up to 200 V for defense or to stun their pray. To humans the electric shocks are very painful, but not life threatening (© Roberto Pillon)

Fig. 5 Benjamin Franklin is one of the Founding Fathers of the USA. He was a highly talented polymath and key person of the American Enlightenment. Aside from his merits as a statesman and his inventions, such as the Franklin stove, bifocals and the lightning rod, he made major contributions to the theories of electricity. (© public domain)

Finally, in the fifth century, the physician Caelius Aurelianus from Sicca in Numidia conveyed the detailed knowledge of migraine in the Greek and Roman antiquity through his translations of the works by Soranus of Ephesus (98–138 AD) [17].

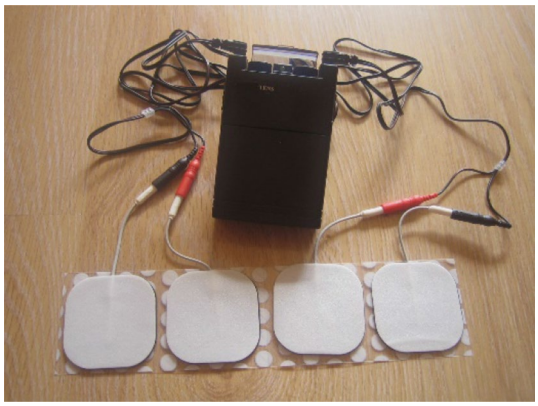


Fig. 6 Transcutaneous electrical nerve stimulator (TENS) (© Yeza)

Various doctors of the Byzantine era, such as Alexander of Tralles (525–605 AD), Oribasius (320–400 AD), Aëtius of Amida (520–575 AD), and Paulus Aeginita (625–690 AD), described numerous cases of headaches. However, they referred extensively to the works of Hippocrates, Galen, and Aretaeus, without much advance of medical knowledge.

Aside from the medical writings on headaches and migraine of medieval North European scholars such as Hildegard of Bingen (1098–1180) and Albertus Magnus (c. 1200–1280) suggesting herbal remedies, the books and contributions of the most prominent physicians of the Islamic Golden Age (traditionally dated from the eighth century to the fourteenth century) are noteworthy.

Al-Zahrawi (Abū al-Qāsim Khalaf ibn al-'Abbās al-Zahrāwī al-Ansari, 936–1013) was an Arab Andalusian surgeon, chemist, and royal physician to the caliph of Cordoba, Spain. In his 30-volume medical encyclopedia, *Kitab al-Tasrif*, he suggested the application of a hot iron on the head of the sufferer or an incision in the temple of the patient and applying garlic to the site.

Avicenna (Ibn Sina, 980–1037), author of *The Canon of Medicine* and *The Book of Healing*, is regarded as one of the most significant physicians, astronomers, philosopher, and father of the early modern medicine. He considered cashews (*Anacardium occidentale*) as an appropriate headache remedy, probably also grains of paradise (*Aframomum melegueta*), a species in the ginger family, Zingiberaceae, and closely related to cardamom [18].

The first scientific approaches to migraine from our current perspective are found in treatises of the seventeenth century, e.g., in *Observationes Medicae* from the famous Dutch physician Nicolaas Tulp (1593–1674), and in *Pharmacopoiea Londinensis* from the well-known English herbalist and doctor Nicholas Culpepper (1616–1654) [19]. In two books, *Cerebri Anatome* of 1664 and *Soul of Brutes* of 1672, Thomas Willis

(1621–1675), physician in Oxford and London, established the modern brain anatomy and coined the term "neurology." He carefully described the symptoms of migraine and detailed numerous triggers of migraine attacks, such as diet, treacherous weather, changes of season and heredity [20].

Further major contributions in the area of migraine research can be attributed to physicians of the eighteenth and nineteenth centuries. Erasmus Darwin (1731–1802), grandfather of Charles Darwin, considered vasodilation as a cause of headache. In 1873, Peter Wallwork Latham (1832–1923) published a monograph *On Nervous or Sick-Headache, Its Varieties and Treatment* in which he summarized his "vasomotor theory on migraine" [21]. He posited that the disorder was caused by a defective tone in the cerebrospinal system, leading to excitement of the vasomotor sympathetic nerves, producing "prodromata" (which we would call today "aura"), followed by "suspension of the function of this nerve," producing vasodilatation and headache [22, 23]. In contrast, Edward Liveing (1832–1919) believed migraine can be caused by "nerve storms" as he described in his book *On Megrim* the same year [24] and finally Sir William Richard Gowers (1845–1915) best known for his two-volume *Manual of Diseases of the Nervous System* (1886, 1888), who identified fatigue, excitement, improper nutrition, visual stimuli, and peculiar odors as potential triggers for migraine attacks. He proposed the consumption of Indian hemp (marijuana) as well as "Gowers mixture" containing ethanol, strychnine, chloroform, and nitroglycerine among other agents, as appropriate remedies [25].

Infobox: Migraine of Celebrities

The history of migraine, which spans several millennia, is not only a Who's Who of the most distinguished physicians, but also features a long list of prominent patients (Table 1) [26].

Alice in Wonderland syndrome

The story of one of the most popular works of English-language fiction commences with the title character Alice, a 7-year-old girl, falling down a rabbit hole and experiencing variations of her own size. In the second chapter, she grows so large that her head touches the ceiling of a tiny room, as illustrated by John Tenniel (1820–1914), and then shrinks to swim in her own tears.

In the 1950s, the British psychiatrist John Todd (1914–1987) at Menston in West Yorkshire, UK, discovered that several of his patients suffered from severe headaches that led to distorted perceptions of objects as well as of their own bodies [50]. Inspired by Carroll's children's books, he coined the term "Alice in Wonderland syndrome" (AIWS) for dysmetropsia, a neuropsychological disorder caused by migraine attacks, but sometimes also by brain tumors and, of course, by the use of psychoactive drugs. Aside from visual distortions, Alice in Wonderland syndrome may also affect sensation, touch, and hearing [51].

Description of migraine

Classification of headache disorders

Today, we have a detailed classification of headache including a distinct delineation of the clinical syndrome of migraine based on clear diagnostic criteria. Cephalalgia, synonym to headache, is a symptom that refers to any type of pain located in the head, face, or neck. According to the International Classification of Headache Disorders, the sum of more than 200 types of headache can be divided into two large categories of primary and secondary headaches [52]. Ninety percent of all headaches are primary headaches. Albeit causing significant daily pain and disability, in most cases they are benign. Examples are migraine, hemicrania continua, cluster headaches, trigeminal neuralgia, primary stabbing headaches, primary sex headaches, and hypnic headaches [53]. In contrast, secondary headaches are often caused by an underlying disease, such as an infection, head injury, vascular disorders, brain bleed, stomach irritation, or tumors, and should be considered as warning signs.

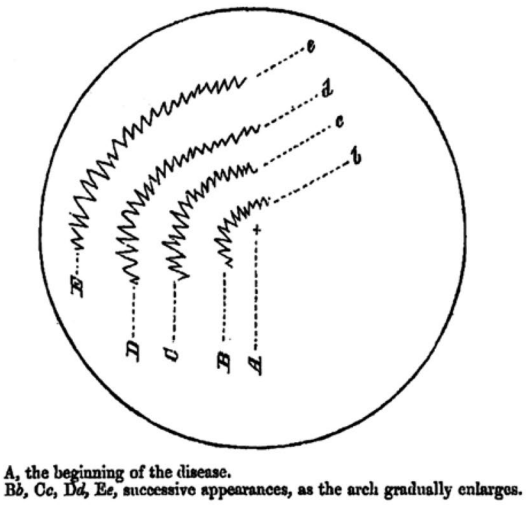
Infobox: Prevalence and socioeconomic burden of migraine

According to some recent studies, migraine globally affects more than 1 billion people, and thus it is ranked as one of the most prevalent disorders in the world [54, 55]. It was estimated that migraine caused 45.1 million years of life lived with disability (YLDs) in 2016, accounting for 5–6% of the global disease burden and more than all other neurological disorders combined [56]. Children as young as 2 years may suffer from migraine. Before puberty the condition is slightly more common in girls. During adolescence and for the rest of the lifespan it also predominantly affects women [57, 58]. Migraine is most burdensome for women aged 15–49 years, causing 20.3 million YLD.

In 2019, age-standardized annual incidence rates for migraine exceeded 1300 per 100,000 population in Indonesia, Thailand, Finland, Sweden, Norway, Italy, Germany, Belgium, France, Spain, Portugal, the UK,

Table 1 Celebrities suffering from migraine

Patient	Biographical data	Profession	Remarks
Paul the Apostle [27, 28]	c. 4–64 AD	Tent maker	He possibly suffered from migraine, which triggered his conversion from Saul to Paul. Later he referred to his chronically recurring ailment as "a thorn in the flesh" (King James Bible, 2 Corinthians 12:7)
Hildegard of Bingen [29]	1098–1179	Benedictine nun and abbess	Hildegard's migraine was retrospectively diagnosed in 1917 by the British historian Charles Singer (1876–1960) in the wake of a new perception of this ailment [30]
William Dunbar	1460–1530	Scottish poet	According to *A Dictionary of the Older Scottish Tongue (up to 1700)* at the time of Dunbar, "magryme" was a rare and specialist term [31]
Thomas Jefferson [27]	1743–1826	Lawyer, 3rd President of the USA	He treated his migraine attacks with cinchona bark, mustard packs, and cold-water soaks. Bravely he wrote: "The art of life is the avoiding of pain"
Sir George Biddell Airy	1801–1892	English mathematician and astronomer	In a letter to the editors of the Philosophical Magazine on 5 June 1865, George Airy intimated his numerous migraine episodes. The paper contains what is generally considered the first published illustration of the pattern of the visual disturbance in course of an aura (Fig. 7) [32]
Charles Darwin [27]	1809–1882	Naturalist and biologist	He noticed that the attacks were triggered by deviation from routine
Richard Wagner [33, 34]	1813–1883	German composer	As we know from Wagner's correspondence and his memoirs, headaches often prevented him from composing, but occasionally he also drew inspiration from his affliction (Fig. 8)
Emily Dickinson [35]	1830–1886	American poet	References to Dickinson's migraines are scattered throughout her poetry
Lewis Carroll [36]	1832–1898	English writer	Carroll may have created the story of *Alice's Adventures in Wonderland* using his own experience of migraine attacks with episodes of dysmetropsia (Fig. 9). It was Latham's book in which Carroll found an appropriate description of his ailment [37]
Friedrich Nietzsche [27]	1844–1900	German philosopher	He was plagued with migraines, as many as 120 attacks per year
Sigmund Freud [27]	1856–1939	Austrian neurologist and the founder of psychoanalysis	He anticipated the importance of vascular and neurogenic mechanisms of headaches
Gustav Mahler [38]	1860–1911	Austrian composer	Alma Mahler called her husband's migraine attacks "horrible hours of tragic agony"
Rudyard Kipling [39]	1865–1936	English journalist and novelist, author of *The Jungle Book* (1894)	Kipling reported on his symptoms of "hemicrania" to his cousin, Margaret Burne-Jones, in a letter from Lahore on 17 June 1886
Giorgio De Chirico [40, 41]	1888–1978	Italian painter	De Chirico suffered from a peculiar migraine aura, named "Alice in Wonderland syndrome"
Harold George Wolff	1898–1962	American neurologist	Wolf was the first who assumed that the aura arose from a vasoconstriction and the headache from a vasodilatation [42]
Princess Margaret, Countess of Snowdon	1930–2002	Member of the British royal family	The first London City migraine clinic was opened in 1970 by Princess Margaret, Patron of the Migraine Trust [43, 44, 45]. Over the years, the Princess Margaret Migraine Clinic became one of the world's leading institutions in migraine treatment. During her life, Princess Margaret sadly suffered from many ailments aside of migraine attacks. She contracted laryngitis, bronchitis, hepatitis, pneumonia, and cancer, and suffered from strokes [46]



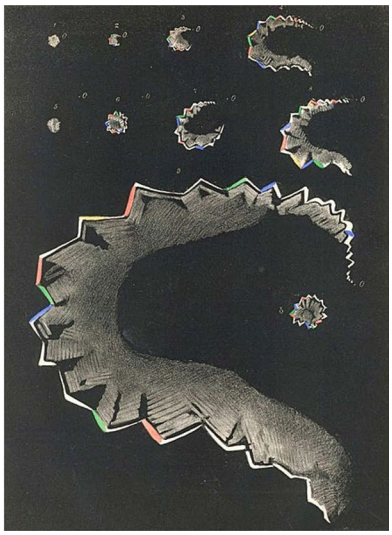


Fig. 7 Drawing by Sir George Biddell Airy, who in his role as Astronomer Royal established Greenwich as the location of the prime meridian, illustrating his visual disturbance in course of an aura (drawing left). His son Hubert Airy (1838–1903), a physician and pioneer in migraine research, stated at the age of 31 that he had experienced about 100 episodes of visual disturbances like those of his father, for which he coined the term "scintillating scotoma" (drawing right) (© public domain) [47, 48]

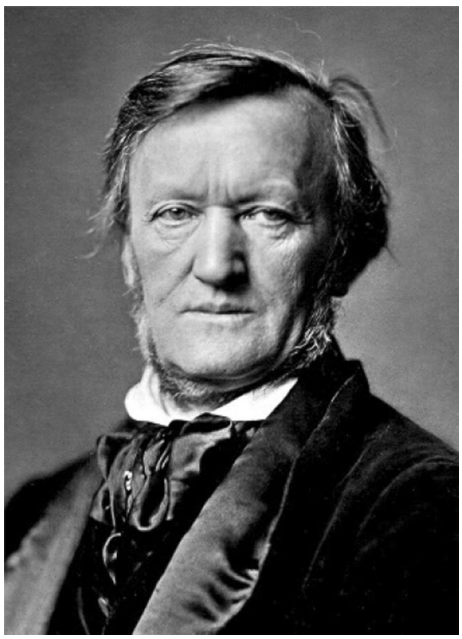


Fig. 8 The German composer, theater director, and conductor Richard Wagner suffered from various ailments such as skin disorders, acute infections, and heart disease, but the condition that he described as the "main plague of his life" was recurring migraine attacks. In the third part of the *Ring Cycle*, *Siegfried*, premiered at the Bayreuth Festspielhaus in 1876, he interwove his personal suffering and his music. The first scene of act 1 of the opera can be considered as a concise, vivid description of a headache episode, which culminates in Mime's cry "Compulsive plague! Pain without end!" [49]. (© public domain)

Ireland, Iceland, the USA, Paraguay, and Brazil. In Asia and Africa, recorded rates of migraine are slightly lower.

The annual economic burden ranges in Europe between €18 billion and €27 billion and at about $20 billion in the USA [59, 60].

Types of migraine

Migraines, according to its specific features and associated symptoms, can be divided into two major classes: migraine without aura and migraine with aura [52, 61].

The *common migraine* is a migraine not accompanied by an aura.

The *classic migraine* involves the experience of an aura episode, which in some varieties as is in the case of *familial hemiplegic migraine* and *sporadic hemiplegic migraine*, can be accompanied by motor weakness. *Basilar-type migraine* involves other symptoms of brainstem-related difficulties, such as dysarthria (motor speech disorder), vertigo, and ringing in the ears.

The *cyclic vomiting syndrome* (formerly called *abdominal migraine*) is a disorder most commonly diagnosed in children. It comprises the symptoms of abdominal pain, nausea, cyclical vomiting, light sensitivity, benign paroxysmal vertigo, and headaches.

In the case of *retinal migraine*, the migraine headache is accompanied by visual disturbances or even temporary blindness in one eye.

Chronic migraine meets all diagnostic criteria for migraine headache, but an episode lasts at least 15 days per month for more than 3 consecutive months.

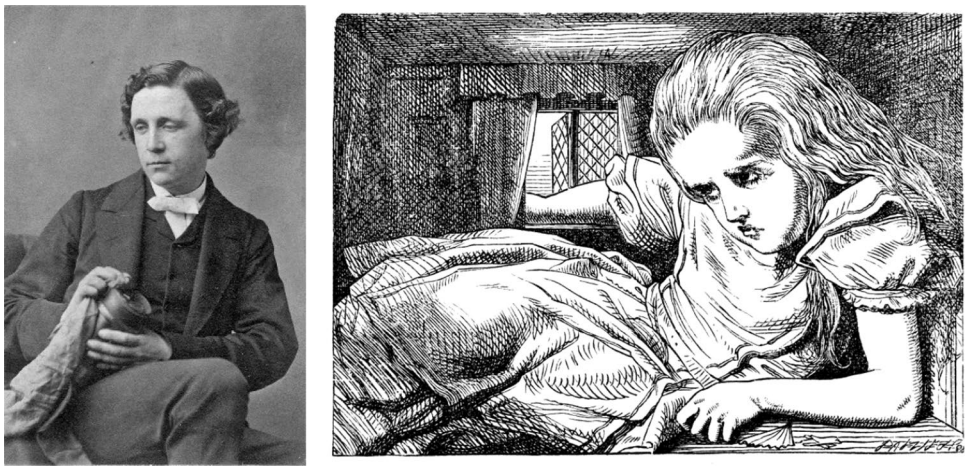


Fig. 9 Charles Lutwidge Dodgson, also known as Lewis Carroll, was a highly talented English author probably best known for his children's books, especially *Alice's Adventures in Wonderland*, and its sequel *Through the Looking-Glass* published first in 1865 and 1871, respectively. (© both public domain)

Phases of a migraine episode

A typical migraine attack can be divided into four distinguishable phases, although not all phases are necessarily experienced.

The *prodrome phase* might onset a couple of days to a few hours before the experience of pain. The symptoms can range from craving for certain foods to constipation or diarrhea, stiff muscles, sensitivity to noise or smells, fatigue, altered mood, irritability, and depression or euphoria.

The *aura* is a transient neurological phenomenon that can emerge before the pain phase. The symptoms comprise auditory hallucinations, delusions (a fixed belief that is not amenable to change considering conflicting evidence), sensory and motoric effects (tingling, numbness, loss of position sense), but most frequently visual disturbances. The visual disorders may consist of scintillating scotoma (alterations in the field of vision, often zigzagging lines) and hemianopsia (blurring and loss of vision in parts of the visual field) (Fig. 10).

The *pain phase* usually arises gradually and aggravates over time. Typically, the headache is unilateral, throbbing, and of moderate to severe intensity. Remarkably, the throbbing is not in phase with the pulse. Physical exercise often worsens pain. The pain phase is frequently accompanied by irritability, fatigue, nausea, vomiting, sensitivity to light, sound, and smells. However, *silent migraine* episodes are also known, in which the aura is not continued by a pain phase.

The *postdrome phase* follows once the acute headache has settled. Many patients feel tired or a hangover, accompanied with cognitive difficulties, impaired thinking, gastrointestinal symptoms, weakness, and mood changes. Some feel unusually refreshed or euphoric, whereas others experience depression and malaise [62].

Triggers of migraine

Migraine attacks might be triggered by multiple factors [63], including stress, fatigue [64], certain foods, and

Fig. 10 **a** The Brandenburger Tor (viewed from the Pariser Platz) is a neoclassical monument in Berlin, built in 1789–1793. The photograph was digitally distorted by Sven Jähnichen from the Vrije Universiteit Amsterdam, to illustrate different states of visual disorders during an aura. **b** Fortification: Fortification is a perceptual disturbance during a migraine aura with characteristic zigzag structures reminiscent of a fort. **c** Positive scotoma: In a positive scotoma, additional structures are perceived. **d** Negative scotoma: In a negative scotoma, structures and contrasts are lost. **e)** Failure of the visual field: The temporary loss of vision is usually limited to one side. (© AlterVista, S. Jähnichen)

weather, although empirical data remain elusive [65–67]. However, there is also some evidence associating migraine episodes with post-traumatic stress disorder and abuse [68], as well as with hormonal influences, e.g., menstruation [69] and pregnancy [70].

Genetics

Aside from environmental triggers, genetic factors might also contribute to the likelihood of experiencing migraines [71, 72]. It is generally accepted that migraine might run in families. *Familial hemiplegic migraine*, for example, is inherited in an autosomal dominant way. Of the four genes associated with this type of migraine, three of them are involved in ion transport, and the fourth encodes an axonal protein associated with the exocytosis complex [73]. Another example is *cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy* (CADASIL syndrome), caused by mutations of the Notch 3 gene on chromosome 19, which may start migraine attacks with aura [74]. Finally, more recent studies suggest a contribution of transient receptor-potential melastatin 8 (TRPM8) to migraine [75]. TRPM8 is predominately expressed in cutaneous tissue and serves as a cold receptor, but it is also found on deep visceral afferents, such as the meninges, where temperature is not likely a stimulus. It has been suggested that activation of meningeal TRPM8 by exogenous agonists can cause headaches. Moreover, several recent studies have revealed that single-nucleotide polymorphisms of TRPM8 are consistently associated with the susceptibility to both migraine with and without aura [76].

Pathophysiology

Vascular theory of migraine

Despite enormous efforts in research and public awareness, our knowledge of migraine pathophysiology remains limited. The throbbing, pulsating pain of migraine, thought to be caused by periodical dilations of the blood vessels, is attributed to Galen and was reproposed by Thomas Willis in the late seventeenth century [77]. But it was not until the early 1940s that Harold G. Wolff (1898—1962) [78, 79], neurologist at the New York Hospital—Cornell Medical Center, demonstrated that the intensity of migraine is closely linked to the pulsating branches of the external carotid arteries (Fig. 11).

Decreasing the amplitude of pulsation alleviates headache. The same effect was achieved using ergot alkaloids to induce vasoconstriction of temporal and middle meningeal arteries, whereas vasodilators, such as nitroglycerin,

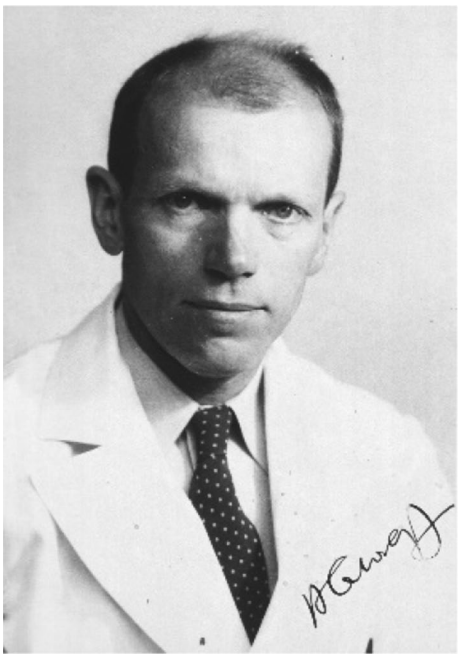


Fig. 11 Harold George Wolff is generally considered the father of modern headache research [82]. He suffered from migraines himself, as many other migraine researchers do, which may also have fueled his passion for research in this area. "No day without its experiment" was the framed motto in his office [42]. (© Courtesy of the US National Library of Medicine)

can trigger migraine attacks [80]. These observations laid the foundation for what later became known as the vascular theory of migraine. It centers on the concept that ischemia, as a result of intercranial vasoconstriction triggered by endothelin 1, which causes the aura [81]. The following rebound vasodilation and activation of perivascular nociceptive nerves lead to the headache.

Over the years, Wolff's theory has been elaborated and modified, but despite some shortcomings still constitutes the generally accepted model on vascular contributions to migraine [83, 84].

In particular, the weaknesses are:

1. The features of the prodrome phase cannot be readily explained by vascular effects.
2. There are some drugs that are effective in the treatment of migraine but do not affect blood vessels.
3. The majority of migraineurs, about 2/3, do not experience auras.
4. Intracranial blood flow patterns are inconsistent with the vascular theory.

From today's holistic concept, the pathophysiology comprises a complex series of neuronal and vascular events leading finally to the symptoms of migraine [85]. According to the neurovascular theory, migraine results

primarily from pathological neurogenic processes. Abnormal vascular effects are an epiphenomenon. They are not the cause but a consequence of this malfunction [86, 87].

Neurovascular theory of migraine

The roots of the neurovascular theory might also be traced back to the early 1940s. In 1941, the American psychologist Karl Spencer Lashley (1890–1958) reported on a scotoma he had experienced in the course of a migraine aura. He calculated a spreading velocity of the neuronal disturbance over his vision cortex in the range of 2–3 mm/min [88].

Three years later, the Brazilian biologist Aristides de Azevedo Pacheco Leão (1914–1993) published a seminal paper on the "Spreading depression of activity in the cerebral Cortex" of a rabbit (Fig. 12) [89]. Later spreading depression of cortical activity has been observed in a wide variety of species from cephalopods and locusts to numerous vertebrates, including rats, hamsters, pigs, and humans [90].

As early as in 1958, the Canadian neuroscientist Peter Milner (1919–2018) from McGill University in Montreal assumed a possible correspondence between the scotomas of migraine and cortical spreading depression of Leão [91].

Fig. 12 Aristides de Azevedo Pacheco Leão (1914–1993) at Harvard in the early 1940s (© courtesy of Dr. Péricles Maranhão-Filho)

Since these early findings, a host of even highly dedicated physicians developed the neurovascular theory of migraine and thereby laid the foundation for an effective treatment of this abundant and debilitating ailment. From our current perspective, the phases of a migraine attack are associated with different physiological processes [92, 93].

Premonitory phase During the premonitory phase, which might begin as early as 3 days before the onset of the headache phase, a complex interplay between various brain regions, including the brainstem and the hypothalamus, leads to nociceptive signaling. There are two main theories of how this might happen:

1. Increasing parasympathetic tone activates meningeal nociceptors

   The onset of the premonitory phase is caused by migraine triggers, which changes homeostasis and activates nociceptive pathways through an increased parasympathetic tone. This hypothesis is supported by the observation that indicators of an altered autonomic function, such as nausea, vomiting, thirst, lacrimation, nasal congestion, and rhinorrhea, are also features of a migraine attack.
2. Modulation of nociceptive signals from the thalamus to the cortex

   A delicate balance of neurotransmitter/neuropeptides from the hypothalamus and the brainstem regulates the firing of relay trigeminovascular neurons. Depending on the type of neurotransmitter, whether it is excitatory or inhibitory, it ultimately modulates the firing of thalamic trigeminovascular neurons and thus determines the transmission of nociceptive signals to the cortex.

Aura/non-aura phase In one-third of all migraine attacks the premonitory phase is followed by an aura. The cortical spreading depression, which is a decreased activity of neurons and glial cells, is caused by the release of potassium ions and excitatory glutamate from neurons leading to transient depolarization and in turn triggering the release of more neurotransmitters. As a result, spreading waves of electrophysiological hyperactivity are followed by waves of inhibition characterized by a negative change of the DC potential by 20–35 mV. They slowly propagate across the cortical surface, but also in subcortical regions, with a speed of 1.5–9 mm/min and coincide with the initiation and progression of aura symptoms lasting for about 30 min [94, 95].

Spreading depolarization decreases metabolism, causing a condition in which the total volume of blood is reduced (oligemia). Positron emission tomography (PET) has shown that blood flow is moderately reduced during an aura episode. It might be a question of a certain threshold to produce this symptom. In cases where this threshold

is not reached, the patient experiences a migraine attack without aura [96].

Headache phase The throbbing pain of a migraine headache results from activation of the trigeminovascular pathway (a network of nerves linked to blood vessels in the head). There is some evidence from animal studies that ATP, potassium ions, glutamate, and nitric oxide (NO) are released in the course of cortical spreading depression. In addition, genes encoding cyclooxygenase-2, tumor necrosis factor alpha, interleukin-1β, galanin, and metalloproteinases are upregulated. The latter lead to the leakage of the blood–brain barrier, facilitating sensitization of the dural perivascular trigeminal afferent endings by potassium ions, adenosine, and nitric oxide [94]. However, in all these events, the pituitary adenylate cyclase-activating polypeptide (PACAP-38) and the calcitonin gene-related peptide (CGRP), also released by cortical spreading depression, play a pivotal role [97, 98].

It has been shown that the intravenous administration of neuropeptide PACAP-38, comprising 38 amino acids, can induce migraine [99]. It leads to dural mast cell degranulation and thereby liberation of inflammatory mediators, such as bradykinin, histamine, prostaglandin E2, and cytokines [100], and causes vasodilation of the middle meningeal artery [101].

Like PACAP-38, the calcitonin gene-related peptide can also induce migraine attacks. During the headache phase, elevated concentrations of CGRP were found in jugular venous blood. The 37 amino acid neuropeptide is a potent vasodilator at the meningeal blood vessels and may also cause sterile inflammation. Mediated by glutaminergic signaling, it acts as a neurotransmitter that enhances synaptic transmission and activates meningeal nociceptors. Once activated, the peripheral trigeminovascular neurons become sensitized to dural stimuli. The increased sensitivity to sensory stimulation is responsible for the characteristic throbbing pain, and the aggravation of pain by bending over or coughing. In the majority of cases, the headache goes along with nausea, phonophobia, and photophobia caused by a general neuronal hyperexcitability including brainstem reflexes and somatosensory, auditory, and visual stimuli. [92].

Postdrome phase In adults the headache phase usually lasts up to 72 h, whereas in children it often persists only

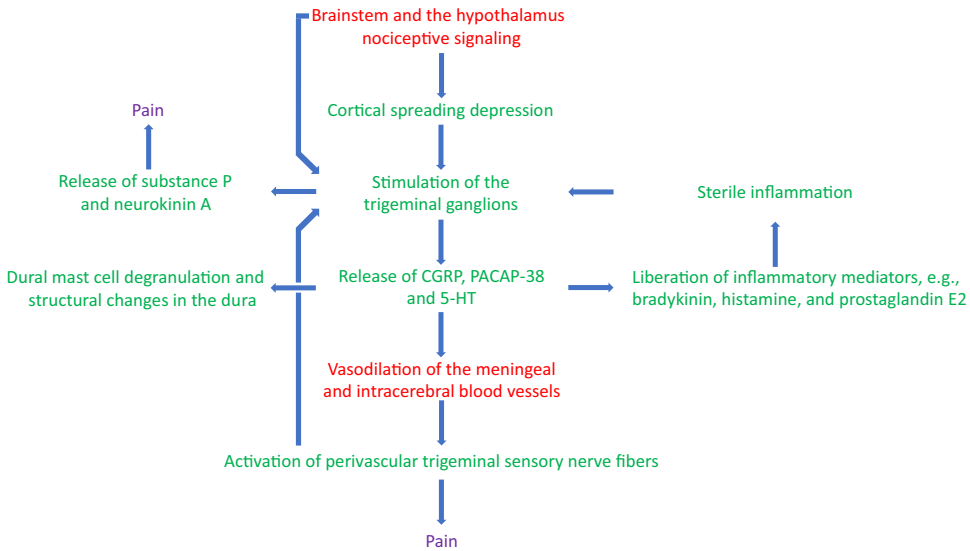


Fig. 13 Migraine is a neurovascular process with both vasogenic and neurogenic contributions [84, 106, 107]. CGRP plays a central role in the pathogenesis of migraine. Once released from activated trigeminal sensory nerves, it dilates cranial blood vessels and transmits vascular nociception [108]

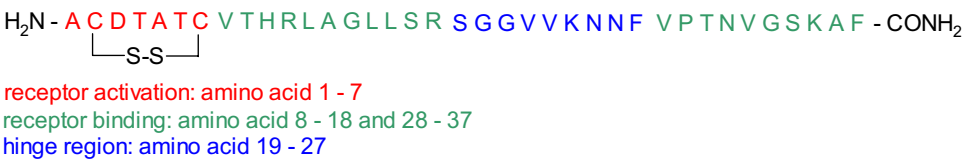


Fig. 14 Amino acid sequence of human α-CGRP (the unconventional representations of the N- and C-termini (H_2N-, $CHNH_2$) were chosen for reasons of unambiguity)

for less than 1 h [102, 103]. The following postdrome phase is marked by symptoms such as a sore feeling in the area where the headache was, tiredness, cognitive difficulties, gastrointestinal symptoms, and mood changes. Some migraineurs feel refreshed or euphoric, whereas others suffer from depression and malaise (Fig. 13) [104, 105].

Infobox: Calcitonin gene-related peptide (CGRP)

The calcitonin gene-related peptide was discovered by Michael G. Rosenfeld at the University of California in 1983 [109]. It consists of 37 amino acids (Fig. 14) [110]. In humans, two isoforms, α-CGRP and β-CGRP are known, which differ by three amino acids [111]. CGRP is encoded on chromosome 11. By alternative splicing, neurons of both the peripheral and central nervous system synthesize CGRP, whereas in the thyroid gland, calcitonin (a 32-amino-acid peptide hormone, contributing to calcium and phosphate homeostasis) is formed [112].

Considerable concentrations of CGRP are found in the sensory ganglia, the trigeminal nerves (nervus trigeminus), the cerebral cortex, and the pituitary gland. CGRP is the strongest vasodilating neuropeptide known in humans [113], mediating vasodilation directly by smooth muscle relaxation via activation of adenyl cyclase and indirectly by liberation of nitric oxide. Furthermore, it acts as an appetite suppressant and inflammation mediator, and it participates in the transmission of nociception [114]. Its hormone-like functions include gastric acid secretion, temperature homeostasis, and a positive inotropic and chronotropic effect on the heart [115, 116]. Insufficient secretion of CGRP in the embryonic or infant stage promotes cryptorchidism (maldescensus testis) and the development of hernia and hydroceles [117].

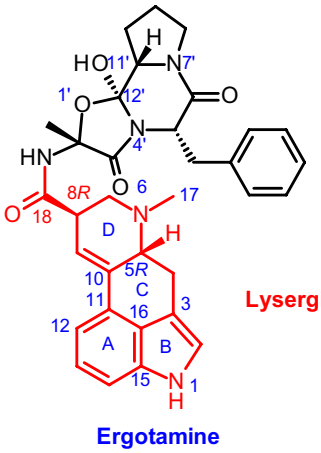
CGRP receptors are found throughout the human body, e.g., in the central and peripheral nervous systems as well as in the cardiovascular system, corresponding to the peptide's endocrine, immune, respiratory, gastrointestinal, and cardiovascular function [108]. Two are of superior relevance: a G-protein-coupled receptor called calcitonin receptor-like receptor (CALCRL) and a receptor activity-modifying protein (RAMP1) [118, 119].

Treatment of migraine attacks

Ergotamine

Since medieval times an enormous number of remedies were used therapeutically in the attempt to relieve the headache caused by migraine. None proved consistently effective. It was not until 1862 that E. Moretti reported the "Story of a scurvy headache cured by the internal use of ergot extract" ("Storia di una cefalalgia scorbutica guarita mediante l'uso interno dell'estratto di segale cornuta") in an Italian journal [120]. It was the English surgeon Edward Woakes (1837–1912) in Luton, who first recommended "ergotine," an extract of ergot of rye (*Claviceps purpurea*, syn. *Secale cornutum*, typically used in obstetrics for centuries) as a vasoconstricting agent for the treatment of migraine headache in 1868 [121–123]. Already in the 1850s, Charles-Édouard Brown-Séquard FRS (1817–1894), a Mauritian physiologist and neurologist, and the French physiologist Claude Bernard (1813–1878) had hypothesized on migraine as a result of vasoconstriction, while the German physician and physiologist Emil Heinrich du Bois-Reymond (1818–1896) had thought it might be caused by vasodilation [124]. It was only in 1867 when Friedrich Wilhelm Möllendorff, a medical practitioner in Berlin [125], provided experimental evidence of vasodilation in course of a migraine attack, applying an ophthalmoscope invented by his colleague Hermann Ludwig Ferdinand von Helmholtz (1821–1894) [126]. It seems reasonable to assume that Möllendorff's observation had a decisive influence on Woakes' concept of migraine. On the other hand, Woakes' method facilitated by numerous German-language publications, spread rapidly in Germany as well [127–130]. However, the remedy gained acceptance only after Arthur Stoll (1887–1971), a Swiss biochemist at Sandoz (now Novartis), isolated pure ergotamine tartrate in 1918, which brought about a standardized drug with reliable properties and predictable effects [131]. It was brought to the market by Sandoz in 1921 under the tradename "Gynergen" for the treatment of postpartum bleeding and subsequently also for migraine treatment [80]. [132, 133].

In 1935, Arthur Stoll reported on another main alkaloid in *Claviceps purpurea*, lysergic acid β-propanolamide, which would obtain some relevance in obstetrics to facilitate delivery of the placenta and to prevent bleeding after childbirth, but also as a lead structure for some semisynthetic ergot drugs [134]. In the same year, John Chassar Moir (1900–1977), at that time First Assistant to the Obstetric Unit of the University College Hospital, London together



Lysergic acid

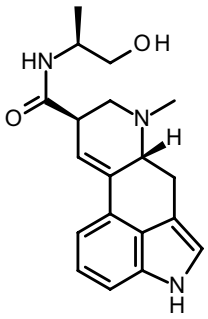


Fig. 15 Arthur Stoll (1887–1971) was a Swiss biochemist at Sandoz, who succeeded in isolating ergotamine, ergometrine, and cardiac glycosides, which became important drugs for the treatment of migraine, some conditions in obstetrics and heart diseases (© public domain)

with H. Ward Dudley published on the same subject. They comprehensively described isolation, chemical properties, and pharmacology of the new substance and proposed the name "ergometrine" [135]. The first partial synthesis was performed by Arthur Stoll and Albert Hofmann in 1937, by reacting the azide of lysergic acid with (2*S*)-amino propanol (Fig. 15) [136].

Infobox: Claviceps purpurea

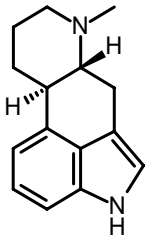
The purple-brown ergot fungus (*Claviceps purpurea*) is an ascomycete fungus belonging to the ergot genus (Claviceps) that grows and parasitizes on the ears of rye and related cereal and forage plants [122]. After infection of the flowering cereals with fungal spores, a mycelium develops, which later matures into a horn-like, dark purple to black sclerotium, the permanent form of the ergot fungus. It contains high concentrations of ergoline alkaloids, in particular ergotamine (Fig. 16).

The enduring ingestion of cereal products contaminated with the ergot fungus causes ergotism, a severe illness, associated with both convulsive and gangrenous symptoms, including spasms, diarrhea, paresthesia, itching, mental effects including mania or psychosis, headaches, nausea, and vomiting as well as dry gangrene as a result of vasoconstriction, edema, loss of limbs, and ultimately death.

Probably the earliest reference to ergotism is found in the *Annales Xantenses* [141] in the year 857. A more detailed description of ergotism dates from the years 944/945. The ergot poisoning claimed about 20,000 lives, half the population of the Aquitaine area of France [142]. Some 50 years later, the regions of Aquitaine, Limousin, Périgord, and Angoumois in France were afflicted by a second massive outbreak of ergotism that caused 40,000 deaths [143]. Throughout the entire Middle Ages until the eighteenth century, there are numerous records of epidemics in Germany, France, and Scandinavia.

Many ergotism-afflicted patients found help at the order of Saint Anthony, a congregation founded c. 1095 by Gaston of Valloire, a nobleman of the Dauphiné. The community set up hospitals in France and later also in Spain, Italy, Flanders, and Germany, to take care for those suffering from "St. Anthony's fire." Lacking a concept of the illness, the success of the Antonines' cures was most probably related to a diet free from contaminated grain. It was as late as 1596 in course of an epidemic that raged in the Landgraviate of Hesse when the German physician Wendelin Thelius, attributed the cause of ergotism to contaminated cereals [144]. In the following centuries, numerous physicians confirmed this connection, but the epidemics ceased only when authorities ordered the inspection of crops and the sieving of the grain.

The first reliable source that describes the use of ergot in obstetrics is found in the fourth edition of the book of herbs (Ger. "Kräuterbuch") by Adam Lonitzer (1528–1586), town physician in Frankfurt am Main, which was published in 1582 [145]. Later, the French pharmacist and agronomist Antoine-Augustin Parmentier (1737–1813) and the physician Jean-Baptiste Desgranges (1751–1831) reported that ergot was frequently used by midwifes as a "childbed remedy." Even small quantities of ergot induce strong uterine contractions. The usage of ergot in gynecology and midwifery spread also in the USA, after the well-known New Yorker doctors John Stearns (1770–1848) and David Hosack (1769–1835)



Ergoline

Fig. 16 Fungal sclerotium of *Claviceps purpurea* growing preferentially on rye (*Secale cereale*). It is assumed that farmers in Sologne, south of Paris, first called it ergot, because it is reminiscent of the spur of a rooster (fr. *l'ergot de coq*). An early written reference of the term "ergot" and its relation to bread poisoning is found in a letter issued by the physician and botanist Denis Dodart (1634–1707) to the French Royal Academy of Sciences in 1676 [137, 138]. Otto von Münchhausen (1716–1774) reported that ergot was a fungus with sponge-like structures, but this theory was only proved in 1815 by the Swiss botanist Augustin-Pyrame de Candolle (1778–1841) [139, 140] (© Dominique Jacquin, public domain)

published on "Childbirth powder" (lat. *pulvis parturiens*) early in the nineteenth century. As late as in 1836 ergot was also introduced into the British pharmacopeia. To make ergot more reliable and safer, Joseph Bonjean (1810–1896) an apothecary and chemist in Chambery, France, prepared an aqueous extract from ergot, which he called "Ergotine" in 1842 [146]. First administered orally by dragées to treat i.a. uterine hemorrhage, it was also later injected subcutaneously, after the Scottish physician Alexander Wood (1817–1884) had invented the hypodermic syringe in 1853. Arthur Stoll's isolation of crystalline, pure ergotamine tartrate in 1918 improved safety even further and paved the route to industrial manufacturing of ergot alkaloids at Sandoz.

The elucidation of the structure of ergotamine took a while [147–149] as it was performed by classical degradation reactions, a tedious and time-consuming process (compared with our current capabilities). The last ambiguities in the structure were not clarified until 1951 by Arthur Stoll and Albert Hofmann [150], and it took another 10 years before Albert Hofmann finally succeeded in confirming the structure by total synthesis [151]. The scaffold of ergotamine consists of two bigger parts, comprising a tricyclic Phe-Pro-Ala tripeptide and lysergic acid.

The latter, named by its preferred way of preparation, the **lys**is of **erg**ot alkaloids, was already known since the 1930s. The first correct structure of lysergic acid, a tetracyclic β-amino acid with two stereocenters, was proposed by Walter Abraham Jacobs (1883–1967) at the Rockefeller Institute for Medical Research, New York City [152, 153] in 1936 and was confirmed by total synthesis of dihydrolysergic acid by Arthur Stoll, Albert Hofmann, and Franz Troxler at Sandoz in 1949 [154]. By 1962, the remaining stereochemical questions were resolved [155, 156]. The first total synthesis of racemic lysergic acid was contributed in the mid-1950s by Robert B. Woodward (1917–1979) in collaboration with chemists at Eli Lilly [157, 158], followed by a second one originating from Marc Julia (1922–2010) in 1969 [159]. Today at least 20 total syntheses of lysergic acid are known (Sect. 4.1).

Infobox: Lysergic acid and other psychedelic drugs [160, 161]

Lysergic acid derivatives from plants

Lysergic-acid-containing alkaloids are produced by *Claviceps purpurea* on cereals, by endophytic fungi of the genus *Neotyphodium* in sleepygrass (*Achnatherum robustum*), and also by other epibiotic fungi of the Clavicipitaceae family, living on and spread by the seeds of the Morning glory family (Convolvulaceae), comprising species such as Christmasvine [*Turbina corymbosa*, syn. *Rivea corymbose* (L)], morning glories (*Ipomoea tricolor*) [162], and Hawaiian baby woodrose (*Argyreia nervosa*) (Fig. 17) [163]. The Aztecs called the seeds of *Turbina corymbosa* Ololiuhqui and of *Ipomoea tricolor* Tlitliltzin (in Nahuatl).

They were used for ritual as well as for medicinal purposes, as reported first by the Spanish priest Hernando Ruiz de Alarcón (1574–1646) in a seventeenth-century treatise "Tratado de las supersticiones y costumbres gentilicias que hoy viven entre los indios naturales de esta Nueva España." The main ergot alkaloids in the seeds are lysergamide and isolysergamide [164].

Serotonin derivatives from trees and toads

Since pre-Columbian times, indigenous cultures of the Caribbean and the Central and South Americas also use psychedelic snuff preparations made from the seeds of *Anadenanthera colubrina* and *Anadenanthera peregrina* trees [166, 167]. The psychoactive components are bufotenin derivatives, which are also found in the latex of the takini tree (*Brosimum acutifolium*) [168], the seeds of *Mucuna pruriens* [169], and most remarkably in the poison of some toads, such as the Colorado River toad

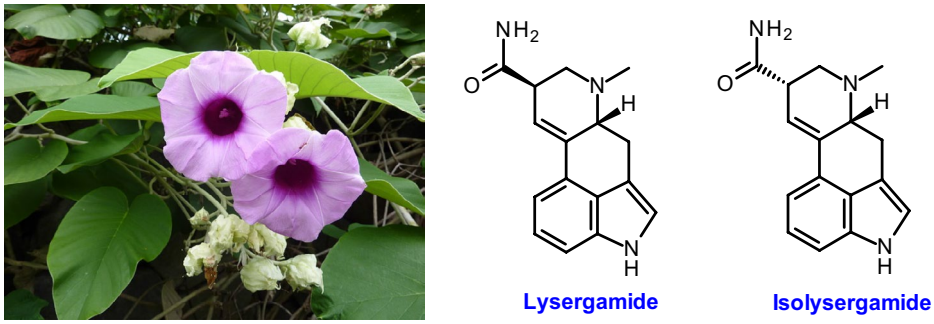


Fig. 17 *Argyreia nervosa* is a perennial climbing vine native to the Indian subcontinent, but also found throughout Hawaii, the Caribbean, India, Bangladesh, Australia, Africa, and Sri Lanka. Its seeds are known for its entheogenic properties, which may trigger psychedelic experiences [165] (© Loi Miao)

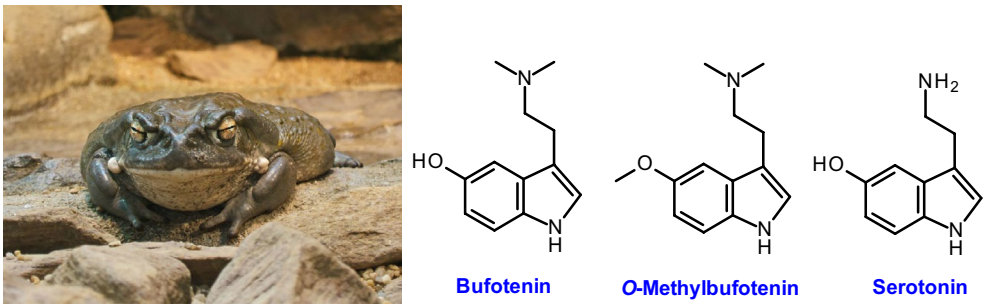


Fig. 18 The parotoid glands of the Colorado River toad produce a poison that may kill a grown dog. Its main components consist of bufotenin and its methylether. When sniffed, the dried poison rapidly provokes brief but strong visual and auditory hallucinations (© Wildfeuer)

(formerly *Bufo alvarius*, now *Incilius alvarius*) (Fig. 18) and the Chusan Island toad (*Bufo gargarizans*) [170, 171].

In 1893, the French physician and biologist Césaire Auguste Phisalix (1852–1906) and the biochemist Gabriel Bertrand (1867–1962) proposed the name "bufotenin" for the toad's poison [172]. It was first isolated as a pure substance by the Austrian chemist Hans Handovsky (1888–1959) in 1920 [173]. Heinrich Wieland (1877–1957) at the Ludwig-Maximilians University in Munich elucidated the structure in 1934, which was confirmed one year later by total synthesis by his former post-doc Toshiro Hoshino [174–176]. In the 1950s, Arthur Stoll and Albert Hofmann became intrigued by its resemblance to serotonin, then just discovered, and its vasoconstricting properties, which it shares with some lysergic acid derivatives. Consequently, they started an extensive research program in this field at Sandoz [177].

Serotonin analogs from mushrooms

Other natural sources for psychedelic drugs are psilocybin mushrooms, including the biological genera of *Copelandia*, *Gymnopilus*, *Inocybe*, *Panaeolus*, *Pholiotina*, *Pluteus*, and *Psilocybe*. These were used since prehistorical times for religious, divinatory, or spiritual purposes in Europe, Africa, and the Americas [178, 179].

In the 1950s, the American ethnomycologist R. Gordon Wasson (1898–1986) [180] and the French botanist Roger Heim (1900–1979) [181] extensively investigated psychoactive mushrooms in Mexico. By 1958, also Albert Hofmann became interested in the active compounds from those. He was able to identify the psychoactive substance and elucidated its structure [182, 183]. As it turned out, the mushrooms produce psilocybin, which is dephosphorylated after ingestion in the liver. The resulting psilocin is responsible for the psychedelic effects (Fig. 19) [184, 185].

Ultimately, it was the similarity of lysergic acid, bufotenin, and psilocin with serotonin and some other neurotransmitters [187] that broadened Hofmann's perspective on ergot alkaloids and set the stage for new areas of drug research, e.g., for the indication of postpartum bleeding in obstetrics, nausea and vomiting, irritable bowel syndrome, cardiovascular diseases, psychiatric disorders [188, 189], and also migraine (Fig. 20) [133].

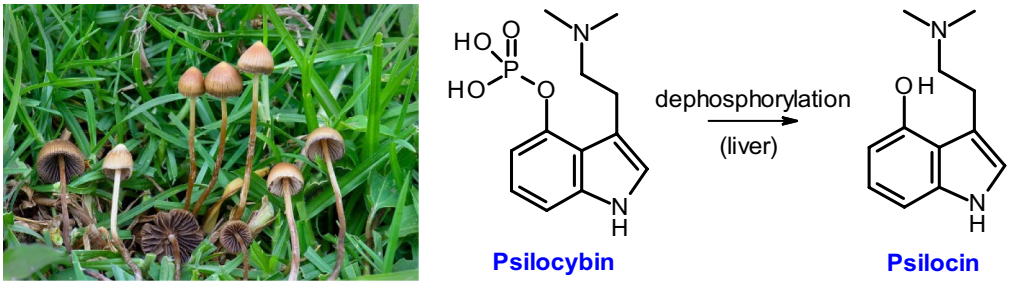


Fig. 19 *Psilocybe mexicana* (Nahuatl: Teonanacatl) was known to the Aztecs since Pre-Columbian times. According to records by the Dominican friar Diego Durán (1537–1588), Teonanacatl was served at the coronation of Moctezuma Xocoyotzin (c. 1466–1520) in 1502, which affected the guests more than if they had drunk much wine [186] (© Alan Rockefeller)

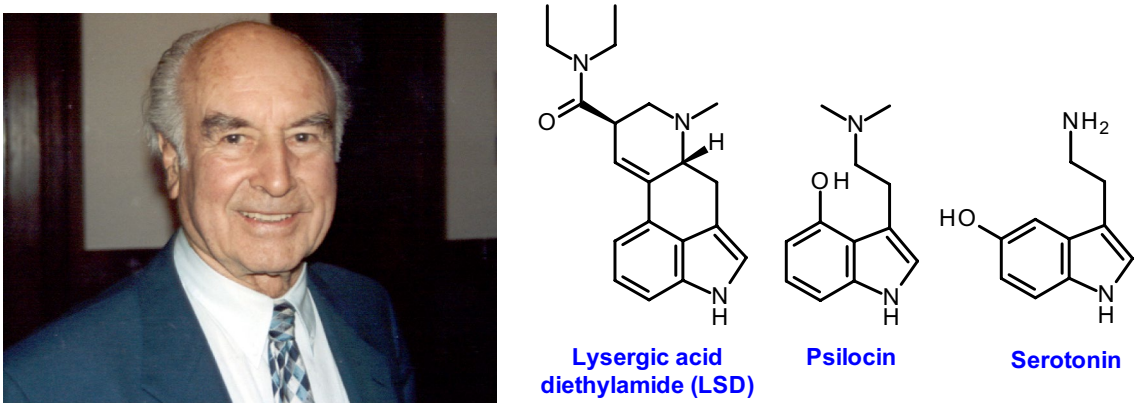


Fig. 20 Albert Hofmann (1906–2008) synthesized lysergic acid diethylamide (LSD), a synthetic homolog of ergometrine, first in 1938, in the search for new respiratory and circulatory stimulants. The first animal tests did not show the expected effect, and Hofmann lost his interest in this compound. However, 5 years later he decided to synthesize the substance again. Doing so, he ingested accidentally an unknown quantity of the chemical, which led to powerful psychedelic effects. Three days later, on 19 April 1943, a date that later became well known as the "bicycle day," he experienced his first LSD trip lasting 14 h by deliberately ingesting 0.25 mg of his readily prepared lab product [142, 190, 191] (© Courtesy of Novartis Company Archives)

Ergotamine-derived drugs

The first artificial migraine remedy was dihydroergotamine, simply obtained by catalytic hydrogenation of ergotamine. The active agent was claimed by Sandoz in 1942 and introduced to the market in 1946. It was sold under the brand names "Dihydergot," "D.H.E. 45," "Migranal," "Ergont," "Ikaran," and others. In 2013, the European Medicines Agency recommended restrictions of ergot alkaloids to prevent migraine headaches, since the risks are greater than the benefits in this indication compared to more selective and readily available drugs [192].

Today, though it was was not known at that time, the antimigraine activity of dihydroergotamine can be explained by its action as an agonist at the serotonin receptors 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F}.[193]. Unfortunately, it has also some interactions with adrenergic and dopamine receptors, but most unfavorably, it is also an agonist at the serotonin 5-HT_{2B} receptor, which has been associated with cardiac valvulopathy [194].

The first effective migraine prophylactic methysergide evolved on the pursuit of better drugs in obstetrics, to stop postpartum hemorrhage. Out of many analogs of ergometrine, Albert Hofmann and Franz Troxler synthesized the (*S*)-butanolamide of lysergic acid, methylergonovine, which proved to be superior in its pharmacological properties compared to the natural product. It was used worldwide in obstetrics under the brand name "Methergine."

Later, however, Hofmann and Troxler obtained, by simple methylation of methylergonovine, methysegide (1-methyllysergic acid-1′-hydroxy-butyl-(2S)-amide), a substance with enhanced specific antiserotonin activity, which was marketed by Sandoz in the early 1960s as the first drug for the prevention of migraine (Fig. 21) [195]. [196, 197].

Its clinical development can be traced back to Harold Wolff's theory of vasodilation in migraine. It is less known that Harold Wolff himself also searched for a perivascular factor that could damage blood vessels and increase pain sensitivity in course of a migraine attack [198]. Already in

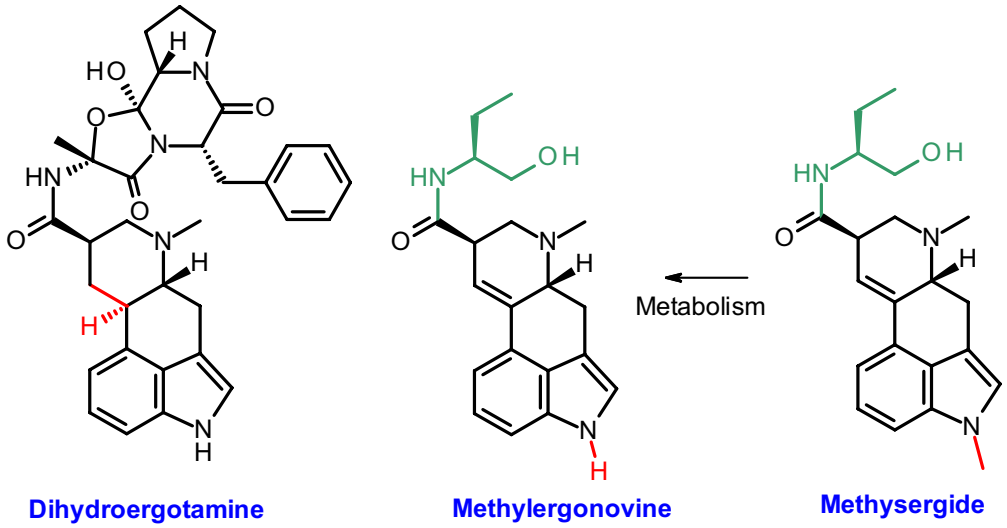


Fig. 21 The first artificial ergotamine-derived drugs were used in obstetrics and for the treatment of migraine

Fig. 22 Vittorio Erspamer became professor of pharmacology at the Faculty of Medicine at the University of Parma in 1955. For many years, he maintained a fruitful collaboration with chemists at Farmitalia company, which resulted in both the isolation and characterization of numerous natural products, especially polypeptides and biogenic amines but also some alkaloids, and in the subsequent industrial syntheses of their analogs. The discovery of serotonin might be considered as his most prominent achievement, but he also contributed considerably to the research on other neurotransmitters, such as the tachykinin peptides, bombesin, dermorphin, and deltorphin (© public domain)

1938, he published a remarkable article on the mechanism of migraine headache and the action of ergotamine [44]. [199]

After the discovery of serotonin in 1948, indications gradually accumulated that serotonin might play a pivotal role in migraine headaches [200]. Serotonin, which was also found in brain extracts, proved to be a strong vasoconstrictor [201]. In the late 1950s, LSD turned out to be the most effective serotonin antagonist, but could not be applied because of its hallucinogenic side effects [202]. On the other hand, methysergide proved to be similar effective, but beneficially lacking the psychotropic effects [203]. It was introduced in the clinic in 1959 by the Italian neurologist Federigo Sicuteri [204]. He succeeded in demonstrating the remarkable prophylactic and therapeutic properties of methysergide. However, it took only a few years until severe side effects, among those cardiac and pulmonary fibrosis, were discovered, which ultimately led to the discontinuation of the drug by Novartis [205–207].

The pharmacodynamics of methysergide is much more intricate, as was known at the time. Methysergide binds to the serotonin 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_{5A}, 5-HT_6, and 5-HT_7 receptors as well as to the α_{2A}-, α_{2B}-, and α_{2C}-adrenergic receptors [208]. Its interaction with the 5-HT_1 receptors is agonistic or partial agonistic, while it acts as an antagonist at the 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, and 5-HT_7 receptors [209–213].

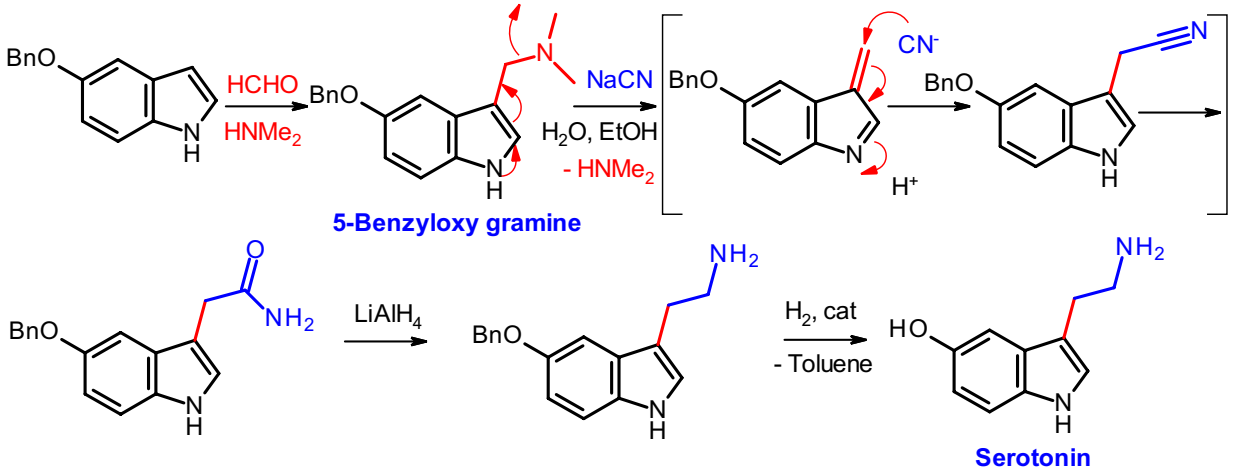
Even so, the beneficial antimigraine effects of methysergide in humans are related to its metabolic degradation into methylergonovine [214, 215]. Methylergonovine, acting as an agonist, is about ten times more potent at the 5-HT_{1B} and 5-HT_{1D} receptors [216]. Unfortunately, it is also an agonist or partial agonist at the 5-HT_{2A} and 5-HT_{2B} receptors, which in the first case is associated with psychedelic effects [217, 218] and in the second case with cardiac valvulopathy [219]. However, the real issue is that the 5-HT_{2A} and 5-HT_{2B} receptor antagonism of methysergide cannot overcome the serotonin receptor agonism of methylergonovine due to its fast metabolism [220].

Infobox: Serotonin and its receptors

It was the German physiologist Carl Friedrich Wilhelm Ludwig (1816–1895) who had first anticipated in 1868 that blood may contain a substance that acts as a vasoconstrictor [221]. But it took more than half a century before the Italian pharmacologist and chemist Vittorio Erspamer (1909–1999) showed in 1935 that an extract from enterochromaffin cells make intestines contract (Fig. 22) [222].

In 1948, the American biochemists Maurice M. Rapport (1919–2011) and Arda Green (1899–1958), and the physiologist Irvine Heinly Page (1901–1991) of the Cleveland Clinic Foundation in Cleveland, Ohio, discovered a vasoconstrictor substance in blood serum. Since it was a **ser**um agent, released from platelets during clotting of blood and affecting vascular **ton**e, they named it serotonin [223, 224]. The structure of serotonin, 5-hydroxytryptamine (5-HT), was proposed by Maurice Rapport in 1949, and was later confirmed by chemical synthesis by K. E. Hamlin and F. E. Fischer from the Abbott Laboratories in 1951 [225, 226]. Starting from 5-benzyloxy indole, 5-benzyloxy gramine is obtained by Mannich reaction. After substitution of the dimethylamino group by cyanide and hydrolysis, the resulting amide is reduced with lithium aluminum hydride. Catalytic debenzylation finally leads to serotonin (Scheme 1).

In 1953, Betty Twarog and Irvine Page discovered serotonin being also a component of the brain tissue [227]. Four years later, at the University of Edinburgh, the British physiologist Sir John Henry Gaddum (1900–1965) discovered the first serotonin receptors [228]. He also investigated the pharmacology of LSD, its interactions



Scheme 1 The synthesis of serotonin by K. E. Hamlin and F. E. Fischer

Table 2 Selected serotonin receptors and the functions in which they are involved

Receptor	Function
5-HT_{1A}	Addiction, aggression, anxiety, appetite, blood pressure, vasoconstriction, cardiovascular function, nociception, respiration, pupil dilation, sexual behavior, sleep, thermoregulation
5-HT_{1B}	Addiction, aggression, anxiety, learning, locomotion, memory, mood, sexual behavior, vasoconstriction
5-HT_{1D}	Anxiety, locomotion, vasoconstriction
5-HT_{1F}	Physiological role remains widely unknown [234], trigeminal neuro inhibition [235], associated with migraine episodes
5-HT_{2A}	Addiction, anxiety, appetite, cognition, imagination, memory, mood, perception, sexual behavior, sleep, thermoregulation, vasoconstriction
5-HT_{2B}	Anxiety, appetite, cardiovascular function, gastrointestinal motility, sleep, vasoconstriction
5-HT_{2C}	Addiction, anxiety, appetite, gastrointestinal motility, locomotion, mood, sexual behavior, sleep, thermoregulation, vasoconstriction
5-HT_3	Addiction, anxiety, emesis, gastrointestinal motility, memory, nausea
5-HT_{5A}	Locomotion, sleep
5-HT_6	Anxiety, cognition, memory, mood
5-HT_7	Anxiety, memory, mood, respiration, sleep, thermoregulation, vasoconstriction

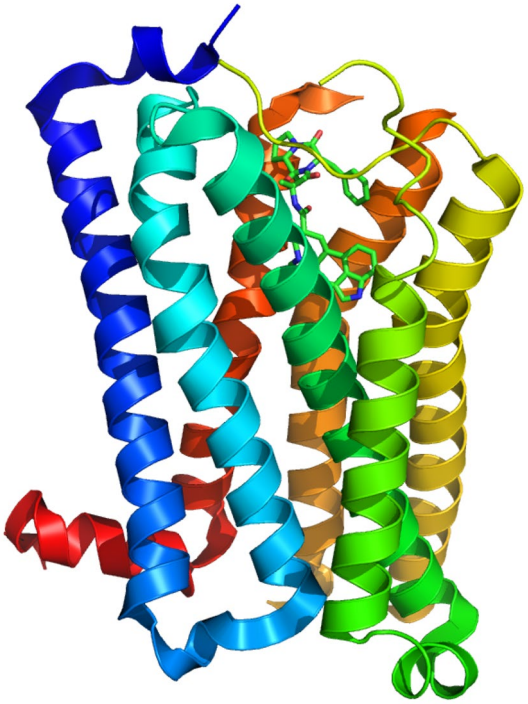


Fig. 23 Three-dimensional structure model of the 5-HT_{1B} receptor in complex with ergotamine, based on crystallographic data from PDB 4IAR (© S. Jähnichen)

with serotonin, and its role in mood regulation, without shying away from self-experimentation [229]. However, it was not until molecular biological methods were established in the 1990s that it became apparent that at least 14 different serotonin receptors exist in humans, which are responsible for the diverse effects of serotonin on e.g. the cardiovascular system, the gastrointestinal tract and the nervous system (Table 2) [230–233].

In the 1990s, the 5-HT_{1B}/5-HT_{1D} receptors soon became a focus of migraine research. They were first cloned in 1992 [236] and after some alignment of receptor nomenclature with the human genome finally named as we know them today [237, 238]. Detailed investigations of the human 5-HT_{1B} receptor protein revealed that it comprises 390 amino acids, distributed over seven helical transmembrane domains [239–242]. The orthosteric binding pocket is located in the deeper interior of the receptor and is defined by helices III, V, VI, and VII and the extracellular loop 2 (Fig. 23).

Phylogenetically, serotonin is considered as one of the oldest neurotransmitters, dating back to the Precambrian, more than 700 million years ago [243]. Together with its receptors, serotonin is omnipresent in almost all species of the animal kingdom, from nematodes to mammals [244–246]. But it is also found in amoeba, plants, and fungi [247–249]. For instance, serotonin contributes to the pain induced by touching stinging nettles (*Urtica*), and it is found in many plant foods, such as walnuts, pineapples, bananas, kiwis, plums, tomatoes, and cocoa [250, 251].

In mammals, serotonin is synthesized from L-tryptophan by a rate-limiting hydroxylation at position 5, followed by decarboxylation. This takes place predominately in the enterochromaffin cells of the intestinal mucosa. Serotonin taken up from food does not compromise the serotonergic pathways of the central nervous system, because it does not cross the blood–brain barrier.

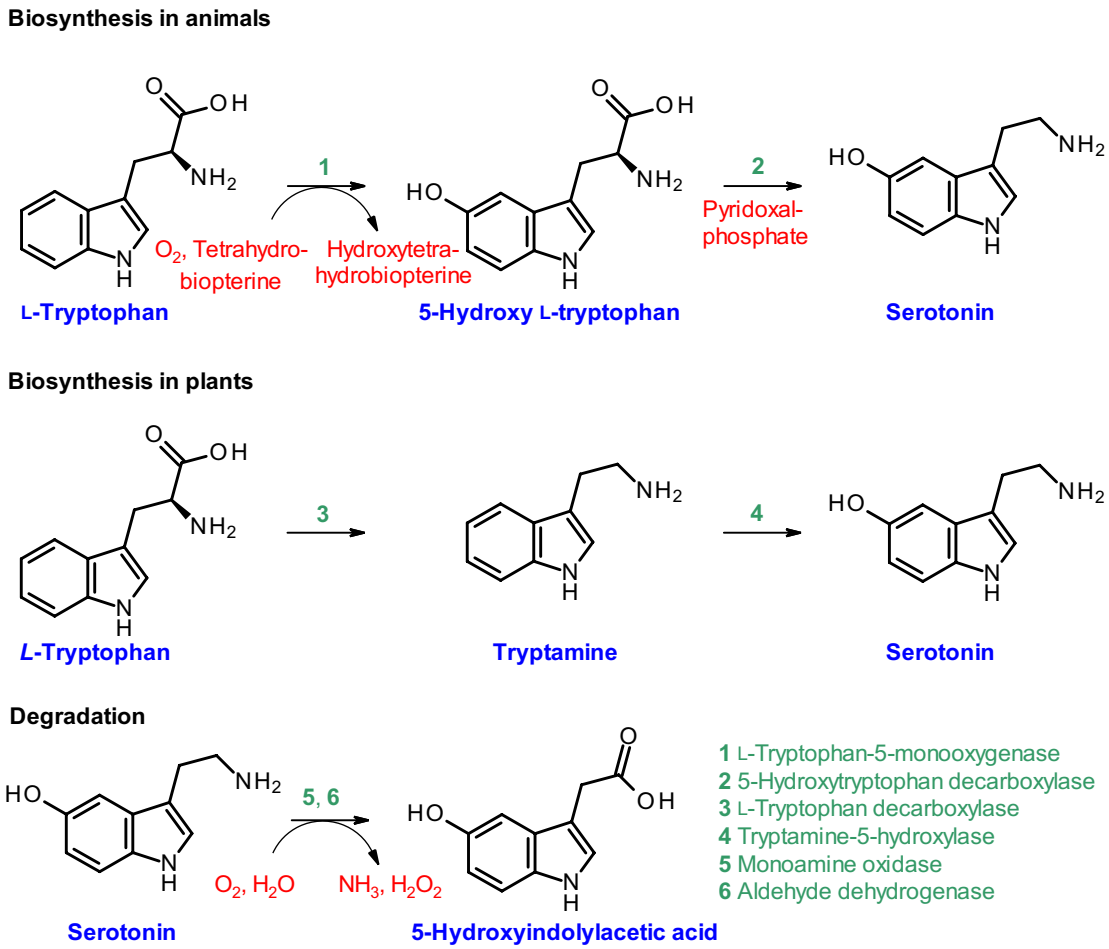
The biosynthesis of serotonin in plants differs in the sequence of its steps from that in animals. In the first step, L-tryptophan is decarboxylated to the intermediate tryptamine by L-tryptophan decarboxylase. In the second step, hydroxylation occurs with the help of tryptamine-5-hydroxylase to the final product serotonin [248, 252]

The degradation of serotonin occurs primarily via the enzyme monoamine oxidase (MAO) type A and to a much lesser extent via MAO type B. The product 5-hydroxyindolyl-acetaldehyde is further degraded by an aldehyde dehydrogenase to 5-hydroxyindolylacetic acid. 5-Hydroxyindolylacetic acid, which can be detected in urine, is the main excretion product of serotonin (Scheme 2).

After its biosynthesis in serotonergic neurons, serotonin is stored in vesicles from which it is released into the synaptic cleft after a nervus stimulus. After crossing the cleft at the postsynaptic neuron, it may bind to 5-HT_3 receptors, which are coupled to ion channels, or to any other G-protein-coupled 5-HT receptors [253]. At the presynaptic neuron, serotonin can also bind to its receptors, or it can be readsorbed via a sodium-dependent serotonin-reuptake transporter. Ultimately, serotonin is degraded in the synaptic cleft by monoamine oxidases (Fig. 24).

Triptans

The search for improved migraine drugs commenced at Allen & Hanburys, a subsidiary of Glaxo at Ware, a small-town north of London in 1972. A recently hired young pharmacologist, Patrick P. A. Humphrey [254] and his graduate assistant Eira Apperley, founded their work on both Harold Wolff's observation that ergotamine administered intravenously can abort migraine attacks, which is correlated with reduced temporal artery pulsation, and that the endogenous neurotransmitter serotonin may act in a similar way. The involvement of serotonin in a migraine episode was underpinned by Sicuteri, who showed that its metabolite, 5-hydroxyindolylacetic acid, is present in urine after an attack [255, 256]. Humphrey assumed that



Scheme 2 Biosynthesis and degradation of serotonin

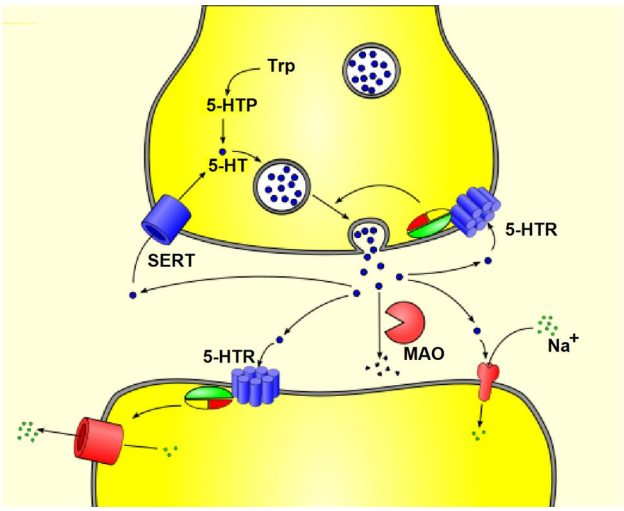


Fig. 24 The biochemistry of serotonin (5-HT) at the synaptic cleft. Tryptophan (Trp), 5-hydroxytryptophan (5-HTP), serotonin receptor (5-HTR), serotonin transporter (SERT), monoamine oxidase (MAO) (© S. Jähnichen)

serotonin should act as a vasoconstrictor on the cranial vessels outside the brain because it is incapable of crossing the blood–brain barrier. However, it could not be used as drug by itself due to many side effects. Thus, the medical need for improved migraine treatment was a preferentially orally bioavailable agent, acting selectively at the cranial vessel as a vasoconstrictor.

In 1974, Pramod Saxena [257], a pharmacologist at the Medical Faculty Rotterdam (now Erasmus Medical Center), reported that intravenous methysergide produced a very localized cranial vasoconstriction leading to reduced carotid blood flow without any effect on blood pressure [258]. Patrick Humphrey went on to show that this effect was mediated by a then unknown vascular serotonin receptor, now known as 5-HT_{1B} receptor. At the time, little was known about the diversity of serotonin receptors. Notwithstanding all these uncertainties, in the 1970s, Glaxo launched a research program in search for serotonin analogs, which may selectively activate the 5-HT_{1B} receptor. After many hurdles and pitfalls, the first compound that turned out to be effective in a dog model was 5-carboxamidotryptamine (AH21467)

Table 3 The development of triptans from serotonin. The triptans are selective 5-$HT_{1B/1D}$ receptor agonists that lack many of the side effects induced by ergot alkaloids

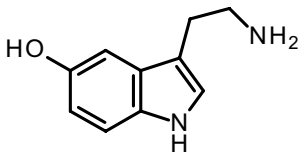
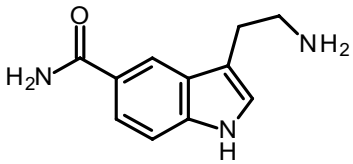
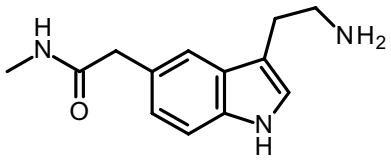
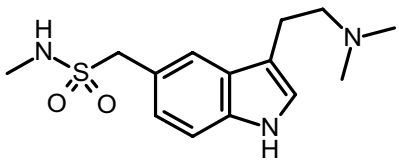
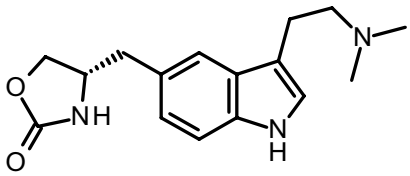
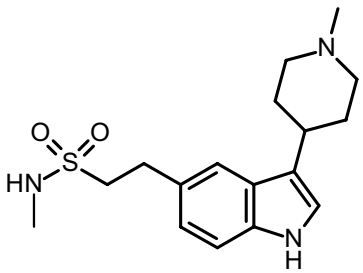
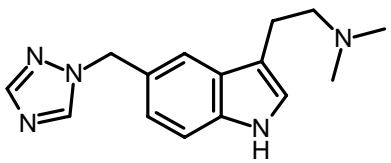
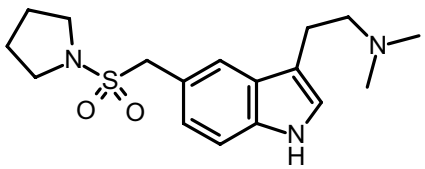
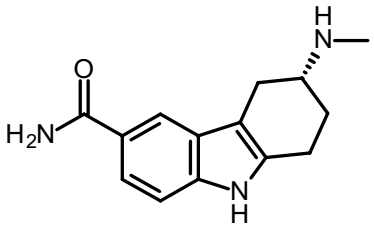
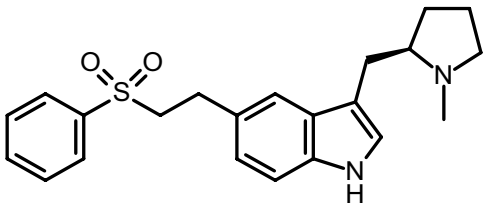
Name	Structure	Company	Launch
Serotonin		Nature	700 million years ago
AH21467		Glaxo	/
AH25086		Glaxo	/
Sumatriptan (GR-43175)		Glaxo	1992
Zolmitriptan		Zeneca	1997
Naratriptan		Glaxo	1997
Rizatriptan		Merck Sharp & Dohme	1998
Almotriptan		Almirall Prodesfarma	2001

Table 3 (continued)

Name	Structure	Company	Launch
Frovatriptan		Smith Kline Beecham	2002
Eletriptan		Pfizer	2002

Compound	5-HT$_{1B}$	5-HT$_{1D}$	5-HT$_{1F}$
Dihydroergotamine	9.2	9.4	6.6
Sumatriptan	8.0	8.3	7.6
Zolmitriptan	8.3	9.0	7.6
Naratriptan	8.5	8.4	8.6
Rizatriptan	8.0	8.4	6.6

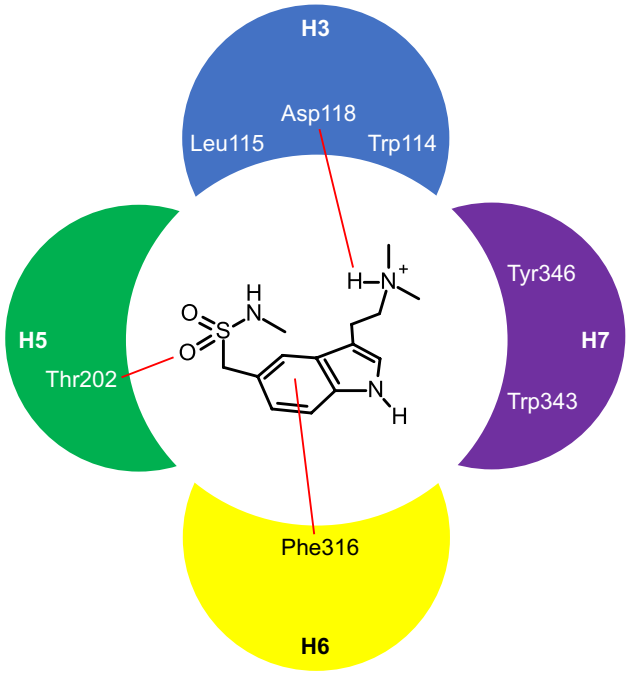


Fig. 25 Binding affinity [K_i (nM)] of some APIs at the human 5-HT$_{1B}$, 5-HT$_{1D}$ and 5-HT$_{1F}$ receptors [269] and a model of interactions of sumatriptan binding to the 5-HT$_{1D}$ receptor. The interacting amino acids are referred to by their three-letter code, and the corresponding helices are indicated by H3, H5, H6, and H7 [266, 268]

[258]. However, by stimulating another 5-HT-receptor, later assigned as 5-HT$_7$, it also caused vasodilatation, and was therefore deemed to be insufficiently selective. The next hit the research team found was AH25086 [259], indeed a selective agonist, but was found to be unsuitable for oral administration (due to its poor absorbance in the gastrointestinal tract resulting from its high lipophobicity [260]) and, therefore, less suitable for clinical development. Much more effort had to be spent before Patrick Humphrey and his team finally found GR-43175, which was named sumatriptan and became available for clinical use in 1991. It proved to be an active ingredient with high selectivity and sufficient oral bioavailability. Sumatriptan was initially introduced in the Netherlands in 1992 and has been marketed in the USA since 1993 [261, 262]. In subsequent years, numerous companies brought more triptans to the market (Table 3) [263].

All triptans share the indole structure and an almost equidistant amino group with serotonin. The main structural difference of the triptans is the side chain at position 5. It ranges from sulfonamides and sulfones, via heterocycles, such as triazole, 2-oxazolidone, to a carboxamide.

All triptans exhibit high affinity to the 5-HT_{1B} and 5-HT_{1D} receptors, and to some extend also to the 5-HT_{1F} receptor [264]. [265].

The 5-HT_{1B} and 5-HT_{1D} receptors are very similar, thus they bind the almost same pharmacophore (Fig. 25) [239]. [266–268]. The 3D QSAR analysis-based model consists of:

1. An indole scaffold, interacting via π stacking with the aromatic amino acid Phe316
2. An ammonium group (a donor of a hydrogen bond), forming a salt bridge with Asp118
3. A hydrogen bond of Thr202 with the sulfonamide moiety
4. A hydrophobic cage around the ammonium group by Trp114, Tyr346, and Trp343
5. Dispersive interactions with Leu115

It is generally accepted that triptans exert their activity by numerous mechanisms of action, which may be additive in their ability to abort migraine [270, 271]:

- By activating the 5-HT_{1B} receptors, the triptans act as potent vasoconstrictors on the vascular smooth muscles of the pain-sensitive intracranial, extracerebral vessels, i.e., of the human middle meningeal arteries.
- They prevent the release of vasoactive peptides by activation of presynaptic 5-HT_{1D} receptors, including substance P and the calcitonin gene-related peptide (CGRP) [235, 272, 273]
- The triptans inhibit nociceptive neurotransmission within the trigeminocervical complex (which contains the major relay neurons for nociceptive afferent input from the dura and cervical structures).

The introduction of the triptans in the 1990s represented a major step forward in the treatment of migraine attacks. Nevertheless, this class of compounds also had some disadvantages resulting from its mode of action, which limited its efficacy and application.

It has been described that in up to 25% of the migraineurs none of the triptans is effective [274, 275]. On the flip side, continued migraine treatment with triptans can be result in medication overuse headache [276] and a certain propensity for recurrence.

Considering that 5-HT_{1B} receptors are not only widely distributed throughout the central nervous system and cerebral blood vessels but also in pulmonary and coronary arteries, there is a strict contraindication for triptans in patients suffering from cardiovascular and/or cerebrovascular diseases, and/or uncontrolled hypertension. Furthermore, triptans pose some risks to patients suffering from particular forms of hemiplegic migraine, and during pregnancy and breastfeeding. Thus, there was an ongoing medical need for even more tolerable drugs.

Fortunately, the past 5 years have witnessed remarkable innovations in migraine therapy. Based on a conceptional paradigm shift in migraine research (vascular versus neuronal dysfunction), novel targeted acute and preventive drugs have emerged on the market, including ditans (5-HT_{1F} receptor agonists), gepants (CGRP receptor antagonists), and monoclonal anti-CGRP/receptor antibodies, which have brought new hope to patients [235, 277, 278].

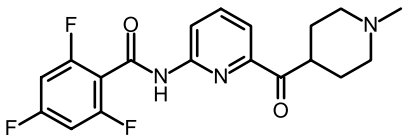
Ditans

In humans the 5-HT_{1F} receptor is expressed in the trigeminovascular system and central nervous system, including the cortex, the hypothalamus, the trigeminal ganglia, the locus coeruleus, the upper cervical cord, and the cerebral blood vessels, as well as in the thyroid and tonsils, kidneys, testes, and ovaries. Its expression in coronary arteries is low, and it is absent in the heart. In all cases the 5-HT_{1F} receptor has no vasoconstrictive properties.

Soon after the discovery of the 5-HT_{1F} receptor in 1993 [279], Eli Lilly started an extensive discovery program for a novel antimigraine compound that selectively addresses this new subtype of serotonin receptors and hopefully thereby lacks any cardiovascular and cerebrovascular effects. Continued research finally yielded a compound LY573144, which proved to have a 450-fold higher affinity at the 5-HT_{1F} receptor than at 5-HT_{1B} and 5-HT_{1D} receptors (Table 4) [235, 280]. The compound was named lasmiditan and gained approval of the US Food and Drug Administration in 2019. As the first member of the "ditans," lasmiditan is considered as a

Table 4 Binding affinity [K_i (nM)] of lasmiditan at human 5-HT receptors

Compound	5-HT_{1B}	5-HT_{1D}	5-HT_{1F}
Lasmiditan	1043	1357	2.21



Lasmiditan

first-in-class medication [281]. In contrast to serotonin and the triptans the structure of lasmiditan does not feature an indole as its core structure, but a 2-pyridinyl ketone. Some resemblance is found at the salt-bridge-forming amine. Lasmiditan shares a methyl piperidine moiety with naratriptan.

Lasmiditan penetrates the blood–brain barrier and exerts its activity by activating the 5-HT_{1F} receptors, centrally at the trigeminovascular system and peripherally at the trigeminal neurons [235]. The activation of the 5-HT_{1F} receptors inhibits the release of neuropeptides and neurotransmitters such as CGRP and glutamate, which decreases neurogenic inflammation of the dura and ultimately inhibits pain signaling pathways in both the central nervous system and the trigeminovascular system [282, 283].

Gepants and monoclonal antibodies

Infobox: The Brain Prize 2021

It is reasonable to assume that the story of CGRP-targeted drugs commenced at a conference in Lund, Sweden in June 1985, organized by Jes Olesen, a Danish neurologist from Copenhagen. Peter Goadsby, at that time an Australian medical student, had come to Sweden to learn more about headaches. There, he listened to an inspiring talk about the trigeminovascular system given by Lars Edvinsson, a young physician at the local university hospital in Lund. The ensuing 35 years of tremendously fruitful partnership, which simply began with a chat over a cup of coffee, was finally honored with the highly endowed Brain Prize in 2021 by the Lundbeck Foundation [284]. Goadsby and Edvinsson shared the prize with Michael Moskowitz (who contributed on neurogenic inflammation [285] and sumatriptan, which reduces CGRP in animals [286]) and Jes Olesen (who hypothesized that CGRP may play a causative role in migraine [287]), two more highly dedicated migraine researcher, who substantially contributed on CGRP-targeted drug research.

With the increasing knowledge of CGRP and its physiological functions, many headache researchers and numerous pharmaceutical companies joined forces to overcome the shortcomings of the triptans and develop new types of migraine drugs, such as CGRP receptor antagonists, but also antibodies, which were expected to be better tolerated, but as efficient as the triptans.

In the 1990s, Goadsby and Edvinsson were able to show that CGRP is elevated during a migraine attack [288], and that the levels of CGRP can be decreased by administration of sumatriptan [289]. Later, Jes Olesen triggered a migraine attack in man by injecting CGRP and could mitigate the symptoms with one of the first-generation small molecules CGRP receptor blockers, olcegepant [287]. [290]

Unfortunately, the clinical development of the CGRP receptor antagonists was a bumpy journey. Numerous first-generation small-molecule CGRP receptor antagonists ("gepants") failed due to various reasons, such as poor oral bioavailability of olcegepant from Boehringer Ingelheim, or hepatic effects of telcagepant from Merck & Co [291]. [292].

However, after further optimization in most recent years, three second-generation gepants have gained FDA approval [293, 294]. Ubrogepant and rimegepant were developed for acute migraine therapy [295]. Atogepant was approved for preventive treatment of migraine [296]. Zavegepant is not available yet, but in advanced clinical development to become the first gepant for nasal administration (Table 5) [297].

The main mode of action of the gepants is the inhibition of the CGRP receptor signaling pathway. There is some evidence that during a migraine attack CGRP is increasingly released from the trigeminal nerve endings located within the meninges. Binding to and thereby activation of the CGRP receptors of cerebrovascular muscle cells located around the meningeal blood vessels ultimately leads to vasodilation and the triggering of pain receptors [Fig. 26 (1)] [107]. Gepants bind competitively to CGRP receptors without activation, which prevents vasodilation [Fig. 26 (2)]. Thus, in contrast to triptans, gepants are not vasoconstrictors. They inhibit vasodilation and by these means mitigate the symptoms of a migraine attack.

In addition to the aforementioned approaches, biologicals, i.e., monoclonal antibodies, can also address the CGRP receptor signaling pathway by targeting (a) the CGRP receptor and (b) CGRP itself [302]. They are Y-shaped proteins 143–146 kDa in size, which:

- Do not cross the blood–brain barrier
- Are not metabolized by the liver, leading to relatively long half-lives in the body
- Must be given parenterally due to very poor absorption from the digestive tract

At present there is one monoclonal antibody, erenumab, on the market, which blocks the CGRP receptor (Fig. 26 (3)) and three antibodies, fremanezumab, galcanezumab, and eptinezumab, binding CGRP like a scavenger and thereby decreasing the concentration in the neuromuscular junction (Fig. 26 (4), Table 6).

Since gepants and monoclonal antibodies do not constrict cranial arteries, they offer the opportunity to become first-line antimigraine medication in patients with cardiovascular risk or as second-line drugs if patients' treatment fails with triptans [277].

Table 5 The development of gepant drugs was not immediately a success story from the start

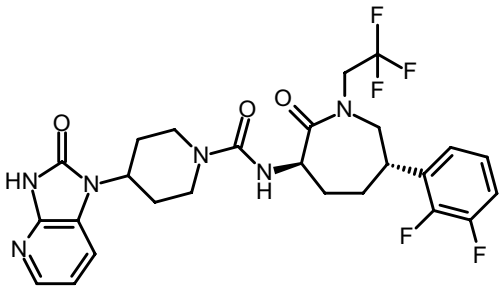
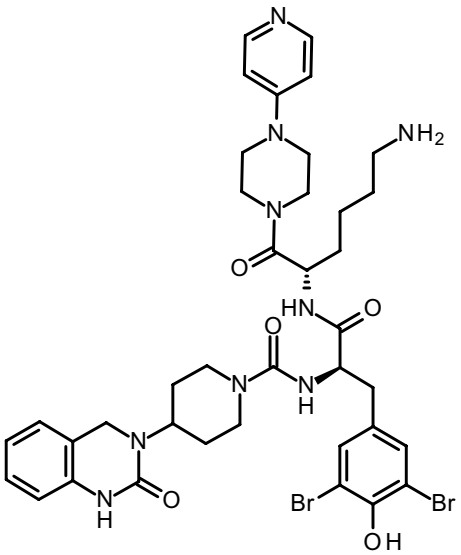
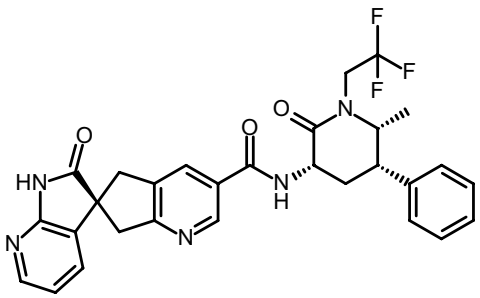
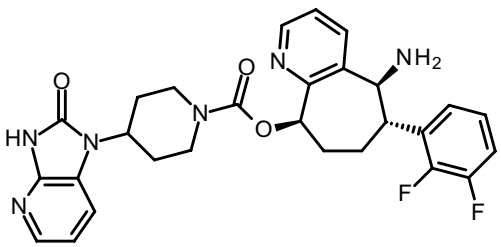
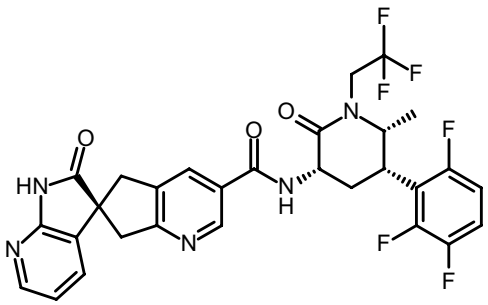
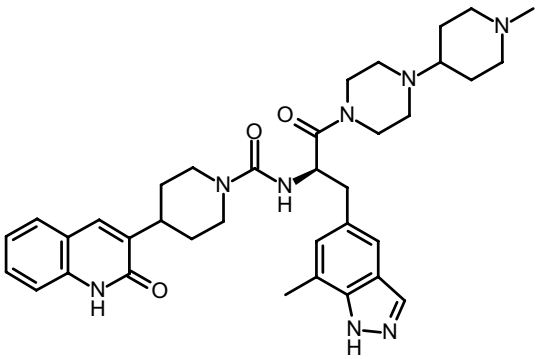
Name	Structure	Company	Launch
Telcagepant		Merck & Co	Terminated in 2009
Olcegepant		Boehringer Ingelheim [298]	Discontinued
Ubrogepant		Merck & Co/Allergan/Abbvie	2019
Rimegepant		BMS/Biohaven Pharmaceuticals	2020

Table 5 (continued)

Name	Structure	Company	Launch
Atogepant		Merck & Co/Allergan/Abbvie	2021
Zavegepant		BMS/Biohaven Pharmaceuticals[299]	Phase 3

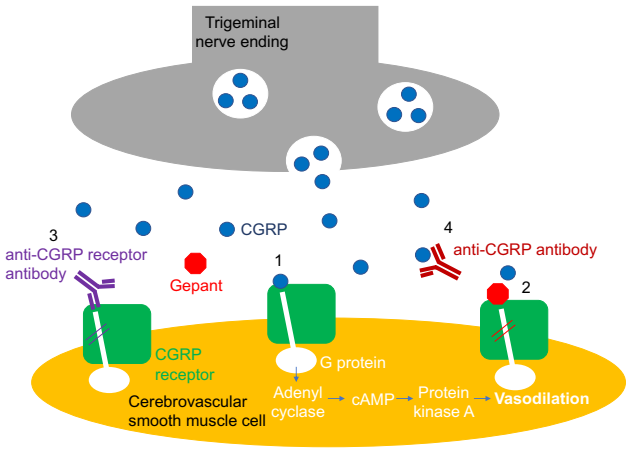


Fig. 26 Inhibition of the CGRP receptor signaling pathway in migraine research [300, 301]. The natural process (**1**) can be affected by gepants (**2**) or monoclonal anti-CGRP receptor antibodies (**3**) binding to the CGRP receptor, or when monoclonal anti-CGRP antibodies are binding to CGRP (**4**)

Chemical syntheses of migraine drugs

The development of modern migraine drugs spans the past 100 years and thus coincides with the era of blossoming medicine and the period of rapidly developing organic chemistry and biochemistry. Both developments were mutually beneficial and an indispensable prerequisite for the synthesis of increasingly selective active substances for the treatment of migraine.

Table 6 Monoclonal antibodies for the treatment of migraine attacks

Monoclonal antibody	Target	Company	Launch
Erenumab [303, 304]	CGRP receptor	Amgen/Novartis	2018
Fremanezumab [305, 306]	CGRP	Rinat Neuroscience, Pfizer, TEVA	2018
Galcanezumab [307, 308]	CGRP	Eli Lilly	2018
Eptinezumab [309, 310]	CGRP	H. Lundbeck A/S	2020

Lysergic acid

Since the 1950s, lysergic acid attracted the attention of numerous researchers in the field of natural product synthesis. To the best of our knowledge, some 20 total syntheses have been published so far. It seems reasonable that almost all syntheses commence with an indole derivative (AB), followed by ring closures of the C and D rings. Until James Hendrickson's total synthesis in 2004, all approaches targeted the racemic product. In the same year, Csaba Szántay from Budapest University published the first synthesis of (+)-lysergic acid via resolution of an advanced intermediate.

Table 7 Compilation of total syntheses of lysergic acid from scientific literature [313, 314]. However, also some recent formal syntheses of lysergic acid [315–318] as well as Peter Vollhardt's total synthesis of racemic LSD in 1994, starting from commercial 4-bromoindole in just seven steps and 1.1% overall yield, might also be appreciated [319]

Main author	Year	Strategy[a]	Stereoselectivity	Steps[b]	Yield (%)[c]
Woodward [158]	*1956*	*AB→C→D*	*(+/-)*	*14*	*0,8*
Julia [159]	1969	AB→D→C	(+/-)	11	Unknown[d]
Ramage [320]	1976	AB→C→D	(+/-)	19	1.5
Oppolzer [321]	1981	AB→CD	(+/-)	17	0.9
Ninomiya [322]	1982	AB→C→D	(+/-)	20	0.03
Rebek [323]	1983	AB→C→D	(+/-)	14	4.4
Kurihara [324]	1986	AB→C→D	(+/-)	14	2.0
Ortar [325]	1988	AB→C→D	(+/-)	12	1.3
Hendrickson[e] [326]	*2004*	*AB→D→C*	*(+/-)*	*9*	*14.5*
Szántay [327]	2004	AB→C→D	(+)	15	0.7
Fujii, Ohno [328]	2008	AB→DC	(+/-)	21	3.1
Fukuyama [329]	2009	D→A→BC	(+)	34	0.9
Fukuyama [330]	2009	D→AB→C	(+)	24	0.08
Fujii, Ohno [331]	2011	AB→ DC	(+)	16	5.9
Fujii, Ohno [332]	2011	AB→ DC	(+)	17	1.8
Jia [333]	2011	AB→D→C	(+)	20	5.1
Fukuyama [334]	*2013*	*AB→D→C*	*(+)*	*19*	*12.0*
Jia [335]	2013	D→AB→C	(+)	12	1.0
Fukuyama [336]	2018	A→B→C→D	(+)	30	0.07
Smith [337]	*2022*	*AB→D→C*	*(+/-)*	*6*	*12.0*

[a]Ring construction/introduction sequence

[b]Longest linear sequence from a readily available commercial precursor

[c]In the longest linear sequence starting from a readily available commercial precursor

[d]Because the yield was not provided at all steps

[e]Disputed by David E. Nichols and Dale L. Boger

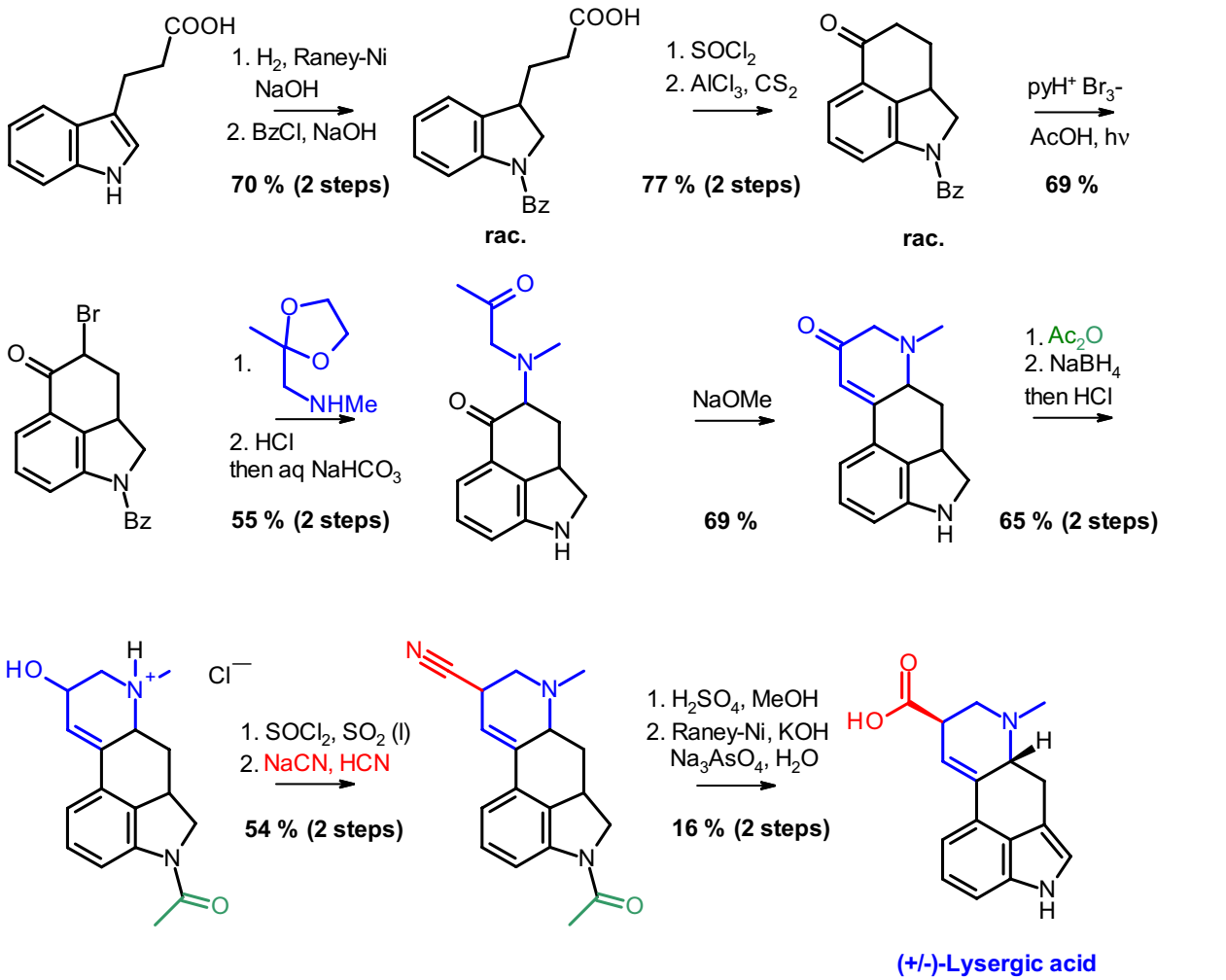
The first enantioselective synthesis is attributed to Nobutaka Fujii and Hiroaki Ohno from Kyoto University. Hendrickson's synthesis is particularly striking because it yields racemic lysergic acid with a 14.5% yield in only nine steps. Unfortunately, according to David E. Nichols [311] and Dale L. Boger [312] this synthesis appears to be controversial. But most recently Joel M. Smith from Florida State University contributed a remarkable concise total synthesis providing racemic lysergic acid in only six steps and 12.0% overall yield. In respect to the number of reaction steps and overall yield, the most efficient total synthesis of (+)-lysergic acid derived from Tohru Fukuyama from Nagoya University in 2013 (Table 7).

Woodward's total synthesis of racemic lysergic acid

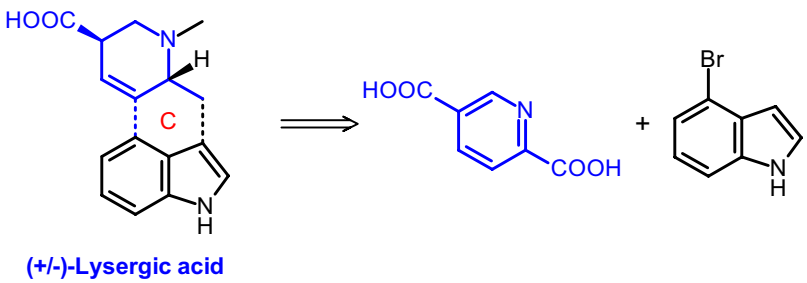
Woodward chose 3-indolylpropionic acid as starting material for his lysergic acid synthesis, though he was fully aware of the high reactivity of the indole compounds that might become an obstacle on later stages. Therefore, he adopted the artifice of reduction at the very beginning to circumvent such problems. Dihydroindole derivatives are much less reactive and more suitable for the envisioned endeavor. After benzoylation of the amino group the tricyclic ketone was obtained by Friedel Crafts acylation in carbon disulfide, while other attempts, such as running the reaction in benzene or applying hydrogen fluoride as Lewis acid, failed. After much experimentation Woodward succeeded introducing methylaminoacetone ethylene ketal directly at position 5, which set the stage for an intramolecular aldol reaction, and providing the desired tetracyclic unsaturated ketone. Subsequent successive treatment with acetic anhydride and sodium borohydride leads to an allylic alcohol, which was converted into the corresponding nitrile. Finally, racemic lysergic acid was obtained by Pinner reaction followed by refluxing in aqueous potassium hydroxide in the presence of sodium-arsenate-deactivated Raney nickel (Scheme 3) [157, 158].

Hendrickson's total synthesis of racemic lysergic acid

In 2004, James B. Hendrickson (1928–2018) [338] from Brandeis University published the ninth total synthesis of racemic lysergic acid, but the first one entirely avoids protecting group chemistry [326]. To increase step economy, Hendrickson considered the assembly of the framework



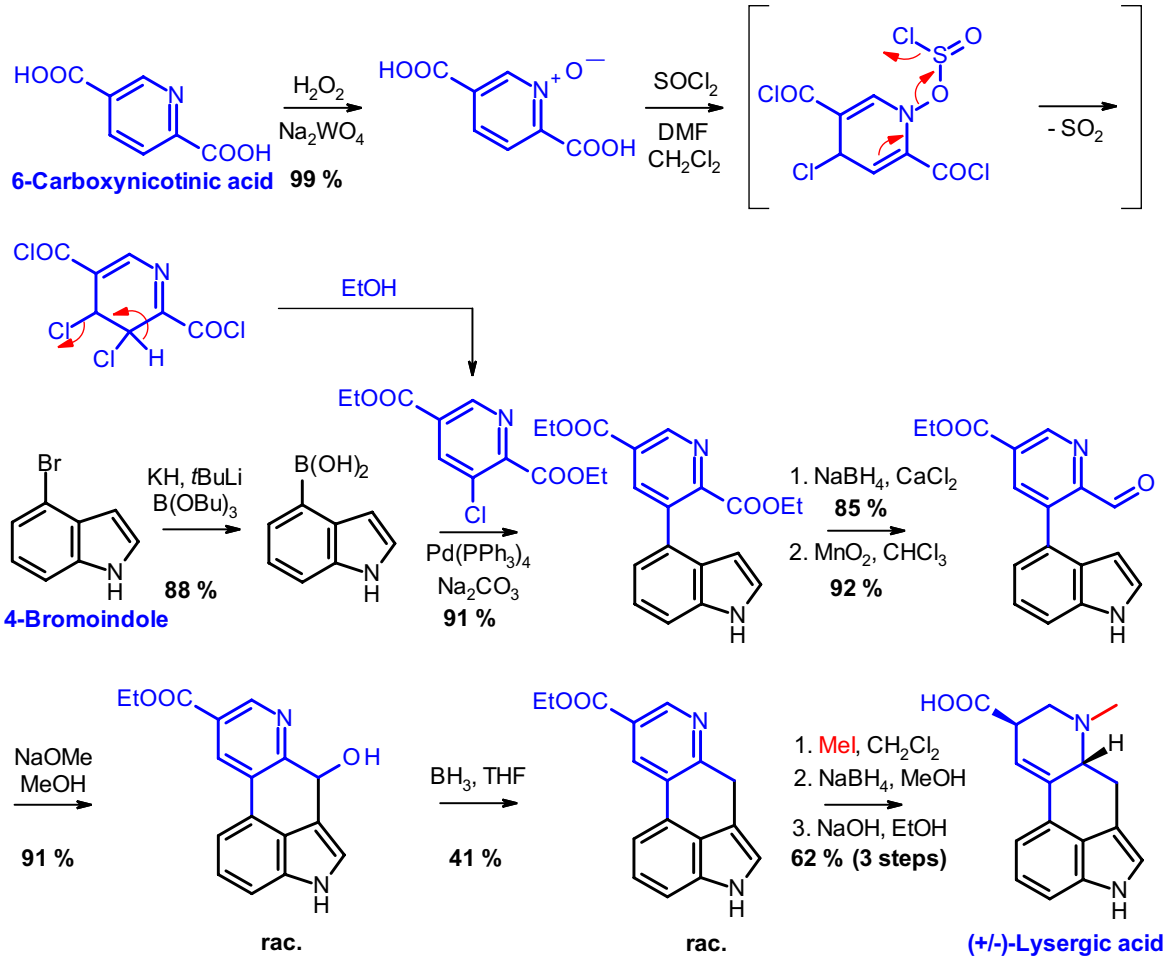
Scheme 3 Woodward's total synthesis of racemic lysergic acid



Scheme 4 Retrosynthetic considerations on Hendrickson's total synthesis of racemic lysergic acid

from readily available indole and nicotinic acid starting materials as the most efficient route and avoided also the initial reduction of the indole, which was frequently performed in previous syntheses (Scheme 4).

The first key step in Hendrickson's lysergic acid synthesis is a Suzuki coupling of indole-4-boronic acid and 3-chloro-pyridine-2,5-dicarboxylic acid diethyl ester, obtained in few steps from 4-bromoindole and 6-carboxynicotinic acid, respectively. Regioselective reduction of the ester in ortho-position and MnO_2 oxidation provides an aldehyde, which, in the presence of a catalytic amount of sodium methanolate, cyclizes readily at room temperature. The alcohol obtained is reduced with borane in THF. The final three steps, comprising pyridine methylation, reduction of the D ring and hydrolyses of the ester are carried through without isolation and purification of the intermediates, finally yielding racemic lysergic acid in nine steps from 4-bromoindole in an overall yield of 14.5%. It should be noted that chirality is introduced only in the final reduction step of the pyridinium salt, which



Scheme 5 Hendrickson's total synthesis of racemic lysergic acid which, according to David E. Nichols, derails upon formation of the C ring [311].

poses a challenging invitation for further improvements (Scheme 5) [339]. [340].

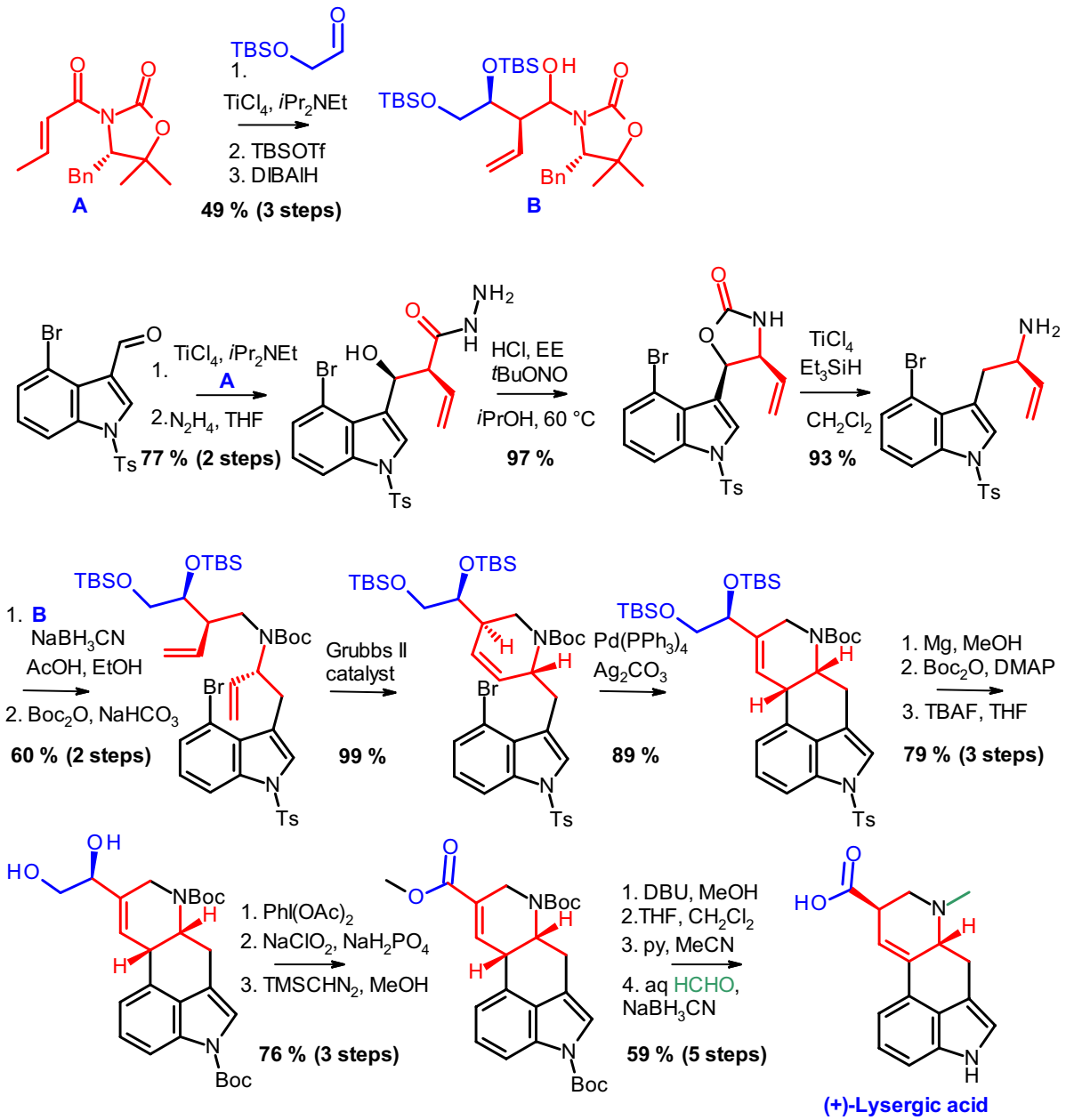
Fukuyama's total synthesis of (+)-lysergic acid

Tohru Fukuyama from Nagoya University published in 2013 an extraordinary, enantioselective total synthesis of (+)-lysergic acid. Key features of the route are the Evans aldol reaction providing the stereogenic centers at the allylic positions, a ring-closing metathesis and an intramolecular Heck reaction to establish the C and D rings [334].

The synthesis commences with two Evans aldol reactions of crotonamide **A** with TBS-protected hydroxyacetaldehyde and an indole carbaldehyde, respectively. By hydrazinolysis the auxiliary is cleaved off and a Curtius rearrangement provides an isoxazolone. Deoxygenation with triethylsilane, titanium tetrachloride leads to an allylamine, which after reductive amination with the other Evans aldol product **B** and Boc protection of the amine, sets the basis for intramolecular ring closing metathesis. Stereoselective ring closure of the C ring by a Heck reaction establishes the lysergic acid scaffold. The remaining transformations comprise the degradation of the diol to the carboxylic acid, double bond isomerization, deprotection and methylation of the D ring with formaldehyde sodium cyanoboranate. The longest linear sequence extends to 19 steps and provides (+)-lysergic acid in remarkable 12% overall yield (Scheme 6).

Smith's total synthesis of racemic lysergic acid

Joel M. Smith's synthesis of racemic lysergic acid commences with a magnesium–halogen exchange of methyl 6-iodonicotinate followed by a Grignard reaction with 4-bromoindole-3-carboxaldehyde. After reduction of the resulting alcohol and re-protection of the indole, the pyridine moiety is reduced to generate a 1,2-dialkyl-3,6-dihydro-2*H*-pyridine, which is repetitively subjected to an isomerization process with lithium tetramethylpiperidide to obtain the corresponding 1,6-dialkyl-3,6-dihydro-2*H*-pyridine isomer. The following Heck annulation with the *anti*-isomer, employing

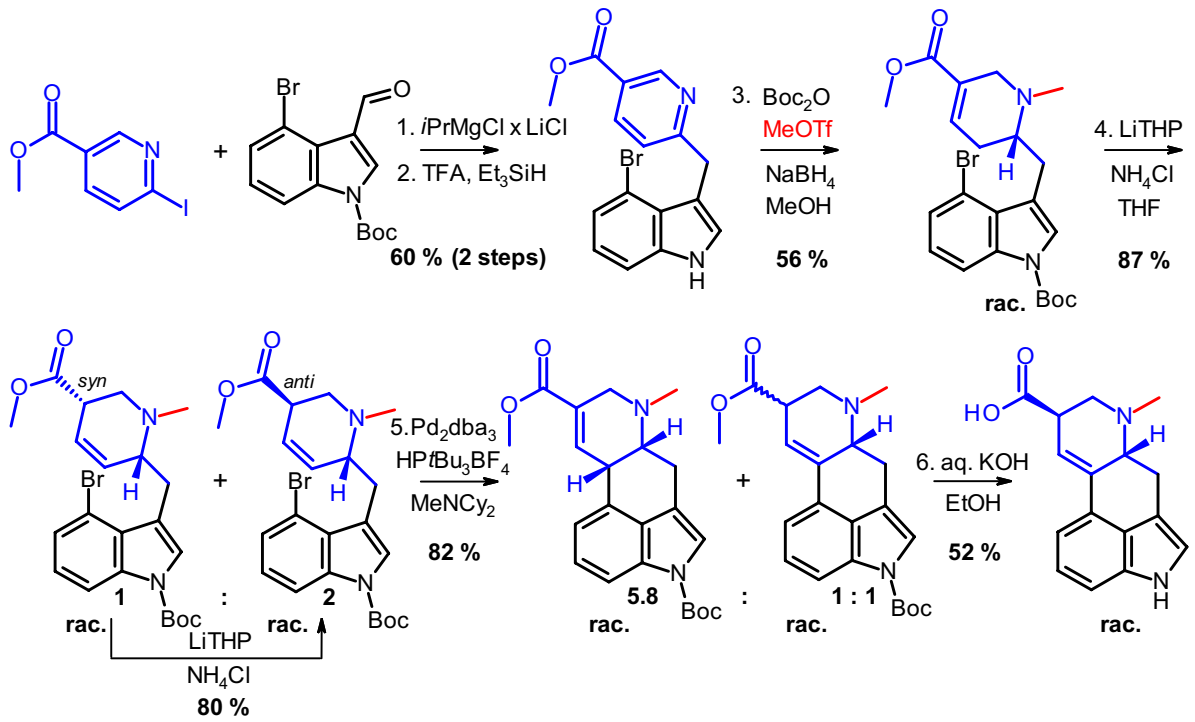


Scheme 6 Fukuyama's total synthesis of (+)-lysergic acid

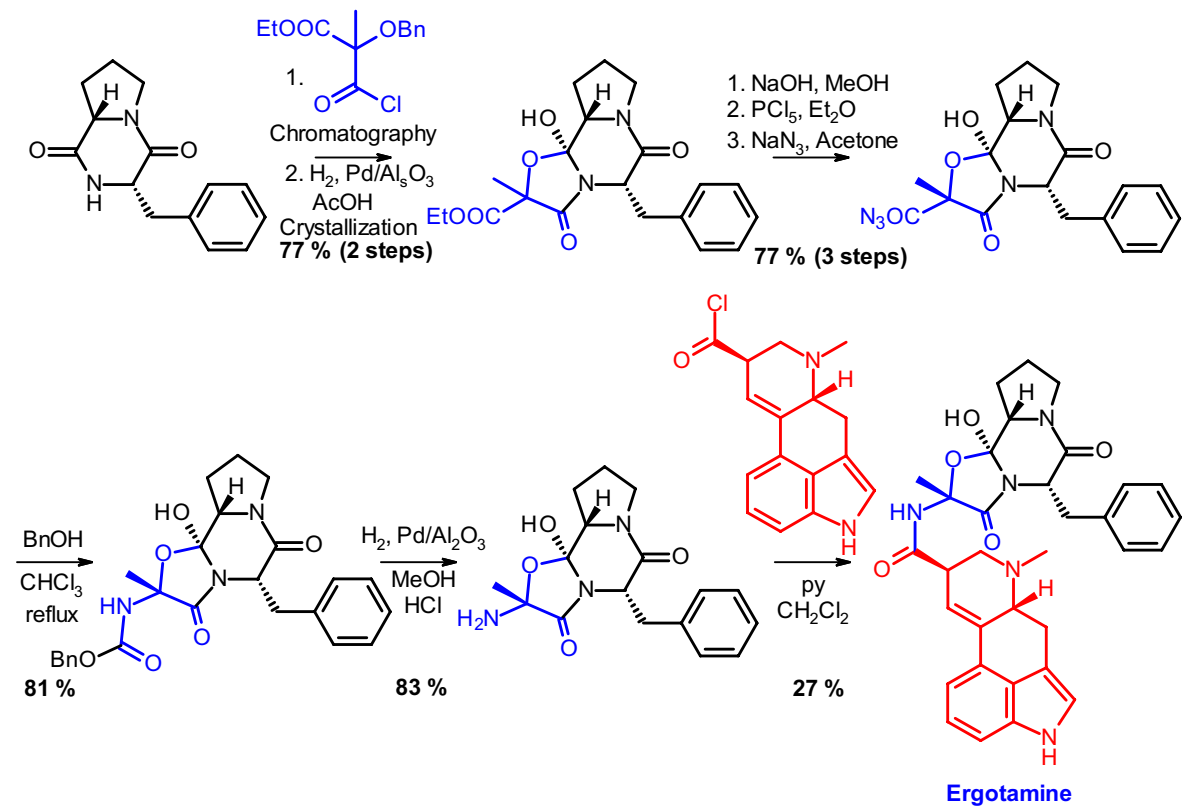
Gregory Fu's in situ generated Pd(0) catalyst [341] provided a mixture of stereoisomers of the Boc-protected methyl ester of paspalic acid and lysergic acid. Finally, racemic lysergic acid was afforded from this mixture by saponification and isomerization in an overall yield of 12% (Scheme 7).

Ergotamine

The first synthesis of ergotamine was published by Albert Hofmann in 1961 [151, 342]. Stimulated by Woodward's total synthesis of lysergic acid, the chemists at Sandoz spent some effort to extend the synthesis to the peptidic part of the molecule. They started from cyclo(L-Phe-L-Pro) ((3*S*,8a*S*)-3-benzyl-2,3,6,7,8,8a-hexahydropyrrolo[1,2-a] pyrazine-1,4-dione), which was reacted with racemic ethyl 2-benzyloxy-3-chloro-2-methyl-3-oxo-propanoate to obtain already the desired tricyclic scaffold, which is part of ergotamine. After hydrolysis of the ethyl ester, the corresponding acyl azide is synthesized, which by Curtius rearrangement and hydrogenolytic cleavage of the resulting carbamate provides the required amine. Ergotamine is finally obtained by its reaction with lysergic acid chloride. The overall yield amounts to just 10.8%, resulting mainly from the poor yield on the last stage of this route (Scheme 8).



Scheme 7 Smith's total synthesis of racemic lysergic acid



Scheme 8 The first synthesis of ergotamine by Albert Hofmann

Fig. 27 Artificial inoculation of a rye field with the ergot fungus. Since the inoculation season usually coincided with the hay harvest, which tied up a lot of labor in agriculture, inoculation machines were developed. The ears were fed between the triangular dividers and inoculated with rollers studded with needles (left). In special cultivated fields, yields of up to 100 kg of ergot per hectare could be achieved. The photograph shows a drum of ergot kernel from the harvest in the Basel area in 1942 (middle). Ergot extraction plant at Sandoz in the 1940s (right) (© Courtesy of Novartis Company Archives)

It must be mentioned, however, that notwithstanding of all the achievements in preparative organic chemistry, we have never in history, nor today, been able to provide ergot alkaloids by total synthesis on an economical basis. Industrial extraction began soon after World War I at Sandoz, and Sandoz dominated the production until the 1950s, when other companies started business in the same field, including Boehringer Ingelheim (Germany), Galena (Czech Republic), Gedeon Richter (Hungary), Lek (Slovenia), and Farmitalia (Italy). Nevertheless, still today, Novartis, the successor to Sandoz, retains leadership in world production of ergot alkaloids [142]. The first quantities of ergotamine were produced from ergot sclerotia found in crop fields. When the demand for ergot for extraction exceeded the amount obtained from collection in rye fields, methods for artificial inoculation of rye were developed (Fig. 27).

However, already in 1960, Federico Arcamone (together with Ernst Boris Chain (1906–1979) at the Instituto Superiore di Sanità in Rome demonstrated that simple lysergic acid derivatives could also be produced in high yield by fermentation in submerged culture by a strain of *Claviceps paspali*, found growing on a hill in the neighborhood of the city [343]. Independently, Sandoz in Basel, Spofa in Prag, and Farmitalia in Milan started research and succeeded soon in manufacturing ergot alkaloids, including ergotamine, with strains of *Claviceps purpurea* [197, 344–348]. Since the 1990s, it became known that ergot alkaloids can also be produced advantageously by *Claviceps fusiformis* and *Claviceps purpurea* in solid-state fermentation [349]. Meanwhile, the main part of production is based on this technology, while field cultivation on triticale [a hybrid of wheat (*Triticum*) and rye (*Secale*)] balances the demand. In recent years, the annual production of lysergic acid, mainly used for the manufacturing of semisynthetic derivatives, has been estimated at 15 tons, not including illegal quantities, of course [142].

Infobox: Biochemical research across the iron curtain

The biosynthetic pathway of ergotamine in *Claviceps* species has been studied since the 1950s in the lab of Kurt Albin Mothes (1900–1983) [350] at the Martin-Luther University Halle-Wittenberg, and since 1958 in the newly founded Leibniz Institute of Plant Biochemistry. Groundbreaking contributions in this field are attributed to Detlef Gröger (1929–2010) [351] in Halle, East Germany and Heinz G. Floss [352] at Purdue University, Lafayette and the University of Washington, USA [353]. Both researchers made biosynthesis of ergot alkaloids a lifelong project and maintained a close friendship. It is most remarkable that they managed to overcome the numerous obstacles that collaboration across the Iron Curtain entailed at the time [354].

As can be easily revealed from the structure, ergotamine is a downstream product of the amino acid and terpene biosynthetic pathways (Fig. 28).

However, at the outset of the elucidation of the biosynthesis of ergotamine, no natural product was known whose carbon framework could be traced back to both the amino acid and terpene metabolism. But this was exactly what Heinz Floss managed to show with radiolabeled mevalonic acid, which had just been discovered as a precursor of the isoprene building block. According to a pathway first proposed by Gröger and Floss, in the first step tryptophan is alkylated in position 4 with dimethylallyl diphosphate [355]. After *N*-methylation with *S*-adenosyl-L-methionine [356], chanoclavine-I is provided by desaturation, epoxidation, and decarboxylating C-ring closure [353, 357, 358]. Oxidation of the alcohol and reductive amination

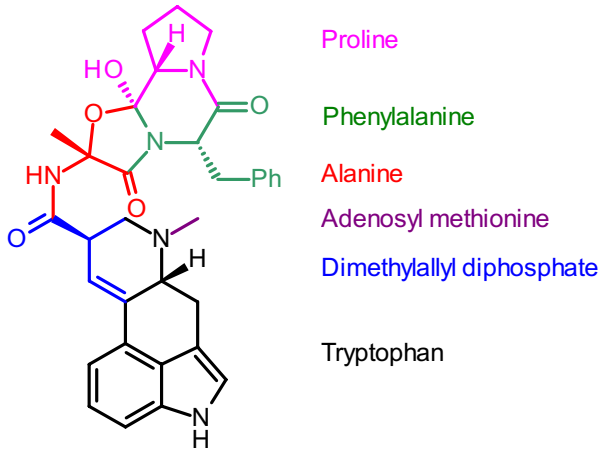


Fig. 28 Ergotamine derives from the amino acid and terpene biosynthetic pathways

takes the biosynthesis to agroclavine [359, 360]. Lysergic acid is obtained by oxidation of the methyl group and isomerization of the adjacent double bond (Scheme 9) [142, 313, 361].

Ergotamine belongs to a group of lysergic acid derivatives, the ergopeptines, in which a bicyclic tripeptide is bound to the carboxylic acid function. In ergotamine, the sequence of amino acids from N- to C-terminus is Ala-Phe-Pro. In other ergopeptines, the first amino acid alanine can be replaced by valine or (L)-2-aminobutyric acid. The group of the second amino acids includes phenylalanine, valine, leucine, isoleucine, (L)-2-aminobutyric acid, (L)-norleucine, methionine, and (L)-homoleucine. In almost all ergopeptines the third amino acid is proline.

In *Claviceps purpurea*, ergotamine is assembled by an enzyme complex consisting of two nonribosomal peptide synthetase subunits lysergyl-peptide synthase 1 and 2 [365]. These subunits exhibit modular structures, responsible for the addition of lysergic acid or an amino acid. A typical module includes an adenylation (A-), a thiolation (T-), and a condensation (C-) domain. The adenylation domain specifies lysergic or the amino acids, which are activated by an ATP-dependent adenylation reaction. Subsequently they form a thioester with the adjacent T-domain and the C-domain links the intermediate to the next amino acid in the chain. The order of subunits corresponds to the sequence of amino acids from its N- to C-terminus. The biosynthesis of ergopeptines culminates in cyclization and release of the product D-lysergyltripeptide lactam. Finally, ergotamine is obtained by hydroxylation of the alanine moiety and spontaneous formation of the amide hemiacetal (Scheme 10).

Triptans

Compared with ergotamine, the triptans are structurally much simpler and can be easily obtained by chemical synthesis [366]. Being indole derivatives, the key step of the first manufacturing processes was a Fischer indole synthesis as one might expect. However, this approach harbored an intrinsic drawback, which also triggered the development of other routes.

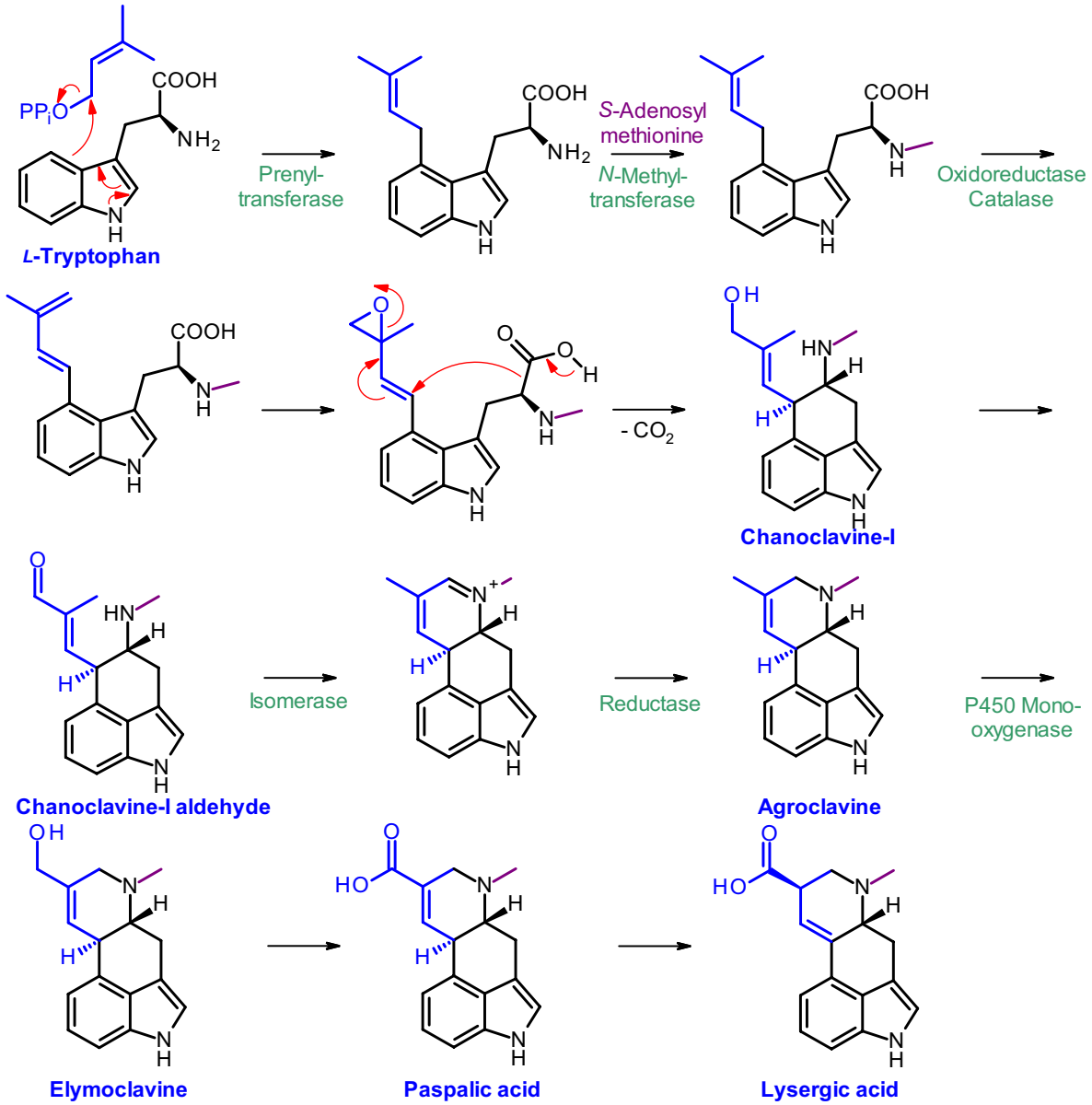
Sumatriptan

Glaxo's sumatriptan [367, 368] synthesis began with the preparation of the hydrazine derivative, required for the Fischer indole synthesis, by hydrogenation of *N*-methyl-4-nitrobenzenemethanesulfonamide, followed by diazotation and reduction of the diazonium salt with tin chloride. Condensation with 4,4-dimethoxy-*N*,*N*-dimethylbutylamine provided a hydrazone that was subjected to the Fischer indole synthesis, applying the Langheld ester (which is an ethyl metaphosphate [369], first prepared from phosphorus pentoxide and diethyl ether by Kurt Langheld at the University Breslau in 1910 [370, 371]) (Scheme 11) [372, 373].

The low yield on the final stage is to some extent related to the formation of side products **A** and **B**. Sumatriptan, which also shares this feature with almotriptan [374] and rizatriptan [375], has the structure of a 3,5-dialkylindole with a nucleophilic center at position 2 and an XCH_2 group at position 5, where X can act as a leaving group under acid catalysis of conventional Fischer indole reactions (Fig. 29) [376, 377].

In 1999, BASF applied for a patent claiming a highly streamlined and optimized synthesis of sumatriptan, which was developed by researchers at a former Boots site in Nottingham, UK [378]. Hydrogenation of *N*-methyl-4-nitrobenzenemethanesulfonamide, diazotation, and reduction of the diazonium salt are performed as a one-pot reaction. The use of sodium dithionite rather than stannous chloride was a significant improvement, avoiding toxicological and environmental concerns. In the next step, known as the Grandberg version of the Fischer indole synthesis [379, 380], the hydrazine is condensed with 4-chlorobutanal dimethyl acetal, followed by refluxing of the resulting hydrazone in the presence of disodium hydrogen phosphate, which leads to indolization and displacement of the chloro group with the ammonia released during the formation of the indole ring. The synthesis of sumatriptan is finally completed by reductive amination with aqueous formaldehyde and sodium borohydride (Scheme 12).

Chemists from Gedeon Richter LTD in collaboration with the Technical University of Budapest focused their attention on the low yields of the Fischer indole synthesis and the formation of byproducts. They also merged the synthesis



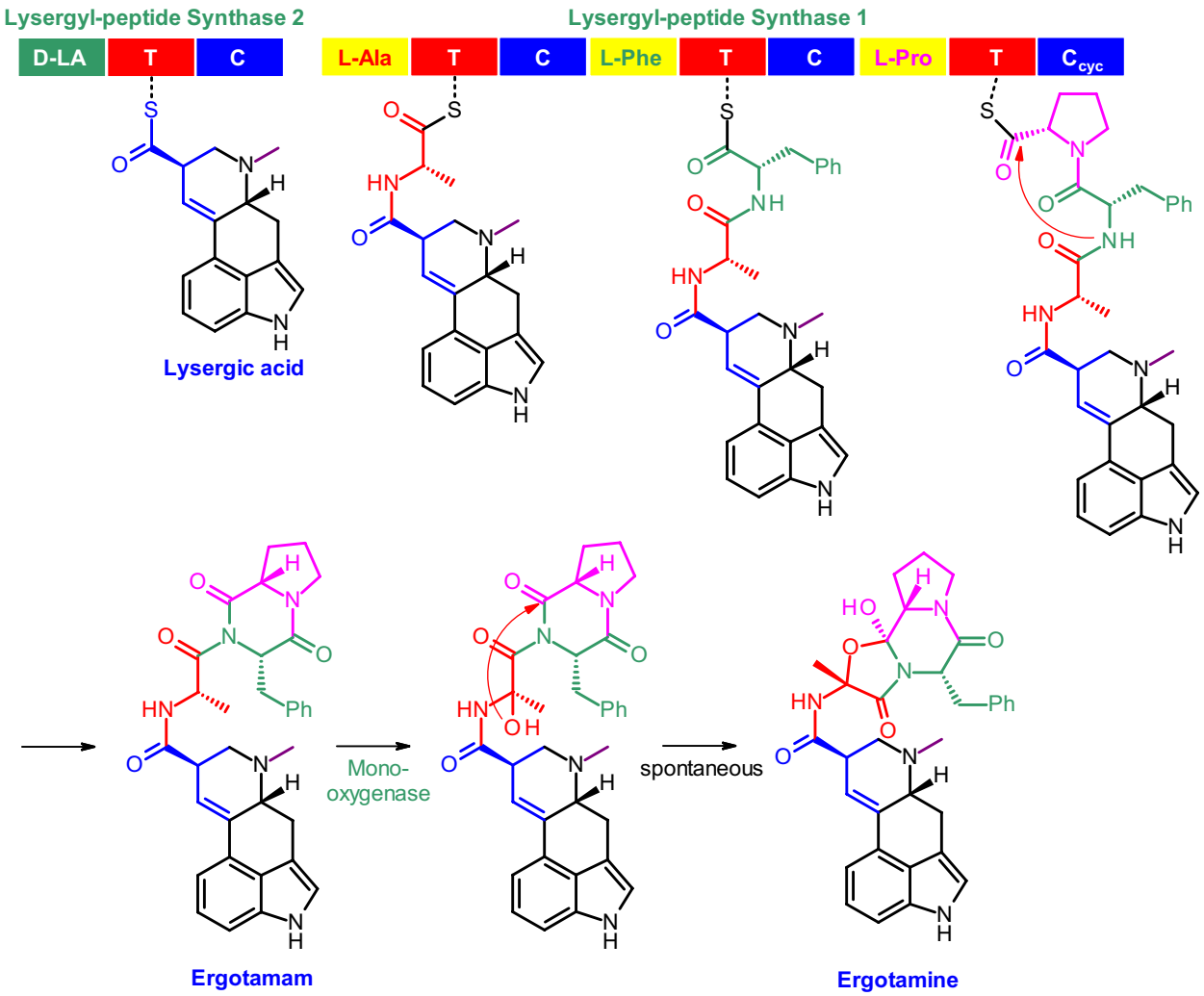
Scheme 9 Biosynthesis of lysergic acid [362–364]

of the hydrazone and Fischer indolization. However, they chose a protected sulfonamide, and by that they were able to avoid byproduct **A**, but not the formation of impurity **B** (Scheme 13) [381].

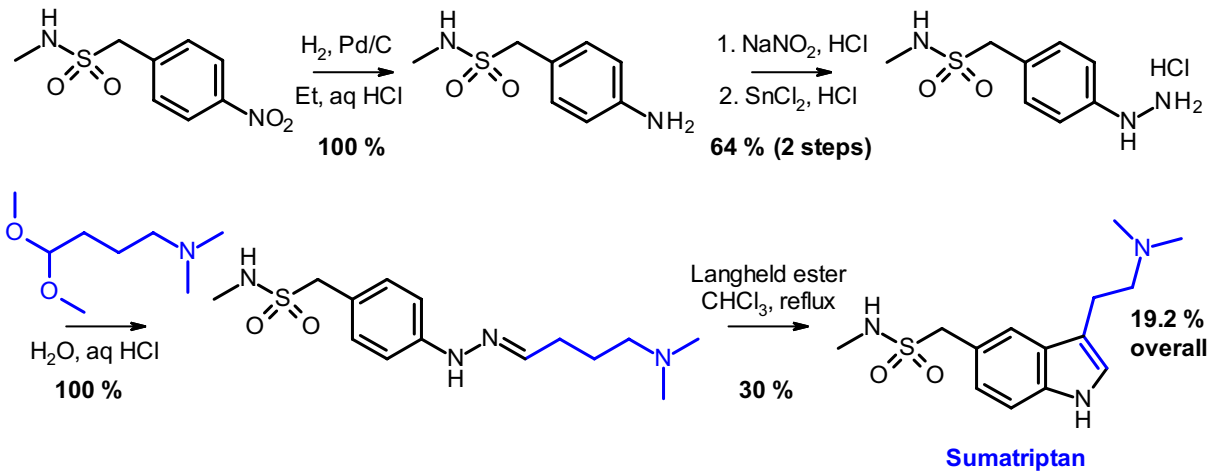
Consequently, they also investigated the Japp–Klingemann approach, which comprises the reaction of the diazonium salt with ethyl 2-(3-dimethylaminopropyl)-3-oxobutanoate and Fischer cyclization. Due to protection at position 2 and at the sulfonamide the resulting indole is not prone to subsequent reactions, which avoids byproducts **A** and **B** and increases yield. After hydrolysis of the esters and decarboxylation, sumatriptan was obtained in improved overall yield (Scheme 14) [382].

Zolmitriptan

Zolmitriptan was discovered by Burroughs Wellcome in the UK in 1990 [383], but upon acquisition of Wellcome by Glaxo, the intellectual property was transferred to Zeneca [384]. In the first part of the synthesis an oxazolidinone is prepared starting from 4-nitro-L-phenylalanine, in which the latter is converted into the methylester, reduced with sodium borohydride, and reacted with phosgene. Hydrogenation, diazotation, and reduction with stannous chloride provided a hydrazine that is subjected to a



Scheme 10 Biosynthesis of ergotamine



Scheme 11 Sumatriptan synthesis by Glaxo

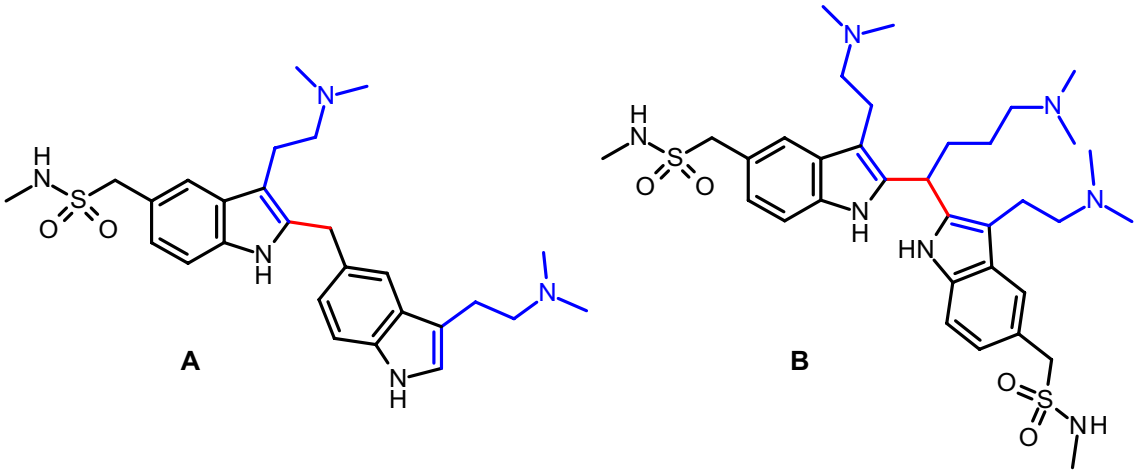
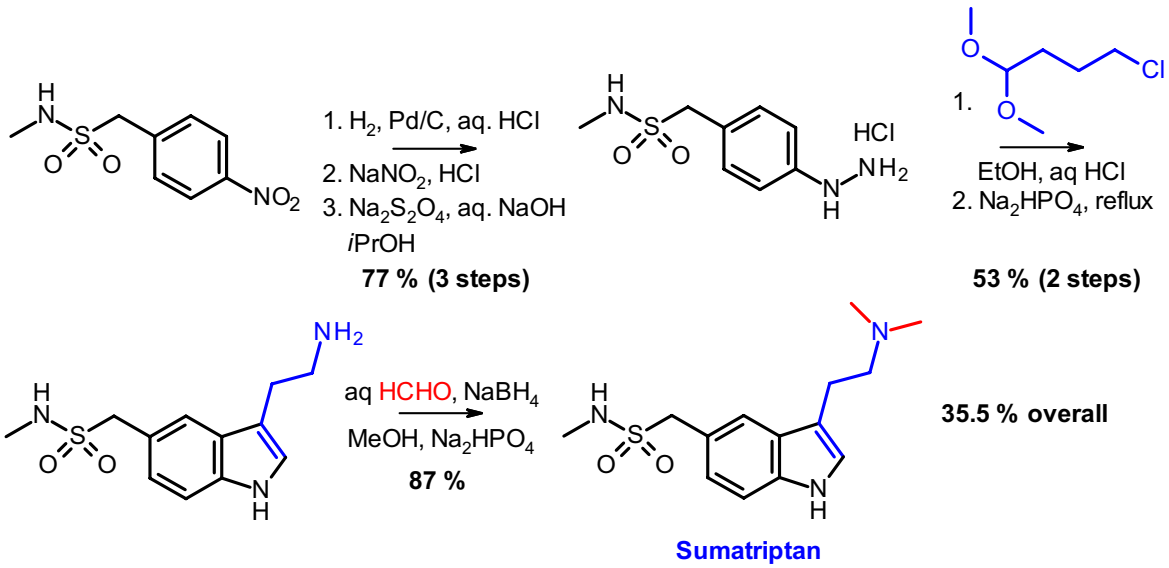
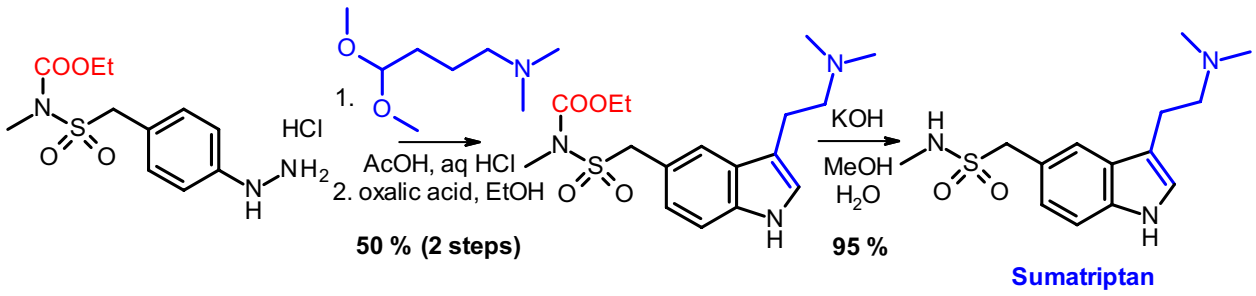


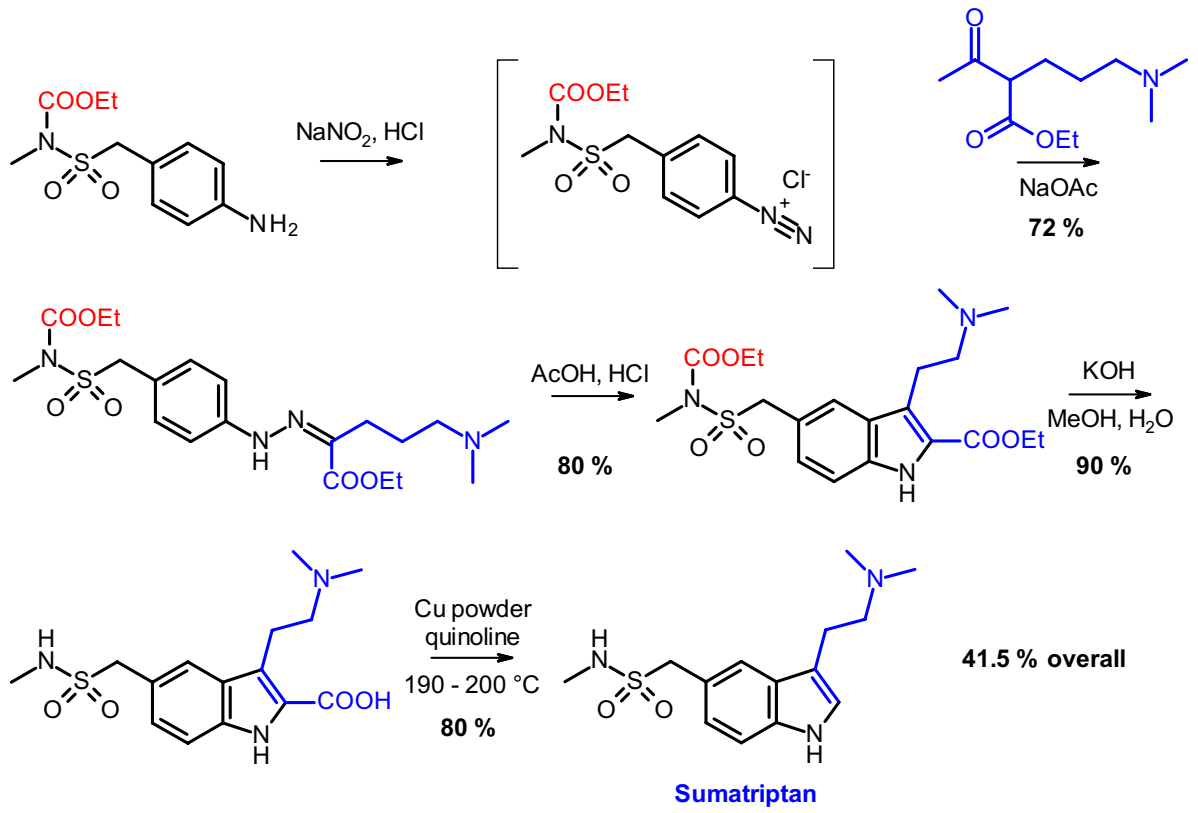
Fig. 29 Side products of Glaxo's sumatriptan synthesis (red bonds are formed by nucleophilic substitution)



Scheme 12 Sumatriptan synthesis by BASF



Scheme 13 Sumatriptan synthesis by Gedeon Richter LTD via a Fischer indole type synthesis



Scheme 14 Sumatriptan synthesis by Gedeon Richter LTD via a Japp–Klingemann approach

Grandberg–Fischer indole synthesis. Finally, dimethylation by reductive amination afforded zolmitriptan (Scheme 15).

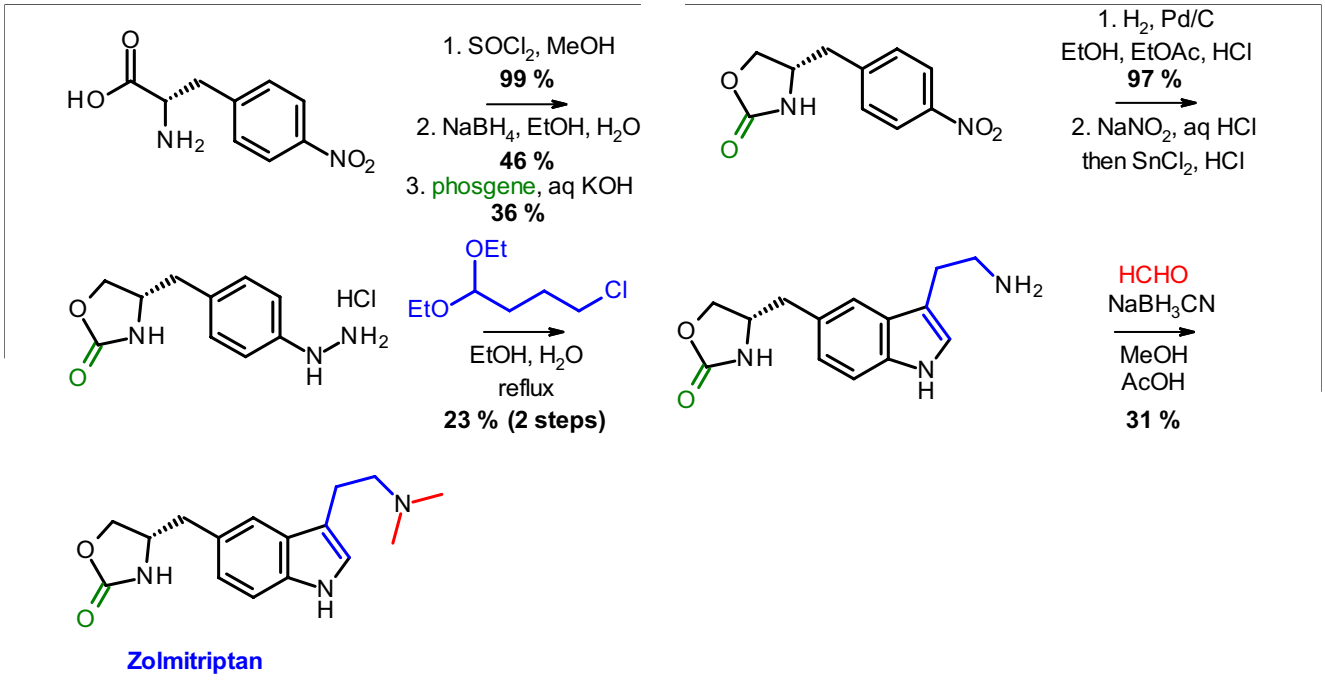
The inventors of this synthesis succeeded in dramatically improving the Fischer indole synthesis by using 3-cyanopropanaldiethyl acetal, but they then lost most of the material in the final reductive transamination (Scheme 16) [384].

In 1995, however, Rajnikant Patel at Zeneca filed a remarkable patent for an elegant, large-scale, so-called one-pot synthesis of zolmitriptan that left all these hurdles and drawbacks behind [385]. The synthesis commenced by reacting methyl 4-nitro-(L)-phenylalanine with *n*-butyl chloroformate. The resulting butyl carbamate is subjected directly to hydrogenation of the nitro group. After solvent swap to butanol, the methyl ester is reduced with sodium borohydride and treatment with sodium methoxide leads to the oxazolidinone, which, after crystallization, is isolated as a solid. Diazotation and reduction of the diazonium salt with aqueous sodium sulfite provides the corresponding hydrazine. Addition of 4,4-diethoxy-*N*,*N*-dimethylbutylamine and boiling to reflux for several hours provide crude zolmitriptan, which is purified be recrystallization. Unfortunately, Zeneca was reluctant to provide the exact total yield, but indicated that it was high. Matrix Laboratories later described an analogous synthesis of *N*-desmethyl zolmitriptan with a yield of 60% (Scheme 17) [386].

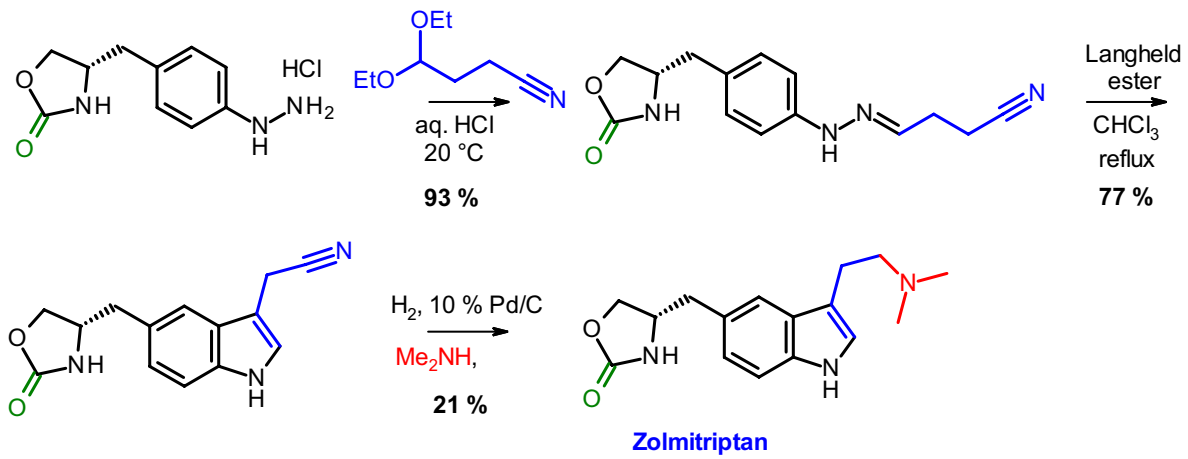
Naratriptan

Naratriptan was a follow-up compound to sumatriptan, discovered at Glaxo in 1987 [387]. The synthesis started with 5-bromoindole, which was condensed with *N*-methyl-4-piperidone, followed by hydrogenation of the resulting enamine. Heck reaction with *N*-methylvinylsulfonamide and hydrogenation afforded naratriptan in 25.3% overall yield (Scheme 18).

More recently, Glaxo detailed a process for the manufacturing of naratriptan on kilogram scale [388]. The synthesis is very similar to their original route. However, the hydrogenation steps were combined, and the others optimized leading to an efficient approach with an overall yield of 75.3% (Scheme 19).



Scheme 15 Zolmitriptan synthesis by Zeneca via a Grandberg–Fischer indole synthesis



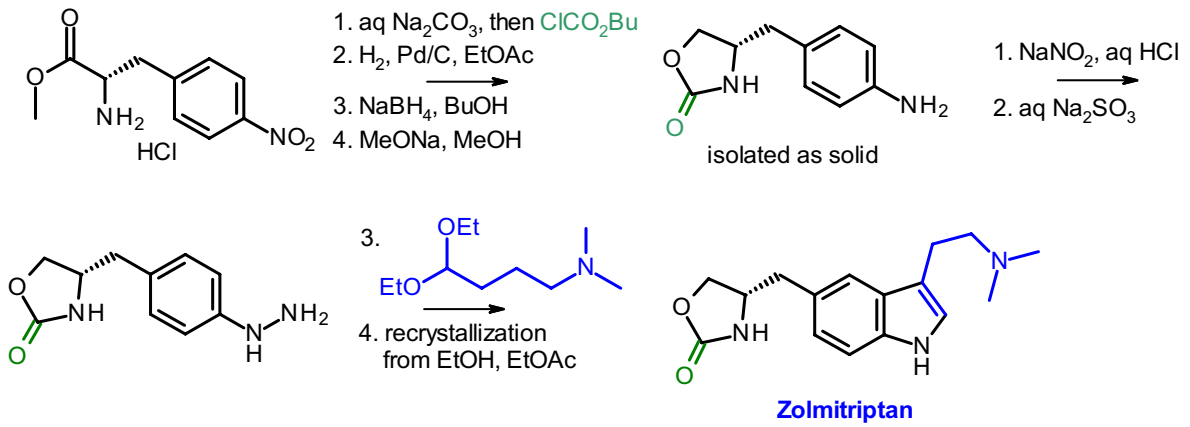
Scheme 16 Improved zolmitriptan synthesis by Zeneca

Almotriptan

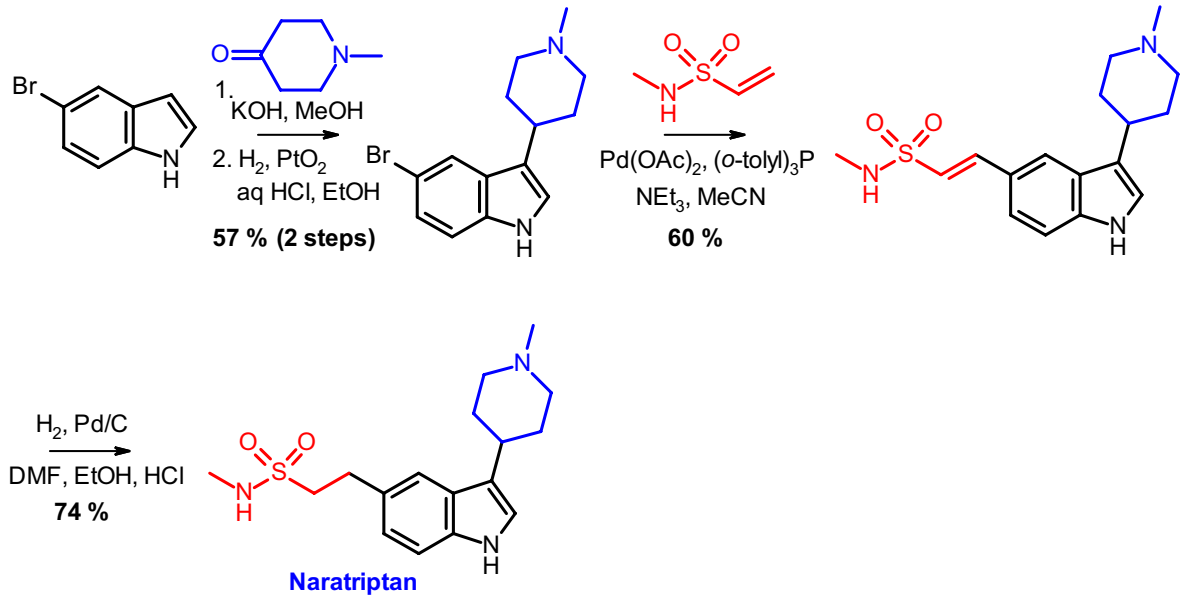
Almotriptan was discovered and developed at Almirall, but later also licensed to Pharmacia and Janssen [374]. Initially, it was prepared by the Grandberg modification of the Fischer indolization, but more recent approaches involve also Pd-catalyzed coupling reactions, such as the intramolecular Heck reaction [389] or the Negishi reaction [390].

The precursor for the Heck reaction is obtained by iodation of an appropriately decorated aniline, followed by protection and alkylation with methyl 4-bromocrotonate. The key step of this route comprises a palladium-catalyzed Heck cyclization with concomitant deprotection of the indoleacetic methyl ester. Almotriptan is obtained via the *N*,*N*-dimethyl carboxamide, which is reduced applying lithium aluminum hydride (Scheme 20).

The starting material for the Negishi reaction is synthesized from commercially available 5-bromoindole, which is reacted with oxalyl chloride and gaseous dimethylamine, followed by reduction with lithium aluminum hydride and



Scheme 17 One-pot synthesis of zolmitriptan by Zeneca



Scheme 18 Naratriptan synthesis by Glaxo

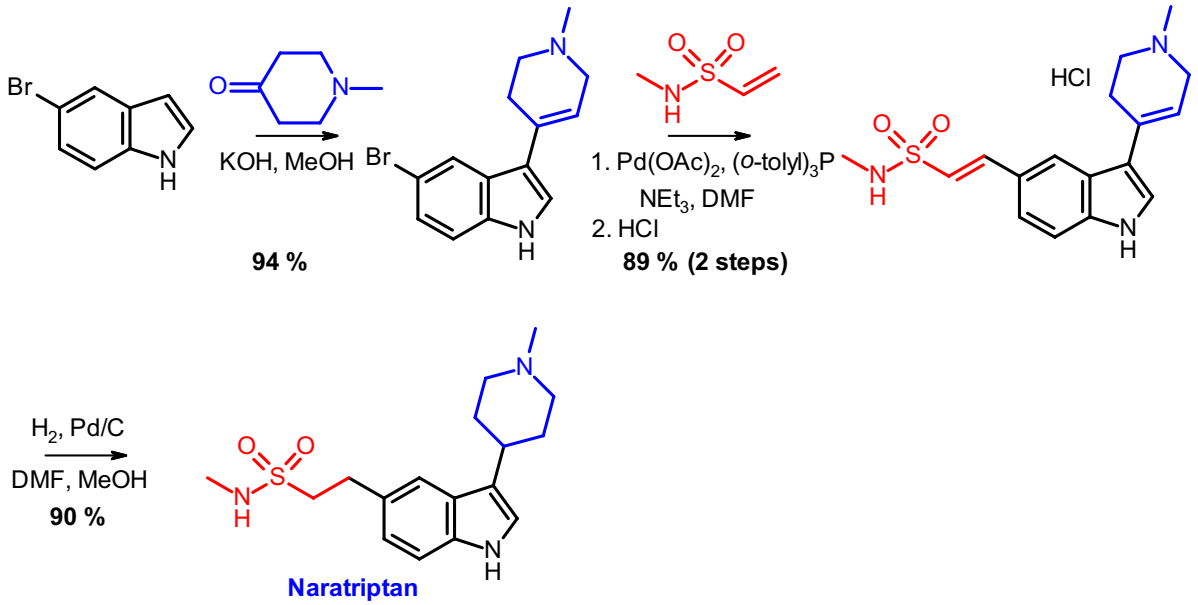
Boc-protection. The Negishi reaction with 1-(methylsulfonyl)pyrrolidine proceeds at 65 °C and affords the desired product in 86% yield. Deprotection finally provided almotriptan in high purity (Scheme 21).

Frovatriptan

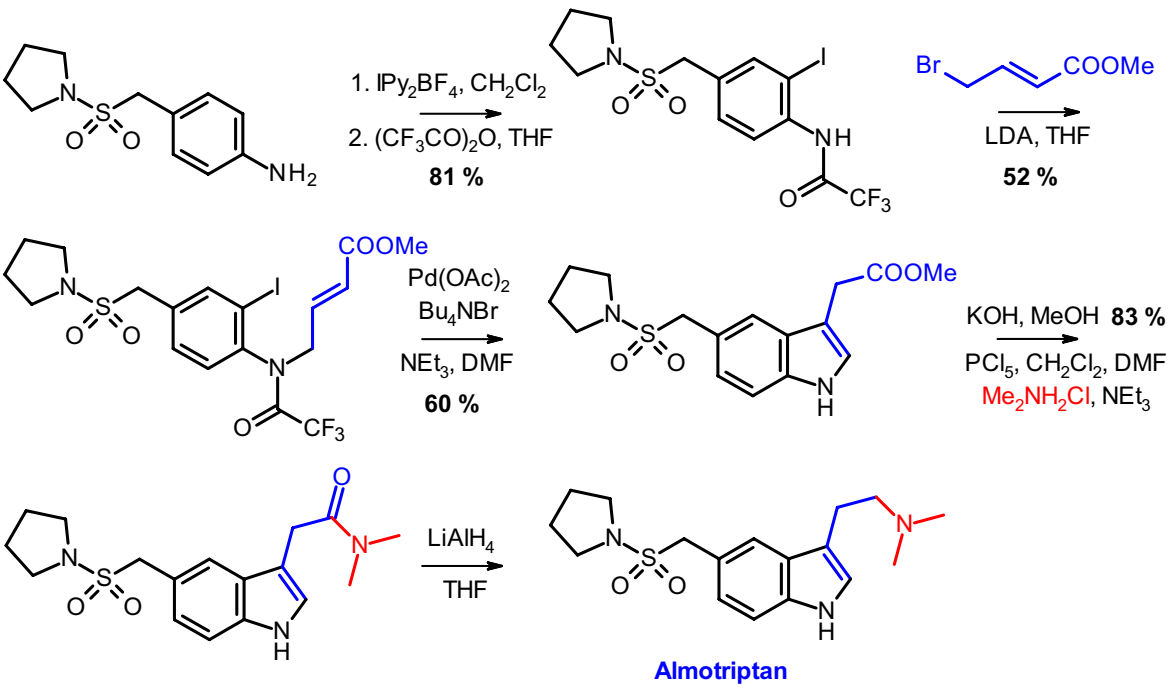
Frovatriptan was discovered in the early 1990s at Smith-Kline Beecham [391, 392], but licensed to Vanguard Medica/Vernalis for development. Its structure is similar to Glaxo's development substance AH21467, however bearing a conformationally restrained cyclohexane, which is condensed to the indole at position 2 and 3. Frovatriptan can be synthesized via Fischer indole synthesis. In a highly convergent synthesis, the building block **A**, obtained by reductive amination of the mono-ketal of 1,4-cyclohexanedione, is reacted in a one-pot reaction with a hydrazine synthesized from 4-aminobenzamide, to produce racemic frovatriptan in an overall yield of 63%. The enantiomers can be separated by crystallization with di-*p*-toluoyl-(D)-(+)-tartaric acid (Scheme 22) [393].

Eletriptan

Pfizer also joined the race for new triptans, leading to the discovery of eletriptan in the 1990s [394]. The first manufacturing process commenced from 5-bromoindole, which was condensed with (*R*)-*N*-methyl proline chloride. After



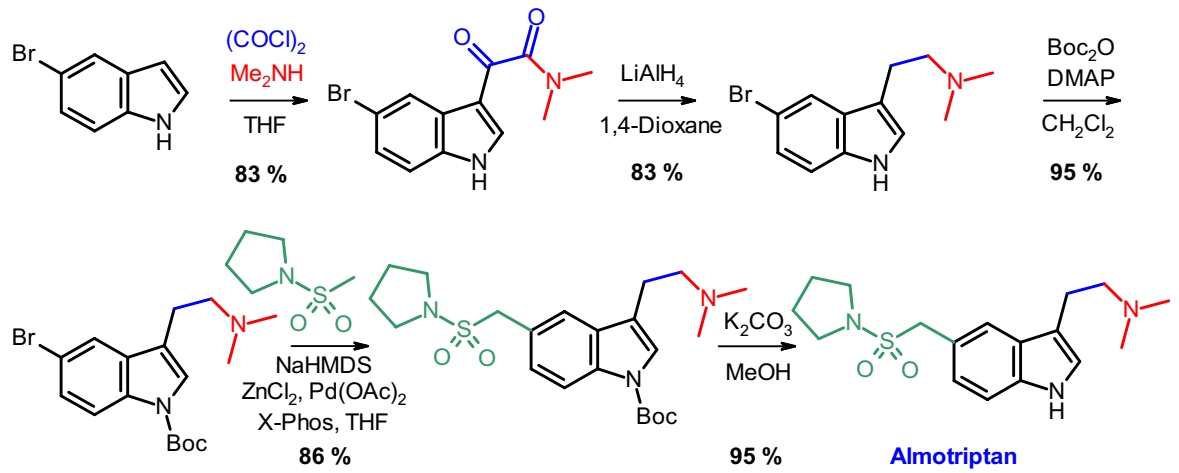
Scheme 19 Improved naratriptan synthesis by Glaxo



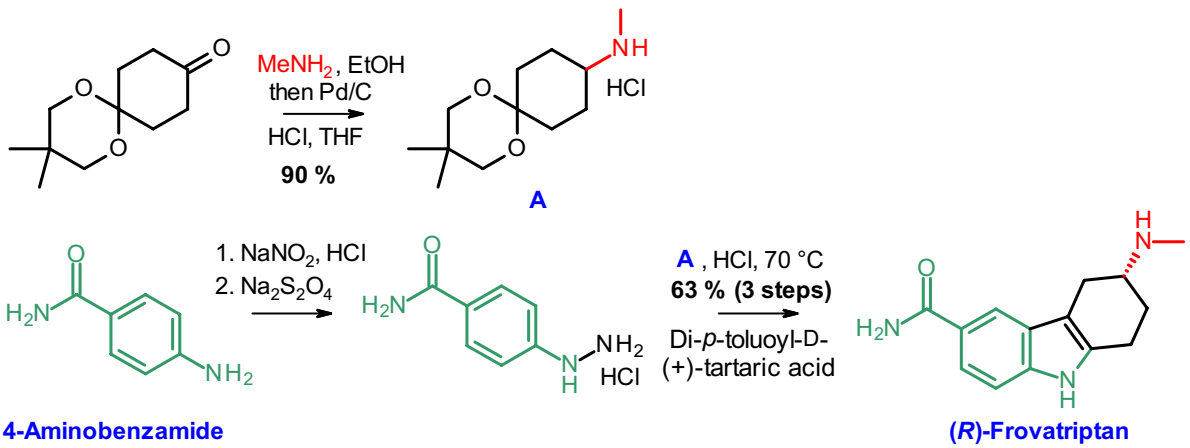
Scheme 20 Almotriptan synthesis by Almirall via intramolecular Heck reaction

reduction of the resulting ketone with lithium aluminum hydride, the indole is protected, and the vinyl sulfone introduced in position 5 by a Heck-type reaction. The final steps of the synthesis of enantiopure eletriptan comprise the hydrogenation of the double bond, deprotection, and salt formation (Scheme 23) [395].

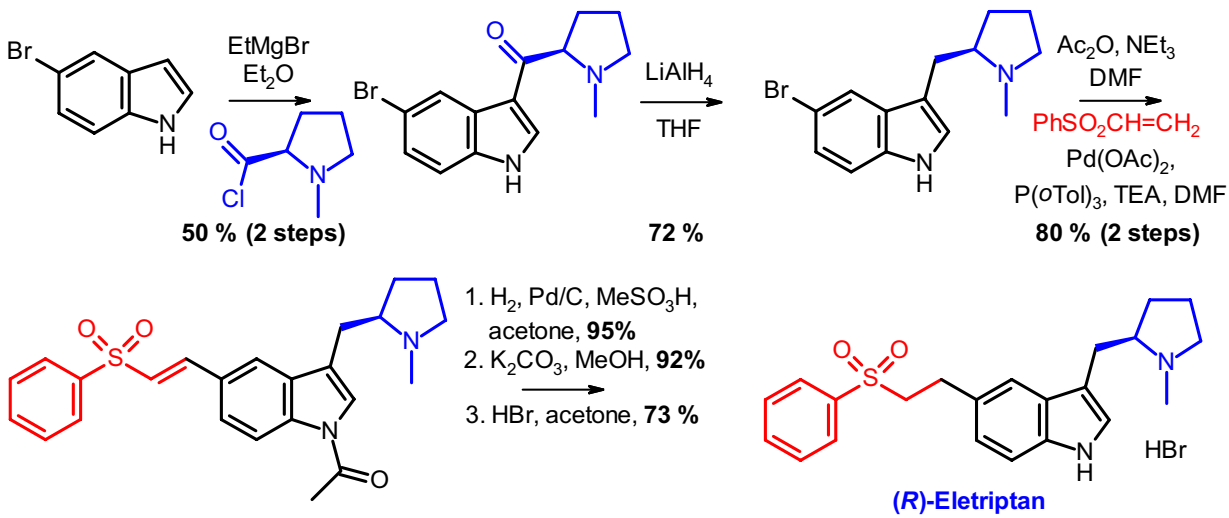
The process proved to be well developed and robust but suffered nevertheless from some shortcomings related to the use of the costly (*R*)-proline derivative, the lithium aluminum hydride reduction, generating large waste streams and the highly noxious and sensitizing reagent phenyl vinyl sulfone. These were sound reasons for Pfizer to search for a better synthesis.



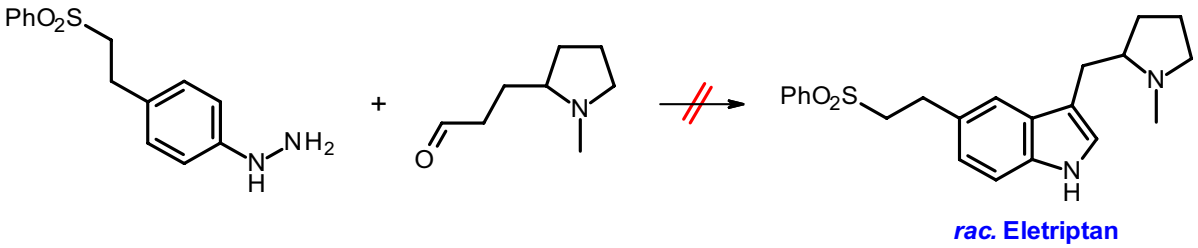
Scheme 21 Almotriptan synthesis by Almirall via Negishi reaction



Scheme 22 Frovatriptan synthesis by SmithKline Beecham



Scheme 23 Eletriptan synthesis by Pfizer

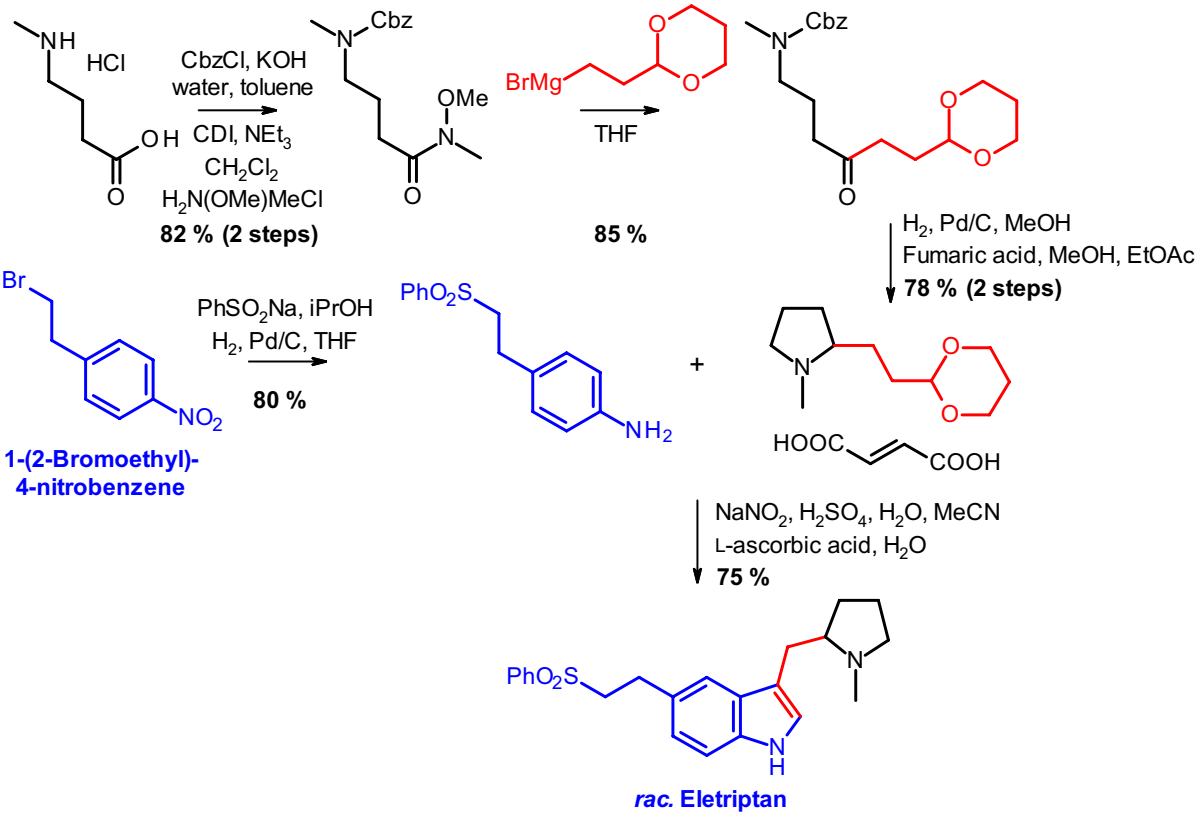


Scheme 24 The first attempts to synthesize eletriptan via Fischer indole chemistry failed

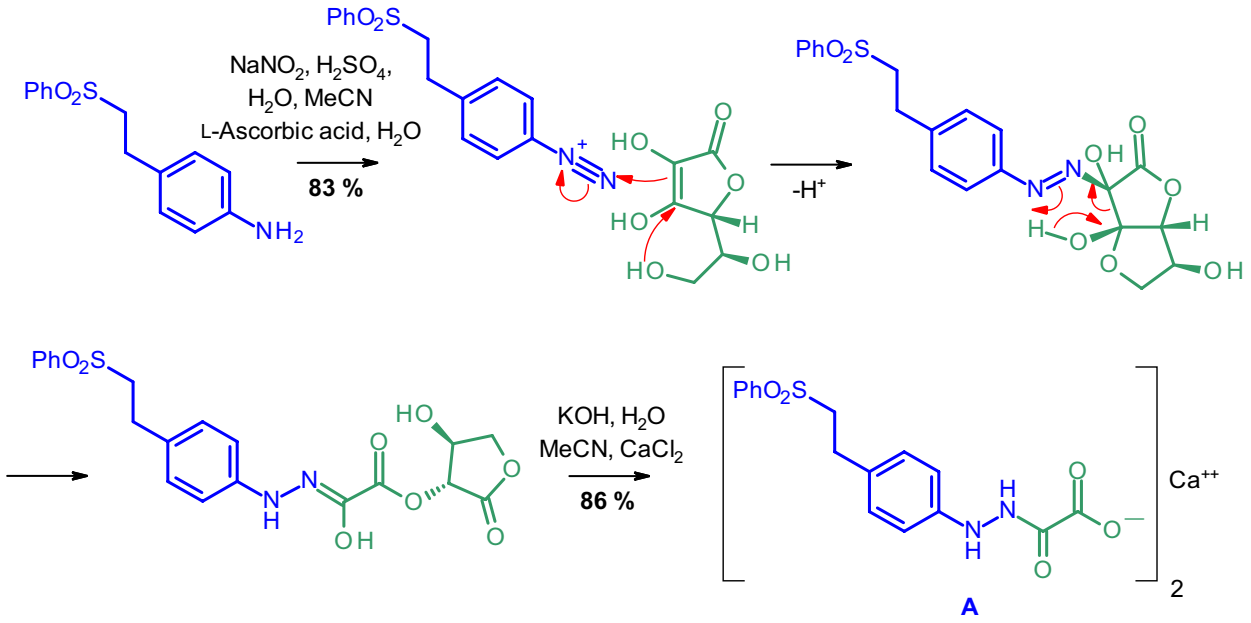
Like many other companies, they chose to center their new approach on Fischer indole chemistry, which was considered a well-researched and highly reliable conversion that should deliver eletriptan in a convergent and highly efficient way. Unexpectedly, however, the first attempts to synthesize eletriptan by this route failed, which was attributed to the instability of the hydrazine under the relatively harsh reaction conditions. Nevertheless, the problem could be solved soon (Scheme 24) [396, 397].

Starting from 4-methylaminobutyric acid, this is first converted into the *N*-protected Weinreb amide and subsequently into a ketone by a Grignard reaction. Hydrogenation furnishes the desired pyrrolidine, which is crystallized as a fumarate salt. The required aniline is obtained from 1-(2-bromoethyl)-4-nitrobenzene by nucleophilic substitution with sodium benzene sulfinate and hydrogenation of the nitro group. Most remarkable, however, is the ending of the synthesis. Pfizer managed to run the remaining steps, i.e., the diazotation of the aniline, the reduction of the diazonium salt, and the Fischer indole reaction under very mild conditions as a one-pot reaction, using ascorbic acid as reducing agent of the diazonium salt. Moreover, the use of ascorbic acid is advantageous, because vitamin C is inexpensive, nontoxic, and environmentally benign (Scheme 25).

The proposed mechanism for the diazonium salt reduction is an electrophilic attack of the diazonium group at position 3 of ascorbic acid, followed by a hetero-ene-like breakdown



Scheme 25 One-pot synthesis of eletriptan under mild conditions by Pfizer



Scheme 26 The proposed mechanism of the formation of a protected hydrazine **A**, an intermediate in Pfizer's eletriptan synthesis

process of the hemiacetal, leading to a protected hydrazine **A**, which can be isolated as calcium salt. In the subsequent indole synthesis, a certain analogy to the Japp–Klingemann reaction can be noticed (Scheme 26) [398].

The utilization of enantiopure pyrrolidine in this process, which can be readily obtained from the racemate by crystallization with dibenzoyl-L-tartaric acid, also provides access to enantiopure (*R*)-eletriptan (Scheme 27).

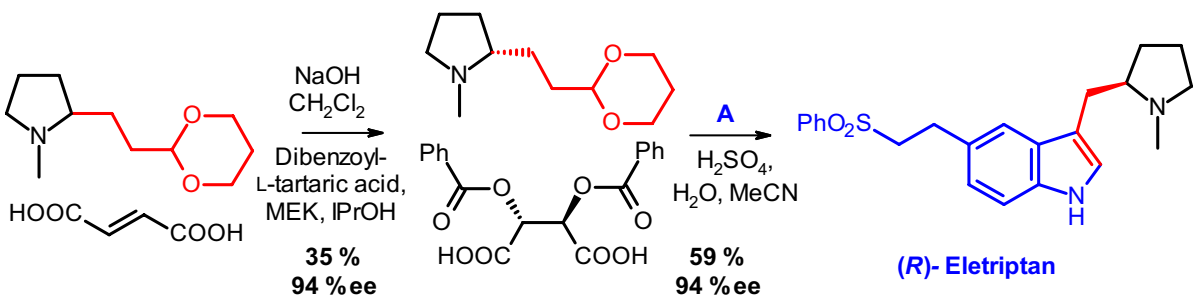
Infobox: Indole Syntheses

It is not only the triptans that carry the indole motif, but there is a whole range of other active pharmaceutical ingredients for very different indications that incorporate this heterocycle as well (Fig. 30) [399–401].

Indole itself was synthesized first by Adolf von Baeyer (1835–1917) by zinc dust distillation of oxindole in 1866 [402]. Three years later he proposed the correct molecular structure [403]. Since then, a wealth of named and unnamed syntheses of this important heterocycle were discovered [404, 405], of which a selection is compiled in the following table (Table 8).

Lasmiditan

The synthesis of lasmiditan by Eli Lilly is mainly based on three building blocks: piperidine-4-carboxylic acid, 2,6-dibromopyridine, and 2,4,6-trifluoro-benzoyl chloride [427, 428]. It starts with piperidine-4-carboxylic acid, which after reductive amination is reacted with dimethylamine to give the corresponding dimethylamide. In the following reaction steps, the two bromine substituents of 2,6-dibromopyridine are replaced by this amide and ammonia, respectively, prior to the final amide formation with 2,4,6-trifluoro benzoyl chloride, eventually leading



Scheme 27 Synthesis of enantiopure (*R*)-eletriptan by Pfizer

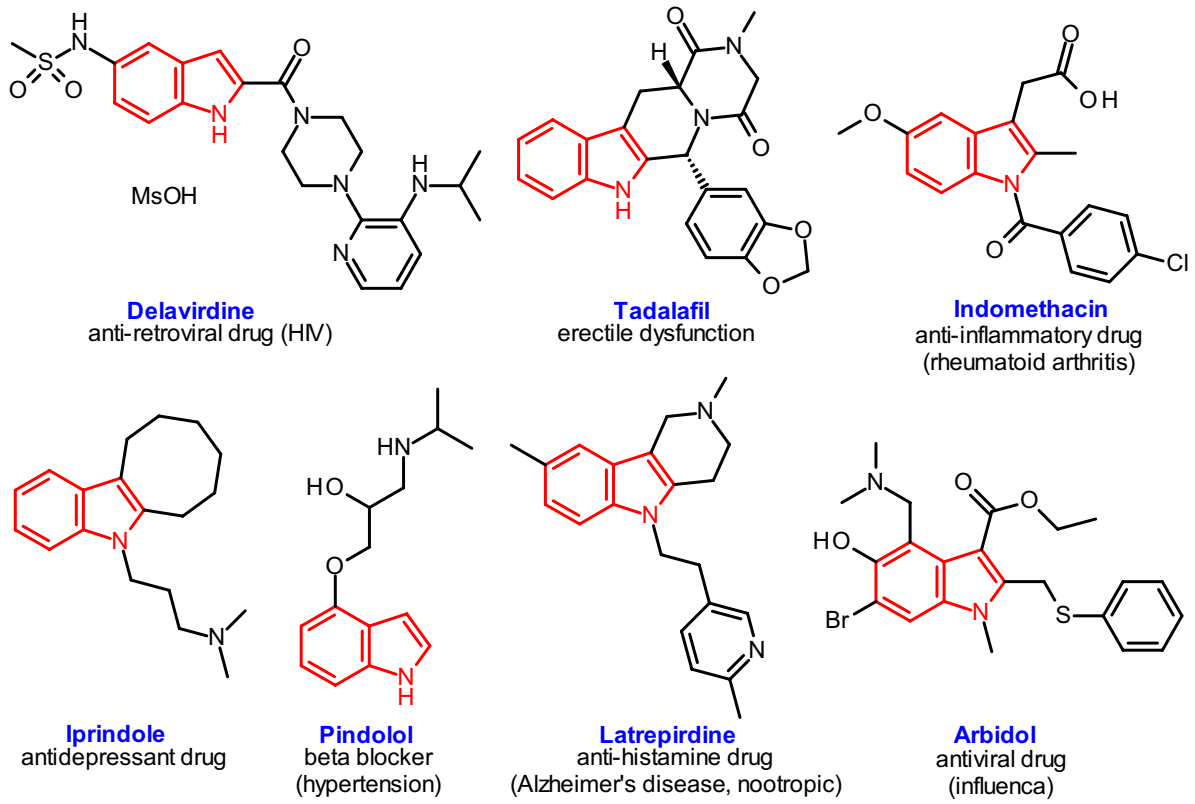


Fig. 30 A range of active pharmaceutical ingredients with an indole motif

Table 8 A selection of named indole syntheses classified according to the type of formation of the last bond (classification is according to 405). The methods are listed in chronological order of first publication, and the strategies are highlighted by the colored formula

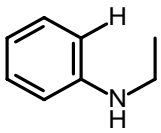
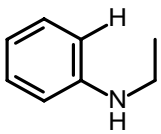
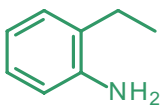
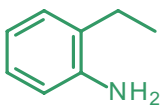
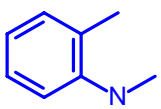
Named reaction	Published in	Strategy*	Classification
Fischer [406]	1883		1, Ar–H to C2
Japp–Klingemann [407]	1887		1, Ar–H to C2
Bischler–Möhlau [408] [409]	1881/1892		5, N to C1
Reissert [410]	1897		5, N to C1
Madelung [411]	1912		6, C1 to C2

Table 8 (continued)

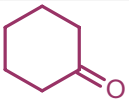
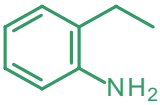
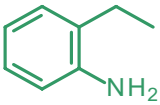
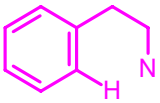
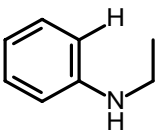
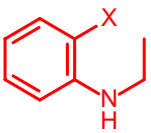
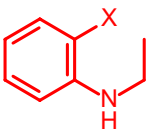
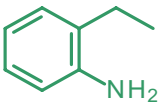
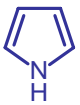
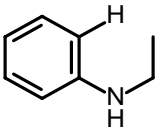
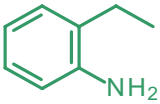
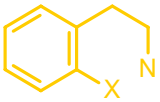
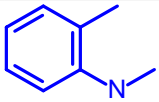
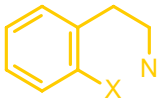
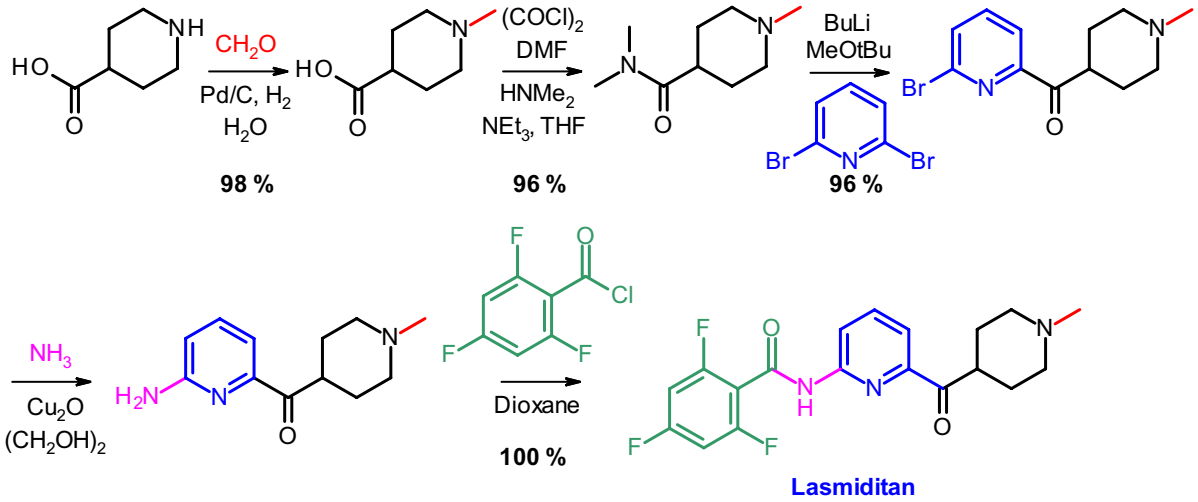
Named reaction	Published in	Strategy*	Classification
Nenitzescu [412]	1929		7, benzene ring from existing cyclohexane
Sundberg [413]	1969		5, N to C1
Batcho–Leimgruber [414]	1970		5, N to C1
Hemetsberger [415]	1970		3, Ar–H to N
Gassman [416]	1973		1, Ar–H to C2
Hegedus [417]	1976		2, Ar-X to C2
Mori [418]	1977		2, Ar-X to C2
Julia [419]	1986		5, N to C1
Kanematsu [420]	1986		9, both rings have been constructed
van Leusen [421]	1986		8, benzene ring onto pyrrole
Bartoli [422]	1989		1, Ar–H to C2
Larock [423]	1991		5, N to C1
Fukuyama [424]	1994		4, Ar-X to N

Table 8 (continued)

Named reaction	Published in	Strategy*	Classification
Fürstner [425]	1995		6, C1 to C2
Buchwald [426]	1999		4, Ar-X to N

*Regarding final bond to be formed



Scheme 28 Synthesis of lasmiditan by Eli Lilly

to lasmiditan in 90% overall yield. More recently other companies have claimed similar processes (Scheme 28) [429, 430]

Gepants

Ubrogepant

Once ubrogepant was identified as a new CGRP receptor antagonist and underwent further clinical trials, Merck also started process development for the manufacturing of this compound [431]. Retrosynthetic considerations indicated that ubrogepant should be readily prepared by amide formation from spiro acid **A** and lactam **B**; however, the real challenge would reside in the preparation of these building blocks. In case of the spiro acid **A** the task centered around the enantioselective spirocyclization potentially starting from two different key intermediates **C** or **D**, to establish the chiral all-carbon quaternary stereocenter.

Even more challenging might be the synthesis of lactam **B** with three chiral centers. The chemists at Merck decided to evaluate enzymatic dynamic kinetic transamination as a method setting the two stereocenters in position 5 and 6 and lactam formation simultaneously. After *N*-alkylation they expected performing a diastereomeric transformation of the stereocenter at position 3, thermodynamically driven by crystallization of an appropriate salt (Fig. 31).

In advance to the process development of spiro acid **A**, the chemists at Merck investigated the two alternative spirocyclization reactions starting from model substances **C** and **D** (R = Br). While cyclization of **D** under phase transfer conditions proceeded smoothly, they encountered substantial problems starting from **C**. This was a guiding result and shaped the way forward. Accordingly, 2,3-dibromo-5-chloropyridine was selected as the starting material. Regioselective transmetalation, followed by quenching with DMF and reduction provided an alcohol, which after protection as THP ether was subjected to a second formylation. Aldol condensation with 1 *N*-*t*-butyl-7-azaindol-2-one resulted in a highly crystalline, *Z*-configurated *α*,*β*-unsaturated ketone. In the following steps the alkene is reduced with sodium borohydride, the THP ether is cleaved, and the resulting alcohol is replaced by chlorine to set stage for enantioselective spirocyclization. In the course of screening a library of chiral phase transfer catalysts, a novel *N*,*N*′-doubly quaternized **PTC** was discovered serendipitously, which turned out as the most selective and potent catalyst of the collection [432]. At the climax of the synthesis of spiro

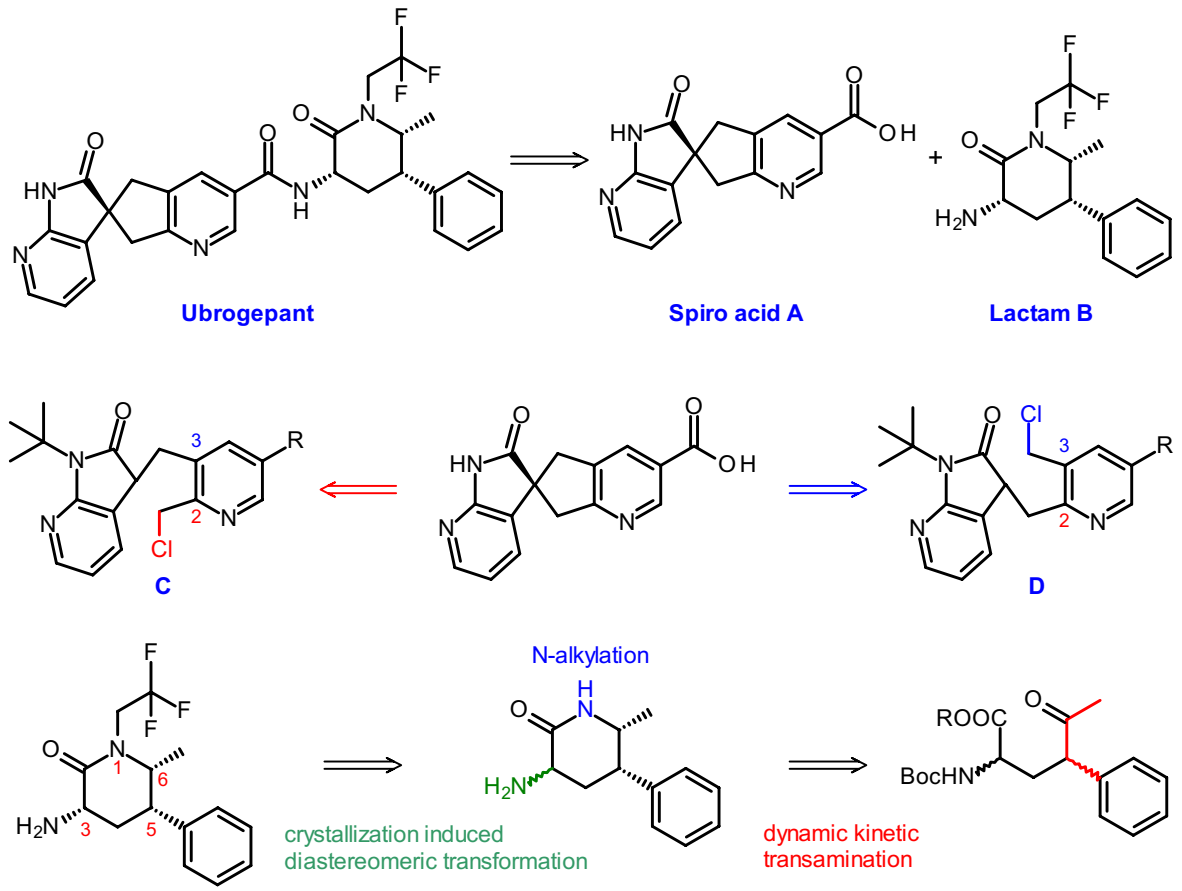


Fig. 31 Retrosynthetic considerations on the synthesis of ubrogepant

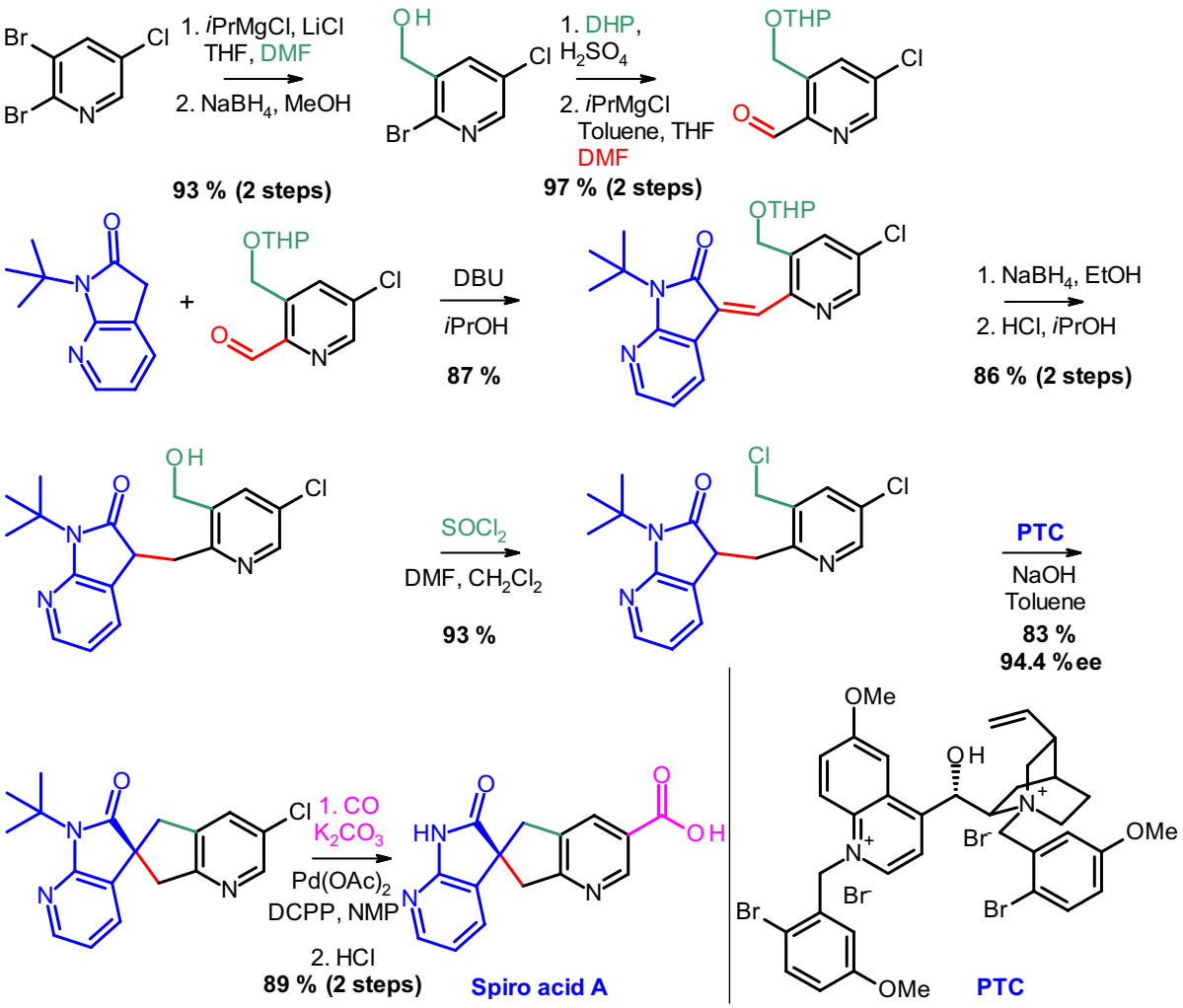
acid **A**, the desired compound was obtained by Pd-catalyzed carbonylation and acidic *N*-deprotection (Scheme 29).

Starting material for lactam **B** was *N*-Boc-serine isopropyl ester, which was first turned to the dehydroalanine derivative by mesylation and elimination, and then condensed with 4-bromophenylacetone [433]. Debromination by transfer hydrogenation with potassium formate provided the intermediate for enzymatic transamination. In the course of a screening program, a transaminase panel from Codexis was searched for activity, followed by protein engineering to enhance solvent tolerance and temperature stability of the enzymes. The outcome was a pyridoxyl phosphate-dependent transaminase, which provided the desired lactam in 92% yield, with > 99% ee at C-6 and a 61: 1 syn/anti ratio at C5/C6. The crystalline product turned out as a 3: 2 mixture of diastereomers, in respect to stereocenter 3, which, however, is prone to epimerization, especially under basic conditions, required for the following alkylation. The conditions, therefore, had to be chosen very carefully, due to a second alkylation at the Boc-protected amino group before complete consumption of the non-alkylated lactam. However, after Boc deprotection and salt formation, the amino lactam was recovered as 4: 1 mixture in favor to the desired diastereomer. In a salt screening *p*-toluic acid turned out superior for the 3,5-dichloro salicylaldehyde-catalyzed dynamic kinetic resolution of the diastereomers by crystallization to finally furnish the lactam **B** salt in 86% yield and 99.6% de (Scheme 30).

With both building blocks in hand on 100 kg scale, the stage was set for the final coupling reaction and the isolation of ubrogepant. The amide formation was performed in aqueous acetonitrile solution with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide as coupling agent and a catalytical amount of 2-hydroxypyridine *N*-oxide, without epimerization at position 3. Ubrogepant was finally isolated as trihydrate by crystallization from aqueous ethanol with 95% yield and excellent optical and chemical purities (Scheme 31).

Rimegepant

Bristol-Myers Squibb's CGRP antagonist rimegepant can be split retrosynthetically at the central carbamate into a 1,3,7-triazaindan-2-one derivative and a remarkable cycloheptanol with three stereocenters, and indeed, the active ingredient is synthesized from these building blocks in a highly convergent approach (Fig. 32).



Scheme 29 Synthesis of spiro acid **A** of ubrogepant

While a few distinct routes towards the triazaindanone were already known from literature, BMS developed two complementary syntheses, mainly to mitigate raw material costs and to increase reaction efficiency [434].

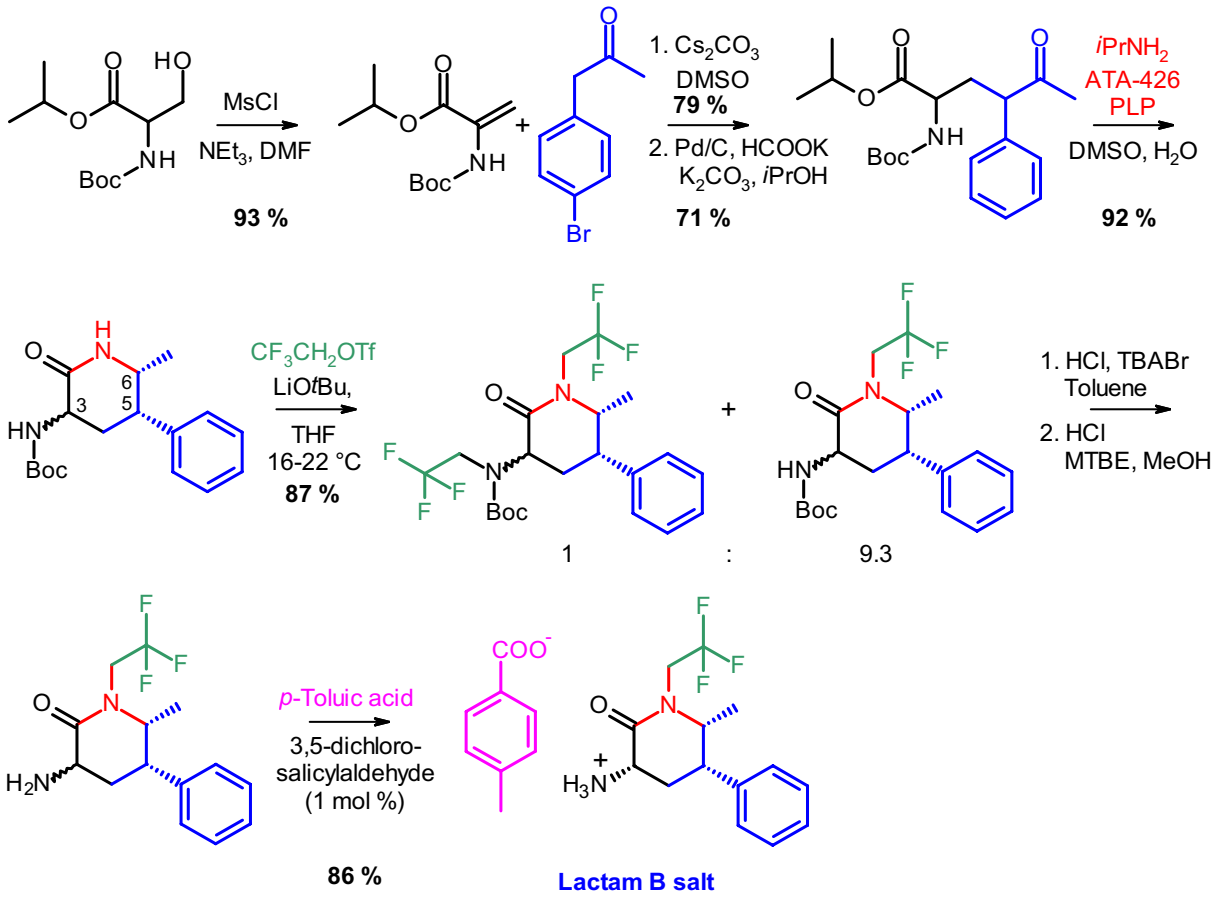
2-Chloro-3-aminopyridine, a readily available and inexpensive bulk chemical, can be subjected to reductive amination with 1-Boc-4-piperidone and sodium triacetoxy boranate. As it turned out, a prerequisite for high selectivity and yield is the use of trifluoroacetic acid, which ensures complete conversion of the starting material with minimal direct reduction of the piperidone. Subsequently, the chloro substituent is replaced by an amino group by Pd-catalyzed amination. Benzophenone imine was used for its bulkiness as an ammonia surrogate, to minimize formation of a byproduct, followed by addition of citric acid, to cleave the resulting *N*-hetarylated benzophenone imine without affecting the Boc protecting group.

The same intermediate can be obtained by reductive amination starting from 2,3-diaminopyridine. Once again, the use of trifluoroacetic acid proved advantageous in minimizing double alkylation.

Finally, the desired building block for rimegepant was obtained, by reacting the intermediate with carbonyl diimidazole and removal of the Boc protecting group with ethanolic HCl (Scheme 32).

The starting material for the second building block, the cycloheptanol derivative, can be synthesized via classical Dieckmann condensation of dimethyl pyridine-2,3-dicarboxylate and dimethyl glutarate followed by hydrolysis and decarboxylation (Scheme 33) [435].

For regio- and enantioselective reduction of 7,8-dihydro-6*H*-cyclohepta[b]-pyridine-5,9-dione, the chemists at BMS, first considered an enzymatic approach, of course; however, they later found superior regio- and enantioselectivity with Rh(*R*-binapine)(COD)BF_4, a highly active transition metal



Scheme 30 Synthesis of lactam **B** of ubrogepant

catalyst [436]. After protection of the alcohol with the bulky triisopropylsilyl group, the next steps targeted Pd-catalyzed *α*-arylation of the ketone. Being fully aware that stereoselectivity of the C–C-bond formation would be limited, there was some hope taking advantage of the readily epimerizable nature of the newly formed stereocenter. Under optimized conditions the *α*-arylation provided a 12 : 1 mixture of diastereomers. Subsequent epimerization with DBU led to the desired product in 57% yield with a ratio of diastereomers of 40: 1.

After diastereoselective reduction of the ketone using lithium tri-*t*-butoxyaluminum hydride, a double inversion strategy was used to turn the resulting alcohol into the corresponding azide preserving the absolute configuration [437].

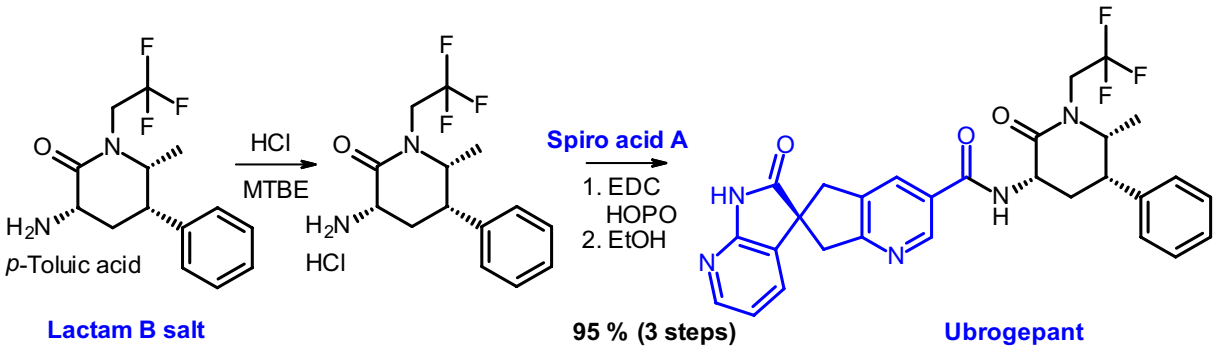
Removal of the silyl protecting group set the stage for the coupling reaction with the carbamate of the triazaindanone with sodium hexamethyldisilazide at −15 °C and rimegepant is obtained finally by reduction of the azide with trimethylphosphane (Scheme 34) [438, 439].

Atogepant

Atogepant, also discovered at Merck, is a close analog of ubrogepant, which has just three additional fluoro substituents on lactam B. Accordingly, the technical synthesis might be the same or at least very similar. Notwithstanding this, another approach will be briefly considered below (Fig. 33) [440, 441].

Here, starting material for the spiro acid **A** is pyridine-2,3-dicarboxylic acid, which after esterification is brominated at position 5. Reduction of both methyl esters and mesylation provides the intermediate ready for spirocyclization with 2-(trimethylsilyl)ethoxymethyl-protected azaindolone. The spiro compound is subjected to carbonylation with subsequent esterification. Following separation of the enantiomers by chiral column chromatography, the desired (*S*)-enantiomer is then subjected to *N*-deprotection with HCl and hydrolysis of the ester (Scheme 35).

The lactam **B′** can be synthesized starting from 5-bromo-6-methylpyridin-2-ol, which after *N*-alkylation with



Scheme 31 Synthesis of ubrogepant

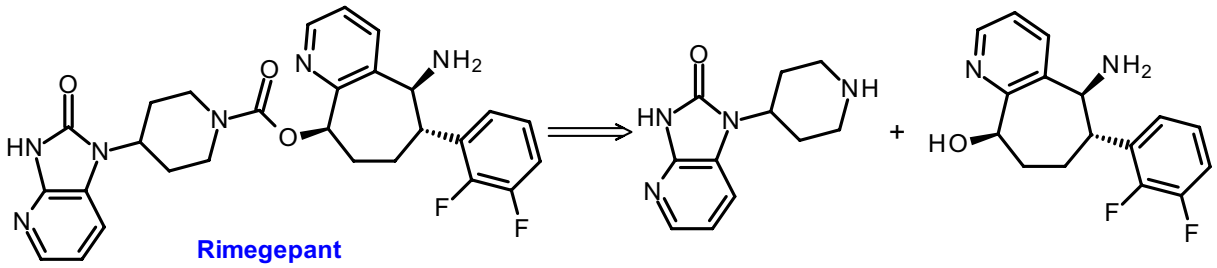
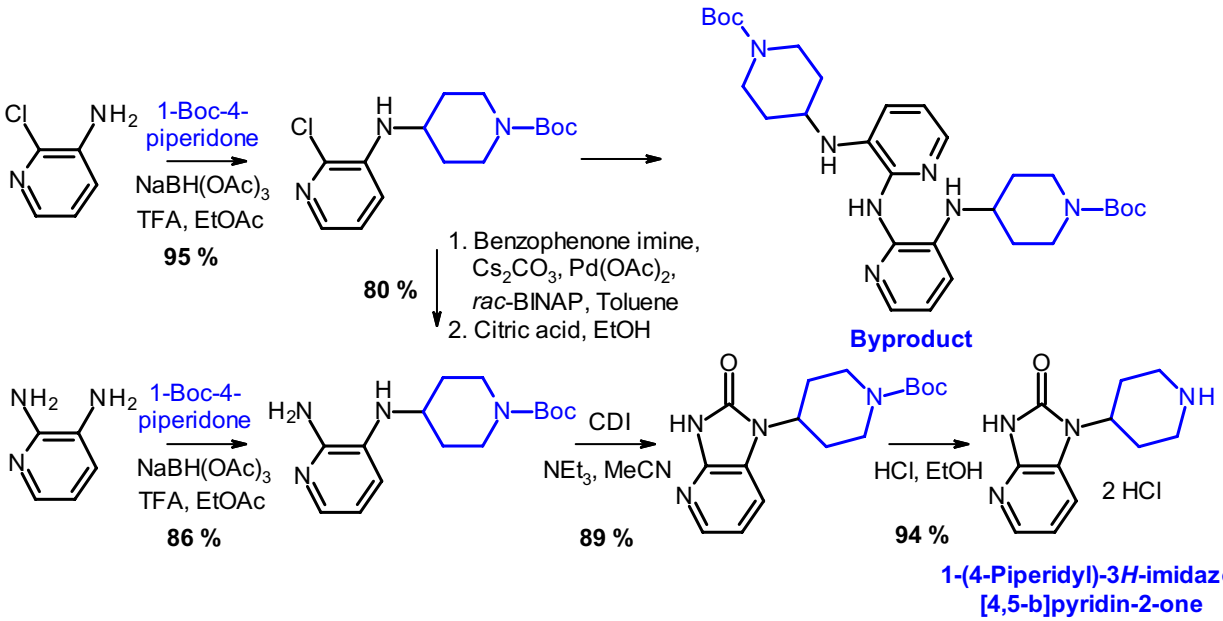
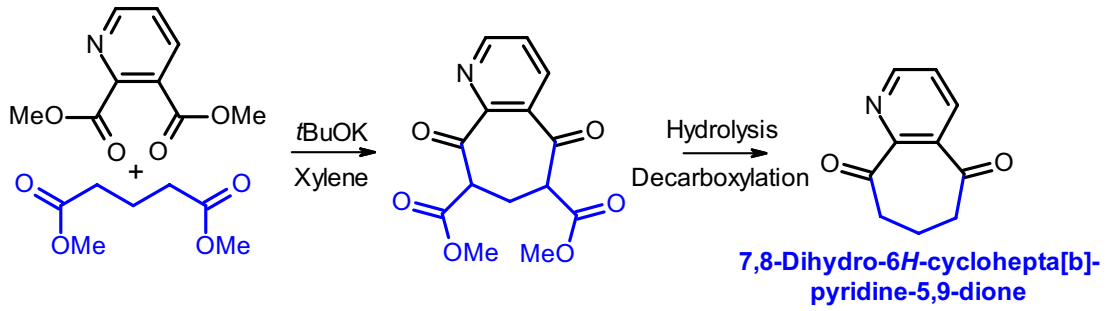


Fig. 32 Retrosynthetic considerations on the synthesis of rimegepant

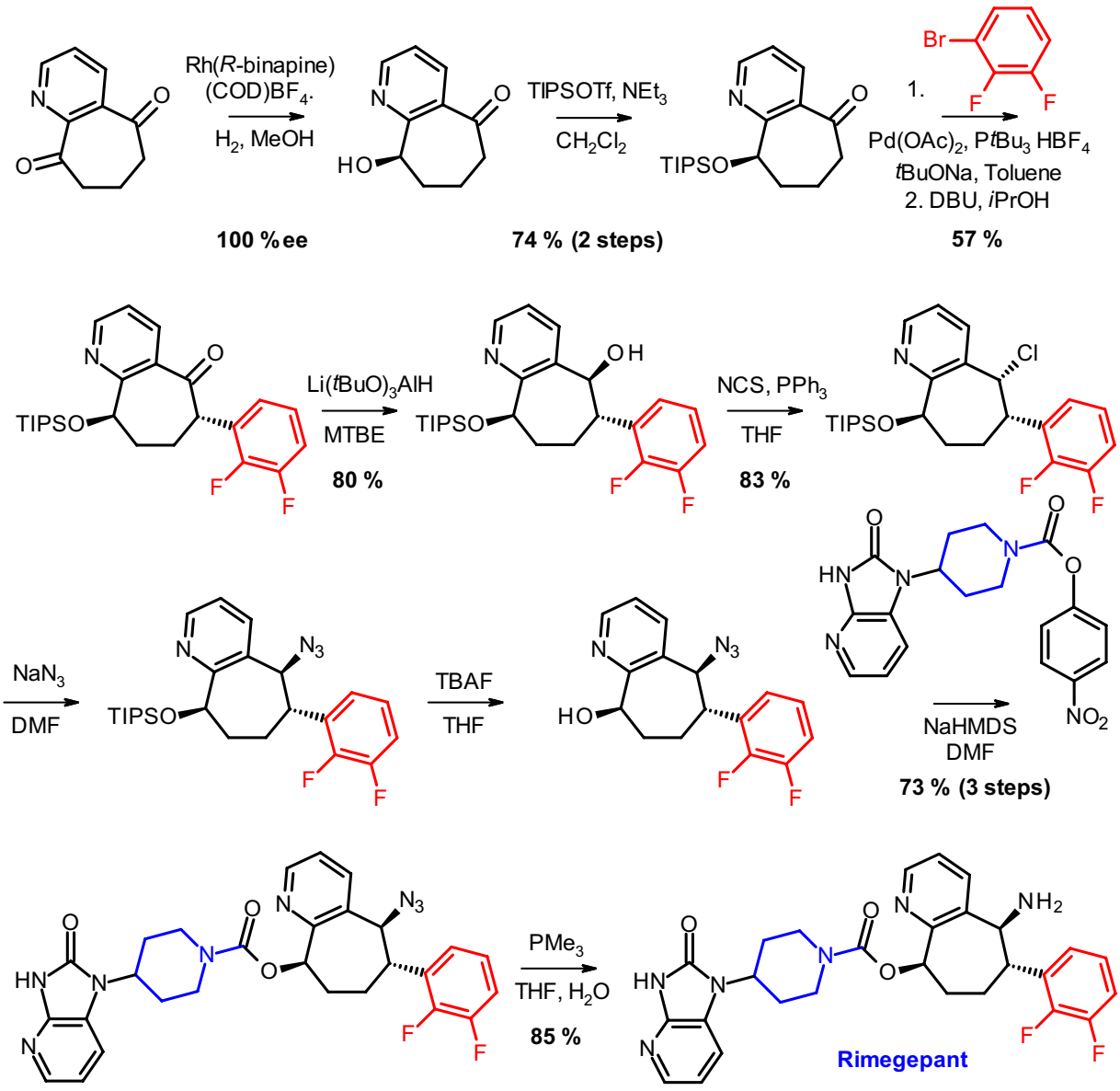
2,2,2-trifluoroethyl triflate is subjected to a Suzuki coupling to introduce the trifluorophenyl rest and subsequently to hydrogenation. The resulting lactam is then treated with sodium hexamethyldisilazide and 2,4,6-triisopropylbenzenesulfonyl azide for electrophilic transfer of an azide group. Simultaneous hydrogenation and Boc protection provide a mixture of stereoisomers, which can be separated by chiral supercritical fluid chromatography (SFC). The desired enantiomer is deprotected and finally coupled with the spiro acid **A** to give atogepant (Scheme 36).



Scheme 32 Synthesis of 1-(4-piperidyl)-3*H*-imidazo[4,5-b]pyridin-2-one



Scheme 33 Synthesis of 7,8-dihydro-6*H*-cyclohepta[b]-pyridine-5,9-dione



Scheme 34 Synthesis of rimegepant

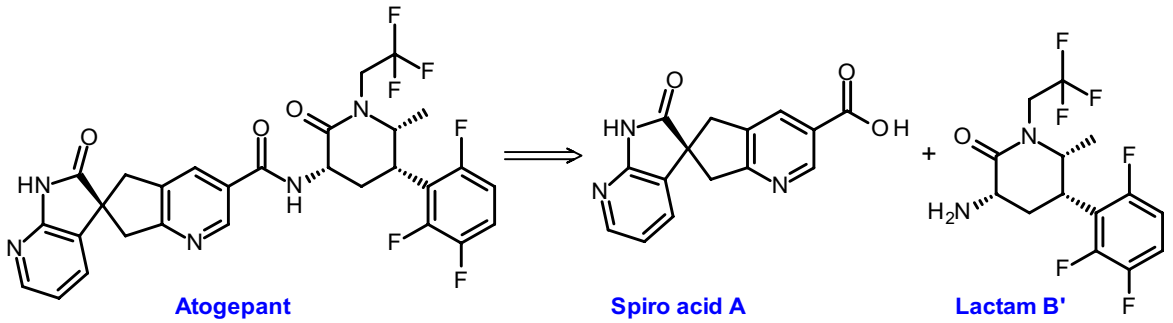
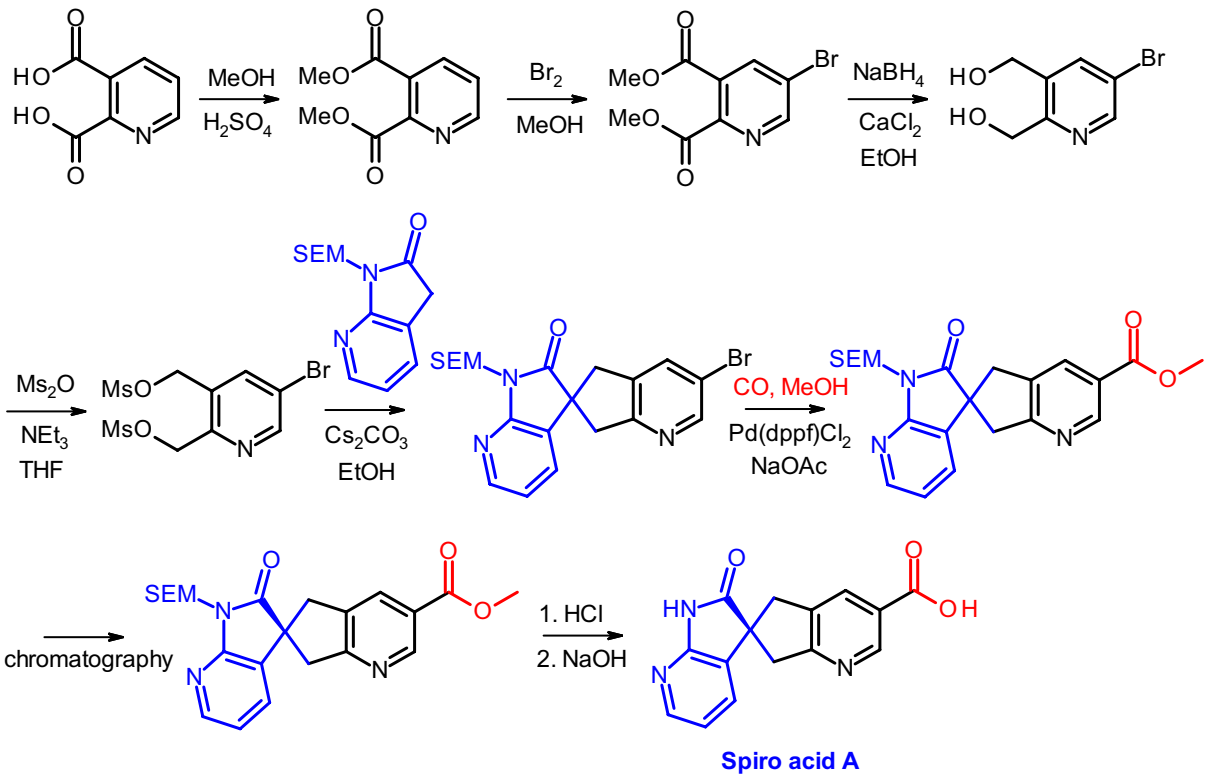
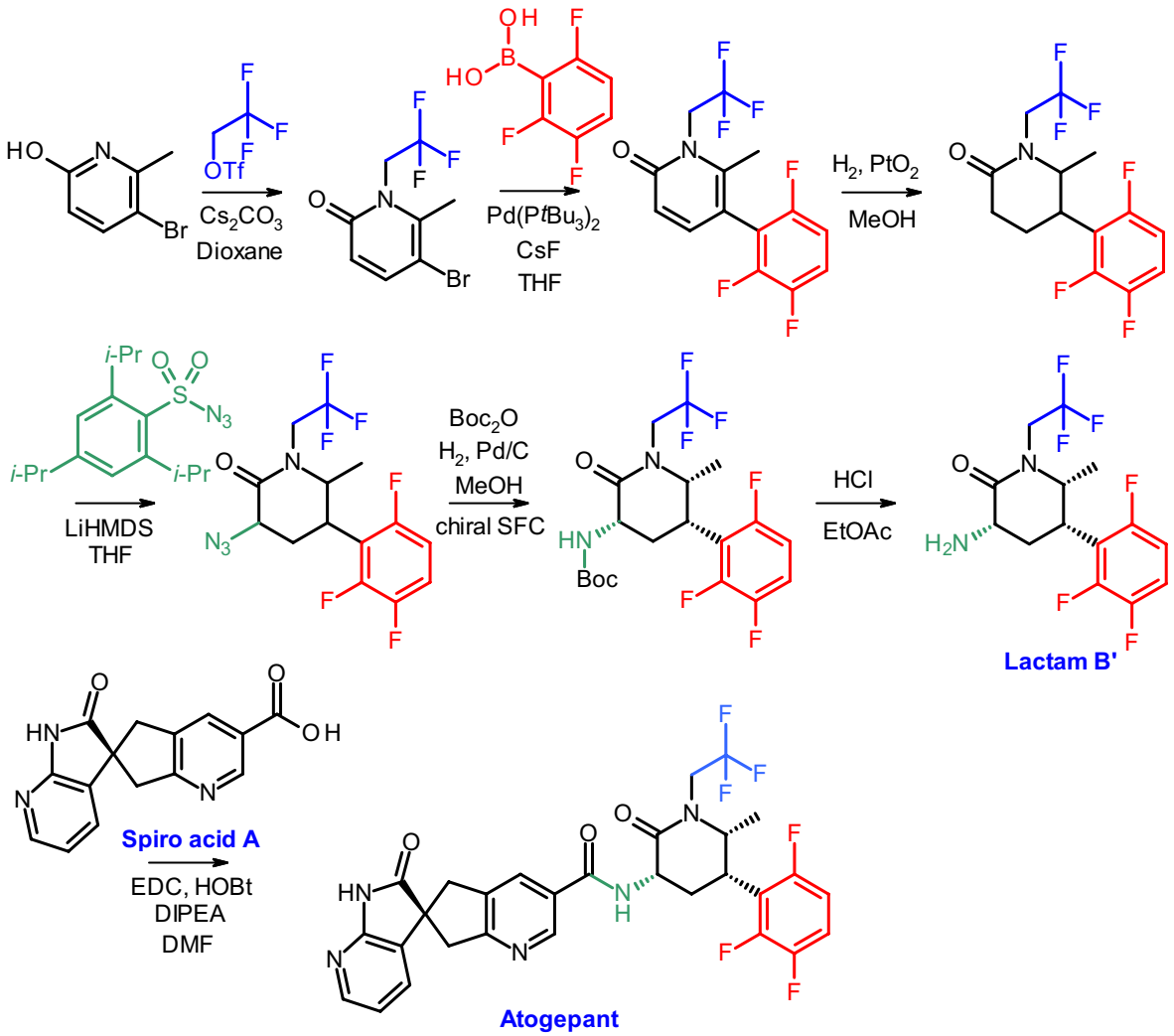


Fig. 33 Retrosynthetic considerations on the synthesis of atogepant



Scheme 35 Synthesis of spiro acid **A** of atogepant



Scheme 36 Synthesis of atogepant

Zavegepant

A second CGRP receptor antagonist discovered and developed at Bristol-Myers Squibb is zavegepant. As shown in the retrosynthetic analysis, the molecule consists of three fragments, which are connected via amide bonds. Since the piperazine building block (blue) is commercially available, the process development focused on the synthesis of the quinolone (red), the enantiopure amino acid (black), and of course the assembly of the final product (Fig. 34) [442].

The first step towards the quinolone is a Horner–Wadsworth–Emmons reaction of *N*-Boc-4-piperidone with trimethylphosphonoacetate. The α,β-unsaturated ester is hydrogenated and subjected to an aldol reaction with *o*-nitro benzaldehyde. Reduction of the nitro group with iron in acetic acid, cyclization, and elimination of water affords 3-(4-piperidyl)-1*H*-quinolin-2-one (Scheme 37) [443].

For the synthesis of the chiral amino acid of zavegepant, the discovery chemists at BMS borrowed conceptually from the classical synthesis of Monsanto's Parkinson's drug (L)-3,4-dihydroxyphenylalanine by rhodium-catalyzed enantioselective hydrogenation [444]. They synthesized the precursor, the amino cinnamic acid, by Heck cross coupling from an appropriately decorated aryl iodide and amino acrylate (Fig. 35).

Like the synthesis of ubrogepant, the aminoacrylate is available from serine methyl ester by *N*-protection under Schotten–Baumann conditions, mesylation, and elimination. When it became apparent that the isolated acrylate tended to polymerize, isolation was abandoned, and the substance was only handled in solution (Scheme 38).

In the original route of discovery chemistry at BMS 2,6-dimethylaniline was iodated using iodine monochloride. After the Heck reaction, enantioselective hydrogenation was performed applying an enantiopure Et-DuPHOS-Rh catalyst

to obtain the corresponding amino acid in excellent selectivity and yield. The indazole was established by nitrosation of one of the methyl groups with isoamyl nitrite and spontaneous dehydration. Finally, the Cbz-protecting group was removed by hydrogenation (Scheme 39).

The process development chemists at BMS adopted this route in their first approach, but addressed several significant issues prior to scale-up. One of these problems was the color of the iodoaniline, which persisted into the product of the Heck reaction. The issue was solved by replacing ICl with commercially available benzyltrimethylammonium dichloroiodate, which afforded the aniline hydrochloride salt as an off-white solid. The Heck reaction worked smoothly, and the product was purified by crystallization of the mesylate. However, in the following enantioselective hydrogenation with the Et-DuPHOS-Rh catalyst, the reaction rate was low and limited catalyst stability necessitated high catalyst loading. Therefore, it was replaced with a more active and robust Et-FerroTANE-Rh catalyst. While the nitrosation went without a hitch, deprotection of the Cbz group by hydrogenolysis unexpectedly became a source of considerable trouble. Under the bottom line it was related to the inevitable liberation of carbon dioxide, which formed a carbonate or carbamate precipitate of the amino ester, preventing the clean separation of the solid Pd/C catalyst. The problem was ultimately solved by purging the reaction mixture after hydrogenation with nitrogen and HCl salt formation in course of the work-up (Scheme 40).

Aside from this enantioselective, transition metal catalysis-based approach, the development chemists investigated also a conceptional different enzymatic synthesis. It was expected that, unlike the metal catalyst hydrogenation, the indazole functionality should be compatible with the biocatalytic transformation. That would allow the preparation of the heterocycle right at the beginning of the synthesis, while the introduction of chirality could be shifted to the penultimate step. Thus, the primary goal of the chemical synthesis was an α-keto carboxylic acid, which subsequently would be converted into the (*R*)-amino acid by a D-transaminase.

The synthesis commences with commercially available 4-bromo-2,6-dimethylaniline, which is reacted with *t*-butyl nitrite similar to previous synthesis to give rise of the corresponding indazole. In the following step, the indazole is deprotonated with *n*BuLi prior to the lithium/bromine exchange with *sec*BuLi, to avoid debromination. By DMF quench a carbaldehyde is obtained, which was next subjected to an Erlenmeyer–Plöchl reaction with hippuric acid. Methanolysis of the azlactone was performed with a catalytic amount of NaOMe in methanol. The hydrolysis with aqueous HCl provided the substrate for the enzymatic step.

For the first transamination runs a commercially available D-transaminase from Codexis and racemic alanine as nitrogen source was used. Later BMS discovered a D-transaminase from the soil bacterium *Bacillus thuringiensis*, which proved to be much more robust and active.

Finally, the amino acid should be turned into the methyl ester, which was hampered by concomitant methylation of the indazole. Only very careful tuning of the reaction conditions with respect to the acetyl chloride equivalents used, the concentration and the temperature applied, and finally the purification of the product by crystallization brought the hoped-for success (Scheme 41).

However, the most challenging part of the synthesis was still ahead, the assembly of zavegepant from the different building blocks by two coupling steps. In particular, the coupling of the quinolone and the amino ester with carbonyl diimidazole proved sensitive to reaction conditions and stoichiometry. It took much effort and diligence to minimize

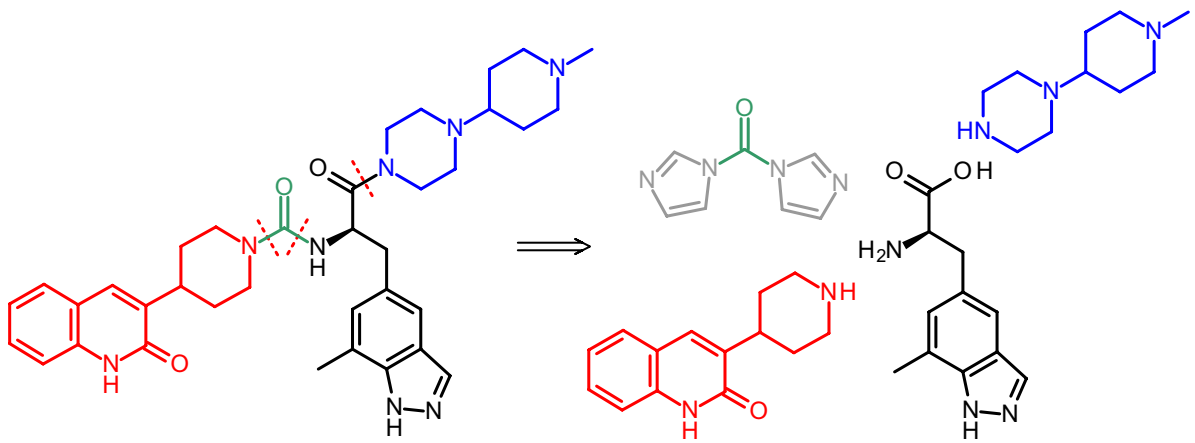
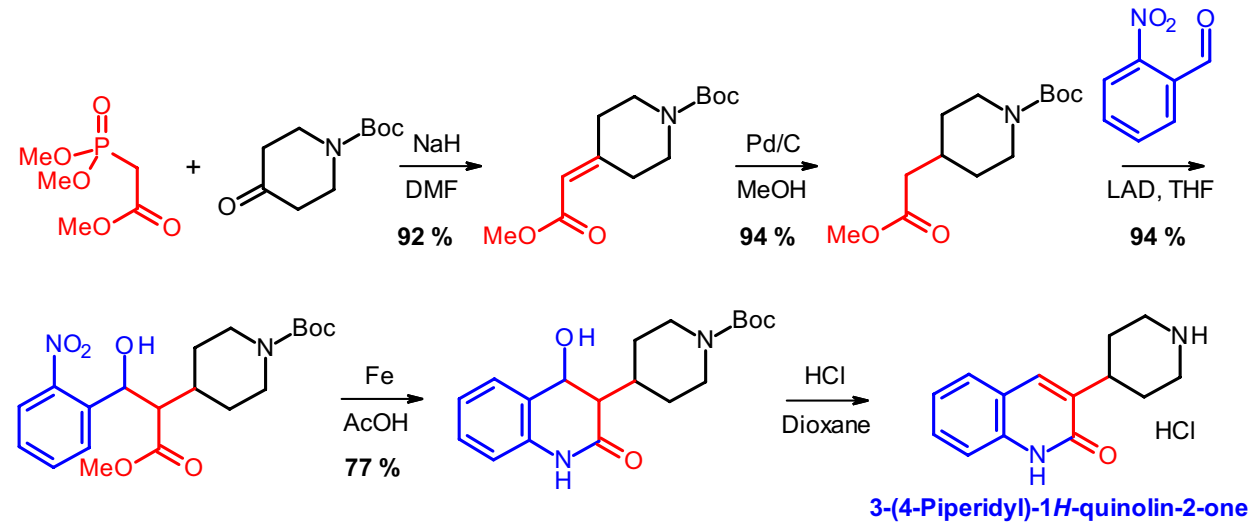


Fig. 34 Retrosynthetic considerations on the synthesis of zavegepant



Scheme 37 Synthesis of 3-(4-piperidyl)-1*H*-quinolin-2-one

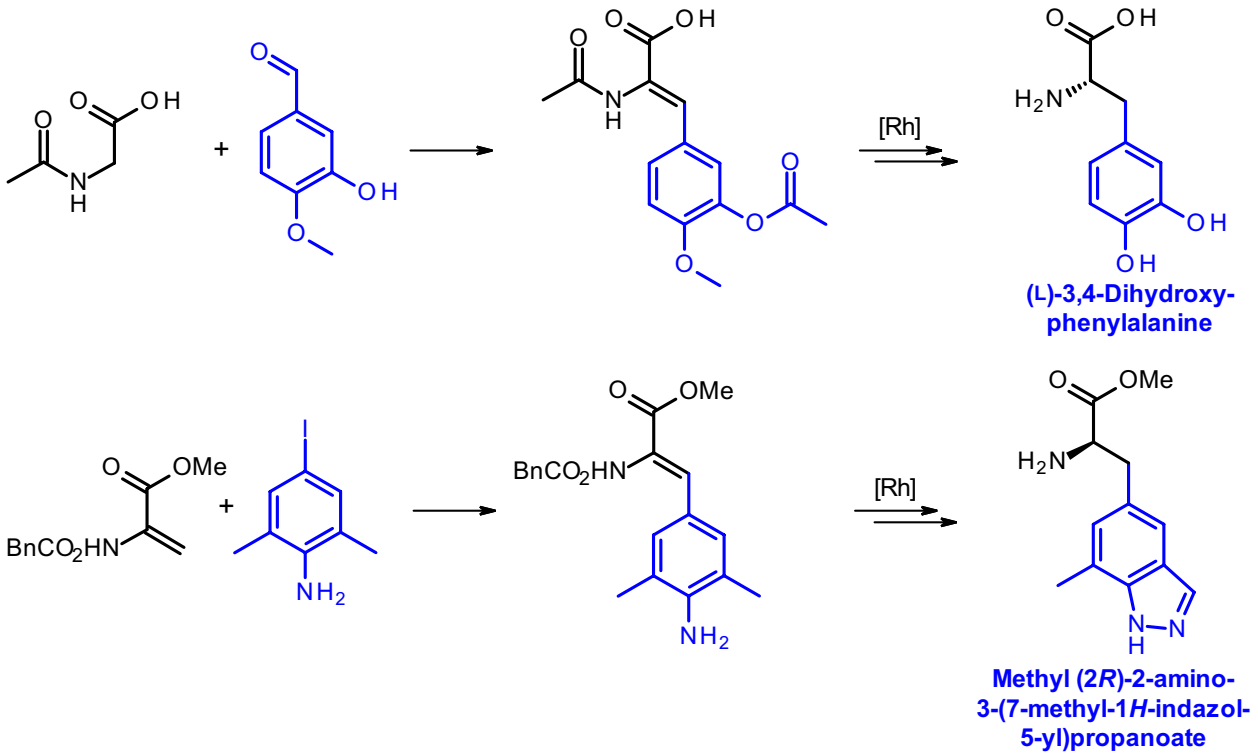
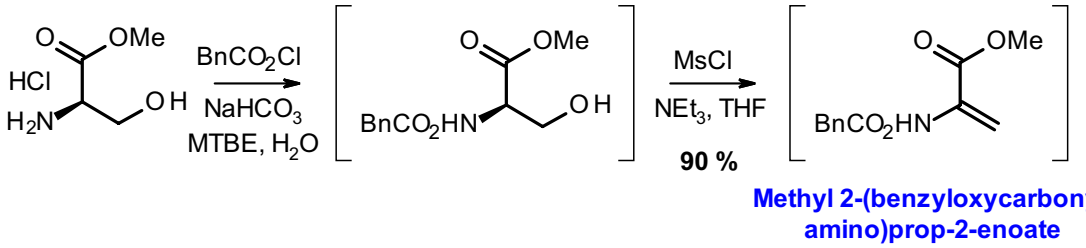
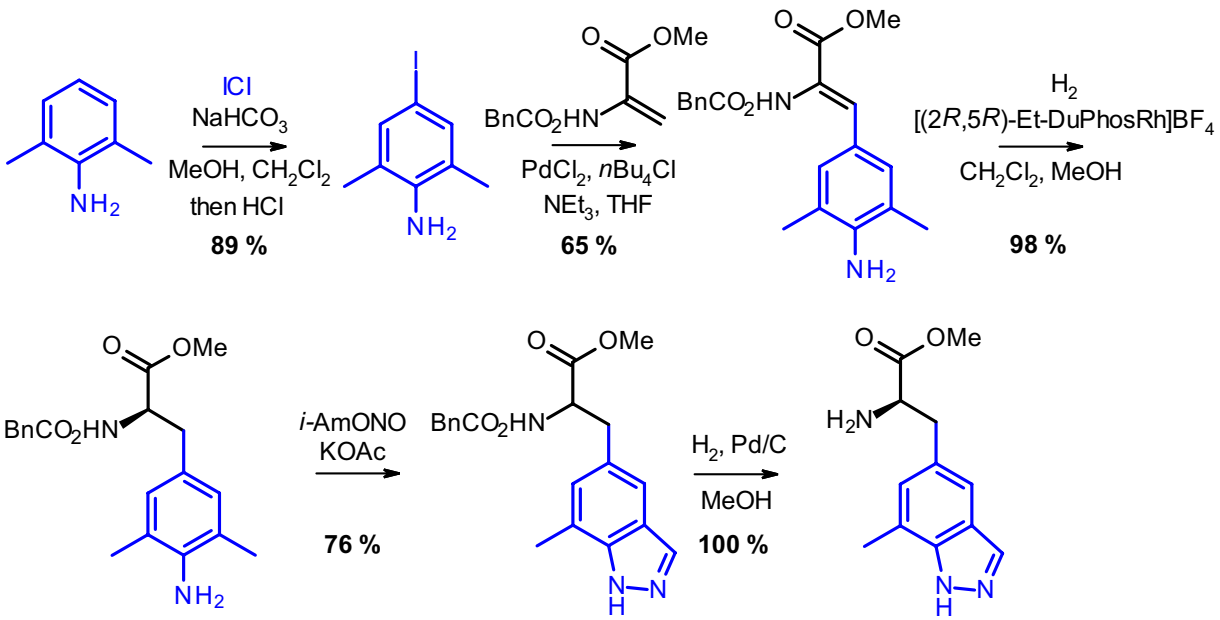


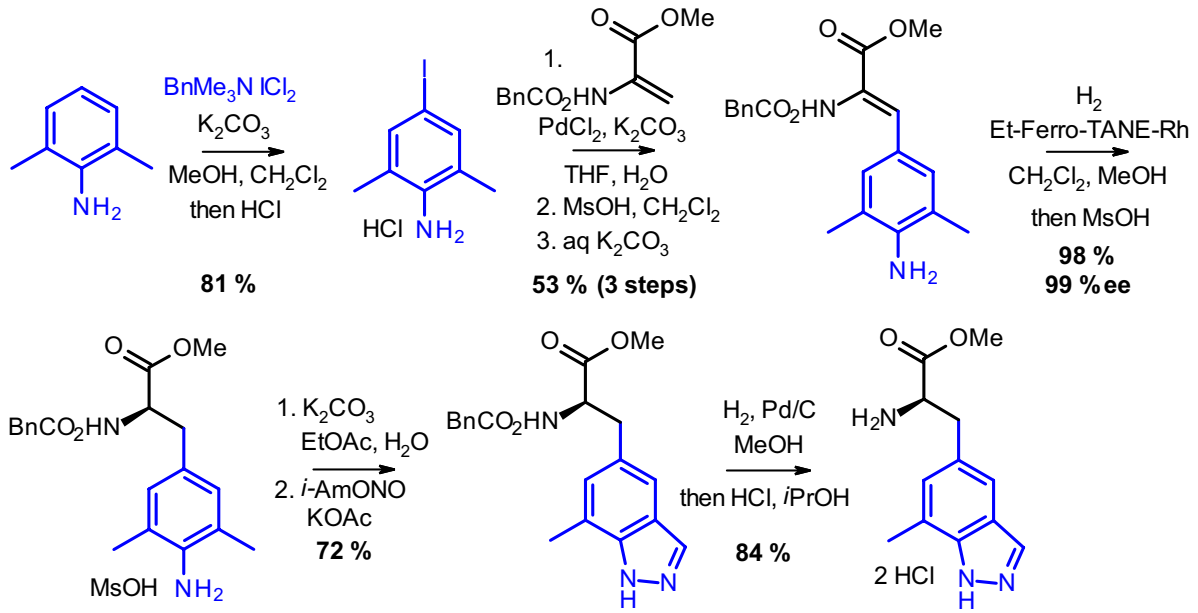
Fig. 35 Retrosynthetic considerations on the synthesis of methyl (2*R*)-2-amino-3-(7-methyl-1*H*-indazol-5-yl)propanoate



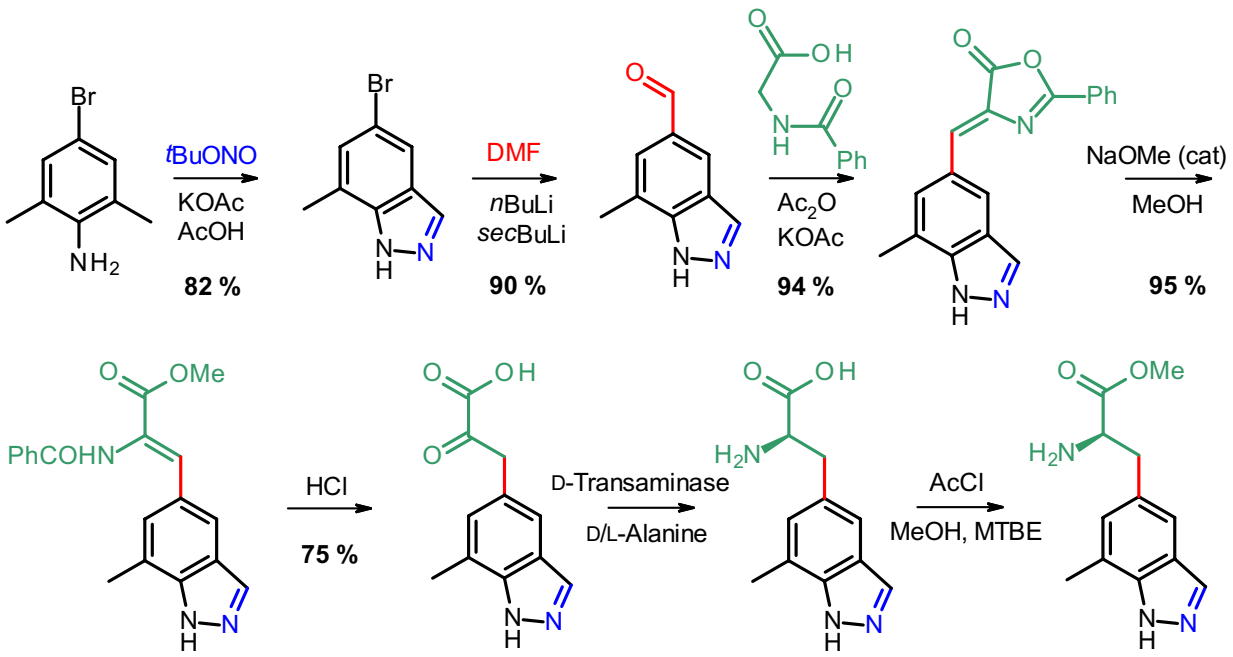
Scheme 38 Synthesis of methyl 2-(benzyloxycarbonylamino)prop-2-enoate



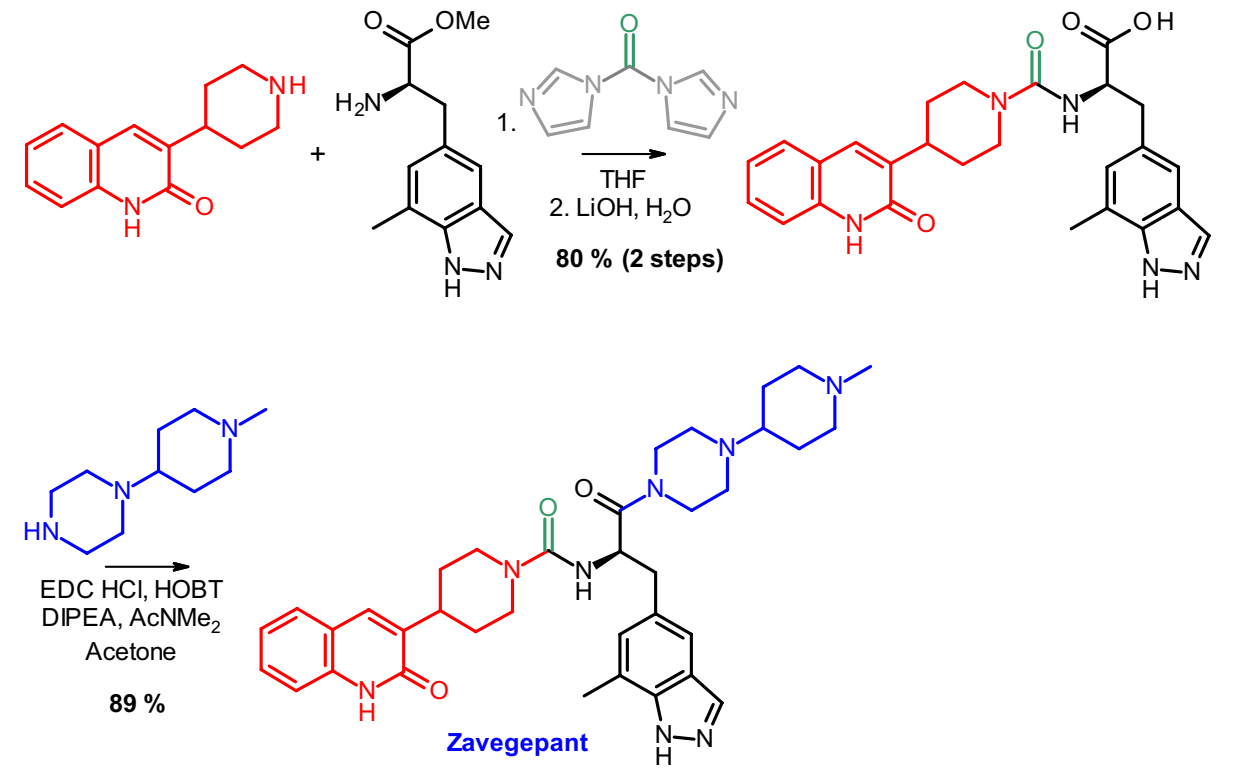
Scheme 39 Synthesis of methyl (2*R*)-2-amino-3-(7-methyl-1*H*-indazol-5-yl)propanoate via enantioselective hydrogenation



Scheme 40 Improved synthesis of methyl (2*R*)-2-amino-3-(7-methyl-1*H*-indazol-5-yl)propanoate via enantioselective hydrogenation



Scheme 41 Synthesis of methyl (2*R*)-2-amino-3-(7-methyl-1*H*-indazol-5-yl)propanoate via transamination



Scheme 42 Synthesis of zavegepant

the side-products, which mainly resulted by inadvertent additional coupling reactions. Fortunately, after hydrolysis of the methyl ester, the final amide formation with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide furnished the desired product in excellent yield and perfect enantiopurity (Scheme 42).

Migraine and natural medicine

In addition to the above-mentioned migraine treatment options based on synthetic and FDA-approved drugs, there is a plethora of remedies derived from herbal medicines as well as traditional and empirical medicine and dietary supplements. The following list of therapies is far from comprehensive but merely highlights a few examples for which there is a range of scientific studies available [445].

Butterbur root extract

Butterbur (*Petasites hybridus*) leaves have been used over centuries in Austrian and Czech traditional medicine for the treatment of infections, fever, flu, colds, hay fever, and allergies (Fig. 36) [446]. The extracts of its rhizomes have also been used for the prophylactic treatment of migraine for many years. In a recent study, it had been shown that pre-incubation of rat and mouse cranial dura mater and trigeminal ganglion neurons with the extract's active ingredients petasin and isopetasin reduced mustard oil- and capsaicin-evoked CGRP release compared with vehicle in an approximately dose-dependent manner [447]. Furthermore, in ex vivo models, the sesquiterpenes petasin and isopetasin have also been found to affect transient receptor potential ankyrin type 1 (TRPA1) and transient receptor potential vanilloid type 1 (TRPV1) receptor channels, leading to a reduction in CGRP levels. However, it remains

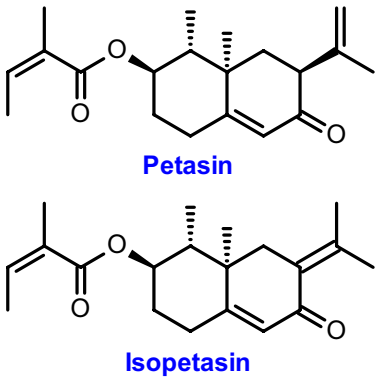


Fig. 36 The English name "butterbur" of *Petasites hybridus* may have derived from the use of its giant leaves to wrap butter, before the first refrigerators became commercially available more than a century ago. Other names for the herb are bog rhubarb, Devil's hat, and pestilence wort (© Viva La Ren)

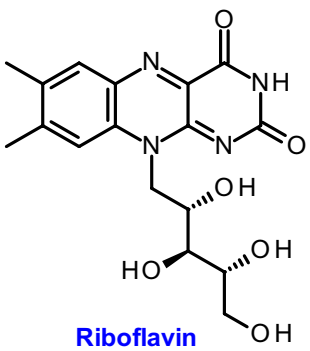


Fig. 37 The first syntheses of riboflavin derived from Richard Kuhn (1900–1967) at the Kaiser-Wilhelm-Institut für medizinische Forschung in Heidelberg and Paul Karrer (1889–1971) at the University of Zurich [449]. [450, 451]

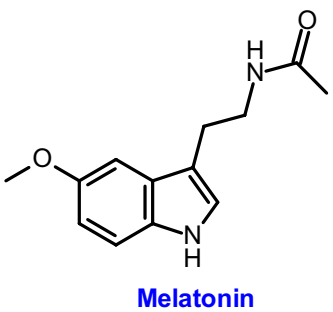
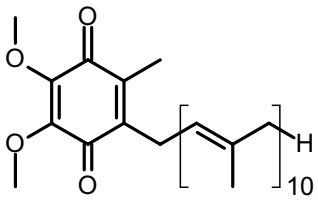


Fig. 38 Melatonin was discovered and named in 1958 by the US dermatologist Aaron B. Lerner (1920–2007) at Yale University, who had already described its sedative effect in humans [455]



Coenzym Q_{10}

Fig. 39 Coenzyme Q10 (Ubiquinone-10) was discovered in 1957 and first isolated from bovine hearts by Frederick L. Crane (1925–2016) at the University of Wisconsin [460]. The chemical structure was elucidated by Karl August Folkers 1906–1997) at Merck Laboratories in 1958 and independently by Otto Isler (1910–1992) at Hoffmann La Roche in Basel [461] [462]

to be demonstrated whether transient potential melastatin type 8 (TRPM8) receptor channels are affected in a similar manner. This is of considerable interest because it may offer novel approaches for the treatment of migraine.

Riboflavin

Riboflavin (vitamin B_2) has been considered effective for the prophylactic treatment of migraine in pediatric, adolescent, and adult patients. Meanwhile, there are numerous small studies demonstrating that riboflavin reduces the frequency of migraine attacks at all ages. Riboflavin is well tolerated even at high doses. However, more data are needed particularly in respect to pharmacokinetics and pharmacogenomics to refine its position in future migraine therapy (Fig. 37) [448].

Melatonin

Melatonin is a hormone, released by the pineal gland in the brain, that is critical for the control of the sleep–wake cycle. It may also play a role in the pathophysiology of migraines by activating melatonin receptors in the hypothalamus [452]. Meanwhile, several studies have been published demonstrating that melatonin is effective in children and adolescent patients. In a 3-month trial in children with migraines, it was shown that melatonin significantly decreases the frequency and duration of headache attacks and disability levels [453]. There is much hope that melatonin might become an alternative in migraine prophylaxis, but more research is required, e.g., in terms of pharmacology and safety (Fig. 38) [454].

Coenzyme Q_{10}

Coenzyme Q_{10} is an electron carrier in the mitochondrial electron transport chain and therefore essential for all energy related cellular processes. The observation that mitochondrial energy is depleted in brain tissues of migraine patients without aura supported the hypothesis that supplementation with coenzyme Q_{10} might be beneficial preventing migraines [456, 457]. While a trial in children and adolescents in 2011 was not convincing [458], a meta-analysis of trials in adult patients shows that coenzyme Q_{10} supplementation reduces both the frequency and duration of migraine attacks, but not their severity compared with the control group (Fig. 39) [459].

Magnesium

The availability of magnesium salts is crucial for many physiological processes in the brain associated with the pathophysiology of migraine. Since the 1990s, there is a growing body of evidence that magnesium deficiency may contribute to migraine development [463, 464]. Magnesium deficiency affects mitochondrial metabolism, which could alter neuronal polarization and may result in cortical spreading depression [465]. Migraine attacks are usually accompanied by low magnesium concentrations in serum and cerebrospinal fluid [466]. The underlying cause of hypomagnesemia in patients with migraine is unknown, but may be due to inadequate uptake, excessive loss of magnesium in the urine, genetic disposition, or some combination thereof. By now, several intervention trials in children, adolescents and adults have been performed. Unfortunately, the strength of evidence supporting oral magnesium supplementation is still limited [467]. But most recently there are some promising studies indicating that supplementary magnesium might be beneficial, especially in pediatric but also in adult patients [468–470].

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Author contributions S.S. came up with the initial idea, B.S. wrote the main manuscript text, and and R.R. made valuable suggestions. All authors reviewed the manuscript.

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Declarations

Conflict of interest The authors declare no competing interests.

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