

# Albert Hofmann's Pioneering Work on Ergot Alkaloids and Its Impact on the Search of Novel Drugs at Sandoz, a Predecessor Company of Novartis

Dedicated to Dr. Albert Hofmann on the occasion of his 100th birthday

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**Abstract:** The scientific research on ergot alkaloids is fundamentally related to the work of Dr. Albert Hofmann, who was able to produce, from 1935 onwards, a number of novel and valuable drugs, some of which are still in use today. The complex chemical structures of ergot peptide alkaloids and their pluripotent pharmacological activity were a great challenge for Dr. Hofmann and his associates who sought to unravel the secrets of the ergot peptide alkaloids; a source of inspiration for the design of novel, selective and valuable medicines.

**Keywords:** Aminocyclole · Bromocriptine Parlodel<sup>®</sup> · Dihydroergotamine Dihyergot<sup>®</sup> · Dihydro ergot peptide alkaloids · Ergobasin/ergometrin · Ergocornine · Ergocristine ·  $\alpha$ - and  $\beta$ -Ergocryptine · Ergolene · Ergoline · Ergoloid mesylate Hydergine<sup>®</sup> · Ergotamine Gynergen<sup>®</sup> · Ergotoxine · Lisuride · Lysergic acid diethylamide LSD · Methyleergometrine Methergine<sup>®</sup> · Methysergide Deseril<sup>®</sup> · Paspalic acid · Pindolol Visken<sup>®</sup> · Psilocybin · Serotonin · Tegaserod Zelmac<sup>®</sup>/Zelnorm<sup>®</sup> · Tropicsetron Navoban<sup>®</sup>

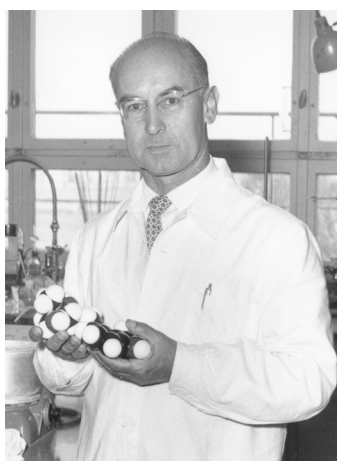


Fig. 1. Albert Hofmann in 1943, 1979 and 2001 (Photos in 2001 taken by J. Zadrobilek and P. Schmetz)

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Dr. Albert Hofmann (Fig. 1), born on January 11, 1906, started his extremely successful career in 1929 at Sandoz Pharma in the chemical department directed by Prof. Arthur Stoll. In this paper, we seek to pay tribute to his pioneering research on ergot alkaloids which delivered several valuable pharmaceuticals and had a substantial and durable impact on the work of medicinal chemists until very recent years.

## From the 'Ergot Poison' to Ergotamine

The scientific research on ergot alkaloids began in 1918 with the isolation of ergotamine (1) by A. Stoll [1], the first chemically pure ergot peptide alkaloid, which exhibits the pharmacological spectrum of action of the drug extracted from *Claviceps purpurea*, the dark violet sclerotia of the fungus that infects ears of rye (Fig. 2).

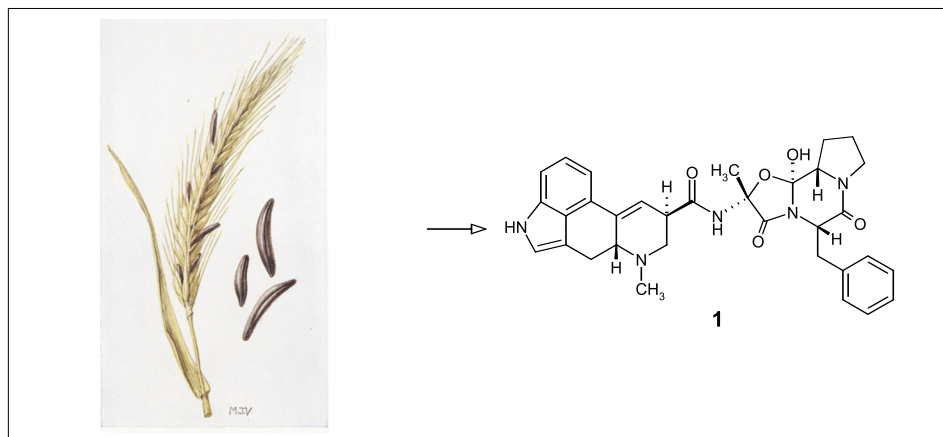


Fig. 2. *Secale cornutum* on ear of rye and ergotamine (1), the first chemically pure ergot peptide alkaloid

In fact during the Middle Ages the ergot (*Secale cornutum*) was used as an agent to hasten childbirth during labour. In 1907 British chemists G. Barger and F. Howard Carr isolated an alkaloid acting on the uterus, which due to its toxic effect was named ergotoxine and was never applied in medicine.

Ergotamine (1) was used under the trade name Gynergen® in obstetrics to control postpartum bleeding due to its uterotonic effect, and also to treat migraine in internal medicine. At that time the chemical structure of the peptide portion had not been elucidated (see also Fig. 7) and a total synthesis was not even taken into consideration. Consequently, great interest was raised in 1935 in ergobasin (2) (Fig. 3), isolated by four independent research groups (Dudley and Moir, Stoll and Burckhard, Kharash and Legault, Thompson [2]), which in contrast to ergotamine (1) was soluble in water and also exhibited strong uterotonic effects.

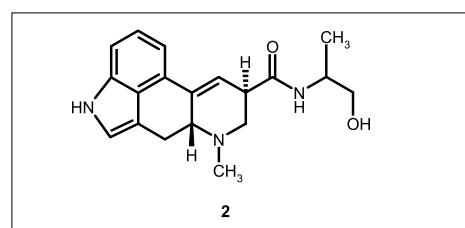


Fig. 3. Ergobasin/ergometrin (2)

### First Synthesis of a Natural Ergot Alkaloid

At this time Dr. Hofmann proposed to Prof. Stoll to attempt the partial synthesis of ergobasin (2), seeking for a proof of structure and eventually a more effective production of this compound, which was present only in tiny amounts in ergot. The condensation of lysergic acid (3), obtained by hydrolysis of ergotamine (1), with alaninol (4) was in fact the first synthesis of a natural ergot alkaloid (Fig. 4), and represented a milestone in ergot research.

The success of this preparative method opened the way to the synthesis of novel compounds related to the ergot alkaloids such as methylergometrine (5) and LSD (lysergic acid diethylamide) (6) (Fig. 5).

Methylergometrine (5) was a more potent stimulant of uterine contraction without causing vasoconstriction and had a most rapid onset of action and was introduced as Methergine® to control postpartum bleeding in obstetrics.

LSD (6) [2][3], which acts specifically on the central nervous system with notorious hallucinogenic properties, led the scientists to discontinue research in this direction. Nevertheless it has been claimed by various scientists that LSD [6], applied at sub-hallucinogenic doses in man, shows anxiolytic and antidepressive activities. It is regrettable that the separation of these highly valuable effects from the hallucinogenic ones by a systematic structural modification of the LSD molecule has never been attempted.

The identification of ergot alkaloid derivatives with fewer side effects and more specific pharmacological activities was in-

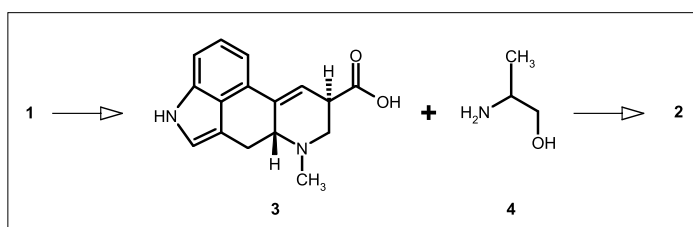


Fig. 4. Partial synthesis of ergobasin (2) from D-lysergic acid (3) and alaninol (4)

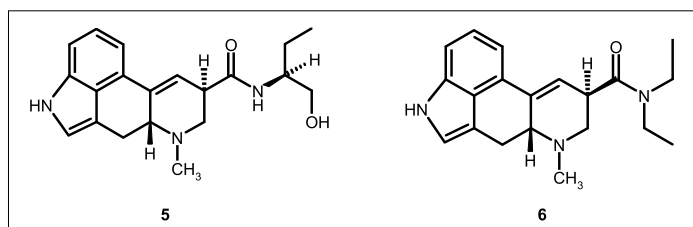


Fig. 5. Methylergometrine (5) and LSD (6)

deed the great recurring challenge for the chemists in ergot research.

### Dihydro Ergot Peptide Alkaloids

In 1943 an important step in ergot research was the catalytic hydrogenation of ergotoxine (7) from natural sources by Hofmann, which was found to be a mixture of the four genuine peptide alkaloids ergocristine (8) (one third), ergocormine (9) (one third),  $\alpha$ - and  $\beta$ -ergocryptine (10 and 11) (one third of a 2:1 mixture), and yielded a new medicine with the generic name ergoloid mesylate and the trade name Hydergine® (12) (Fig. 6) which is still widely used today [4][5].

This drug was introduced into therapy as a mild antihypertensive agent for elderly people. Later clinical investigation revealed an additional indication: Hydergine® (12) improves many symptoms of cerebral insufficiency in elderly people by stimulating their intellectual capabilities, ameliorating their social behaviour, and promoting mood elevation. In addition Hydergine® (12) improves cerebral metabolism, especially of oxygen, and stabilizes the tonus of intra- and extracranial blood vessels. Furthermore it was demonstrated that it stimulates dopamine and serotonin receptors, blocks particularly presynaptic  $\alpha$ -adrenoreceptors, thus enhancing the liberation of endogenous noradrenaline in the rat brain.

It is interesting to note that the structure of lysergic acid (3) was elucidated by Jacobs and his associates [6], its stereochemistry by Stoll, Hofmann and Troxler in 1949, and until the 1950s, *i.e.* before Stoll, Hofmann and their associates were able to elucidate the structure of the peptide portion of ergotamine [6], the chemical formula of ergot alkaloid merely indicated the degradation products of the peptide portion. In case of

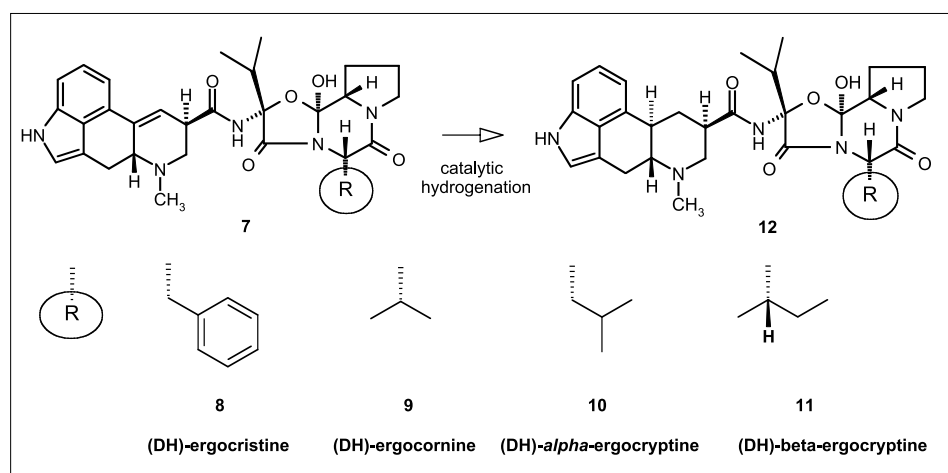


Fig. 6. Catalytic hydrogenation of ergotamine (7) (a mixture of four alkaloids) to Hydergine® (12)

ergotamine (1), these are pyruvic acid, ammonia, phenylalanine, and proline (Fig. 7).

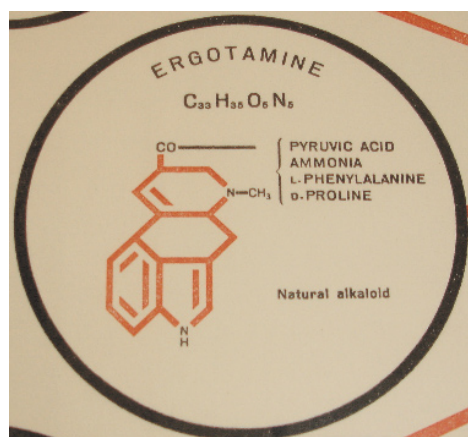


Fig. 7. 1950: not yet fully elucidated chemical structure of ergotamine (1)

The difficulty of the structure elucidation was due to the instability of the aminocyclole (13), which is prone to fragmentation in non-protected form (Fig 8). This chemical instability was also the main challenge for the total synthesis, which was eventually realized by Hofmann and his associates A. Frei and H. Ott by condensation of lysergic acid (3) (the isomerisation product of paspalic acid (18), which itself was obtained by fermentation) with the aminocyclole moiety (13) (prepared *via* the intermediates 14–17) (Fig. 9) [7–10]. The ergot challenge initially addressed by Prof. Stoll thus appeared to have been solved.

### Antimigraine Ergot Compounds

Another hydrogenation step transformed ergotamine (1) into dihydroergotamine (19, DHE), a drug with improved pharmacological profile (Fig. 10) and better tolerability. As Dihyergot®, DHE (19) was successfully used in the treatment of orthostatic hypotension and vascular headaches.

### Dopaminergic Ergot Compounds

One of the last ergot alkaloids to enter the annals of medical history was bromocriptine (20) (Fig. 11). 2-Bromo-alpha-er-

gocryptine (20) (Parlodel®), a dopaminergic agonist, was introduced for the indication hyperprolactinemia and associated female infertility, as well as Parkinson's disease, acromegaly, and for the treatment of pituitary tumours. The introduction of bromocriptine opened a new chapter in neuroendocrinology. Bromocriptine (20) has enabled countless couples to fulfil their desire to have children.

### Pluripotent Biological Actions and Pharmacophores of the Ergolene System

Ergot alkaloids have stimulated continuous interest in pharmacology because of their unique ability to interact directly with various neurotransmitter receptors in the periphery as well as in the CNS. This due to the presence of three aminergic pharmacophoric groups serotonin, noradrenaline, and dopamine in the tetracyclic ergolene ring system (Fig. 12). Depending on the

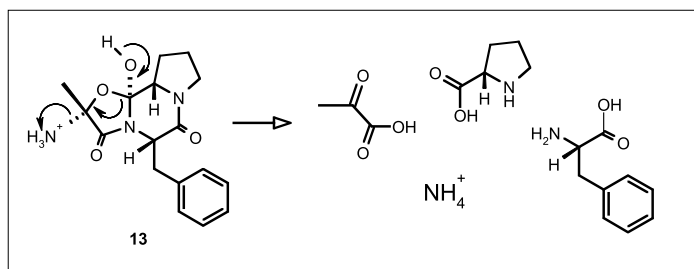


Fig. 8. Fragmentation products of the aminocyclole (13)

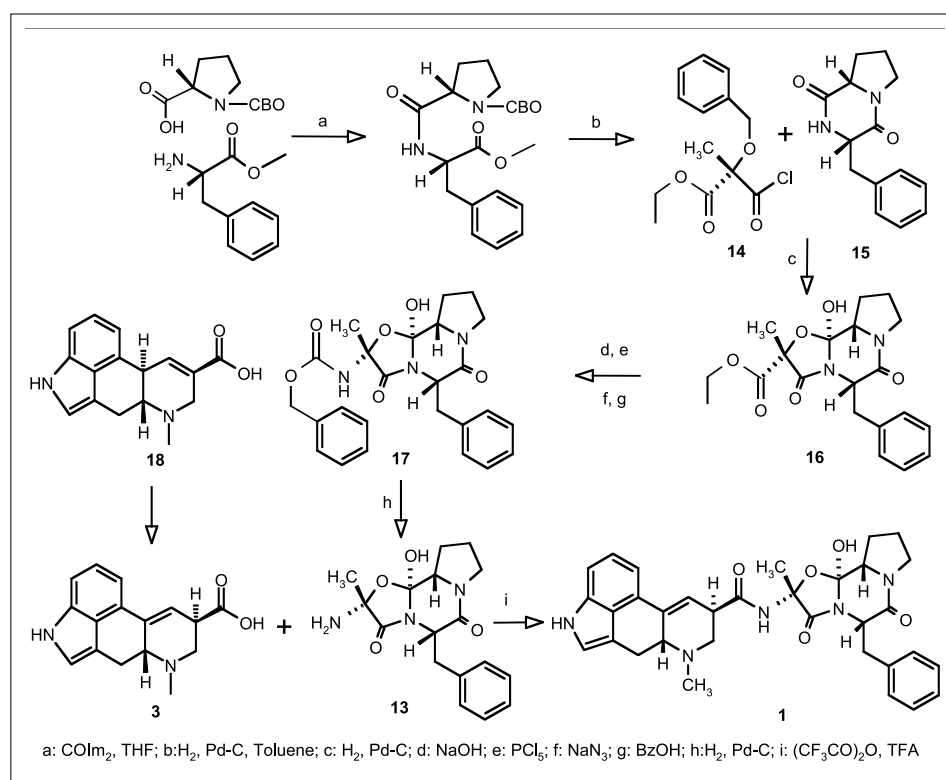


Fig. 9. Synthesis of the aminocyclole (13), isomerisation of paspalic acid (18) to lysergic acid (3), and condensation of (3) and (13) to give ergotamine (1)

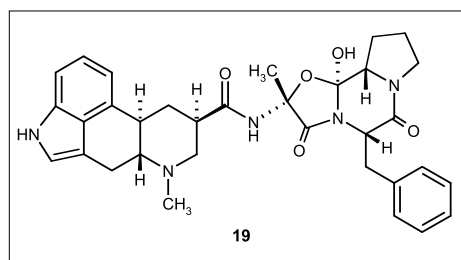


Fig. 10. DHE (dihydroergotamine) (19)

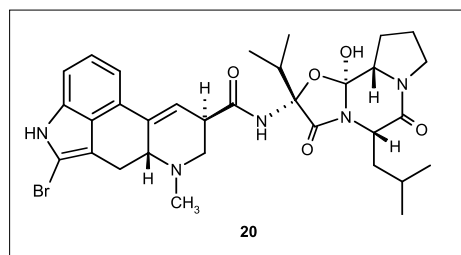


Fig. 11. Bromocriptine (Parlodel®) (20)

substitution pattern the alkaloids behave as receptor agonists or antagonists.

### Peculiar Biotransformation of Ergot Alkaloids

The sensitivity of the indole moiety toward oxidation, in particular metabolic attack, might eventually lead to metabolites with even higher biological activity or even to compounds which exhibit an opposite pharmacological profile, *i.e.* from parent antagonists to agonists. For instance this is the case for lisuride (21) (Fig. 13). In fact its 12-hydroxy metabolites 22 possess 80-fold dopaminergic activity compared to lisuride (21).

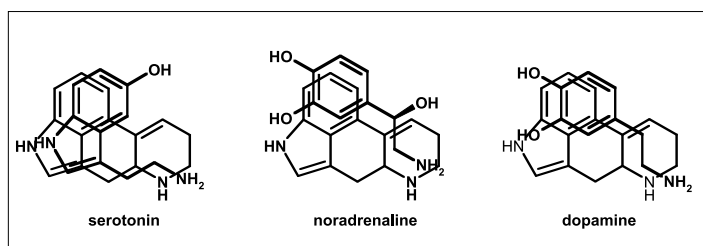


Fig. 12. Superposition of serotonin, noradrenaline, and dopamine on the tetracyclic ergolene ring system

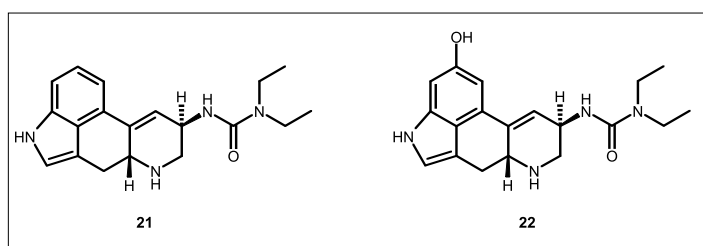


Fig. 13. Lisuride (21) and its 12-hydroxy-metabolite (22)

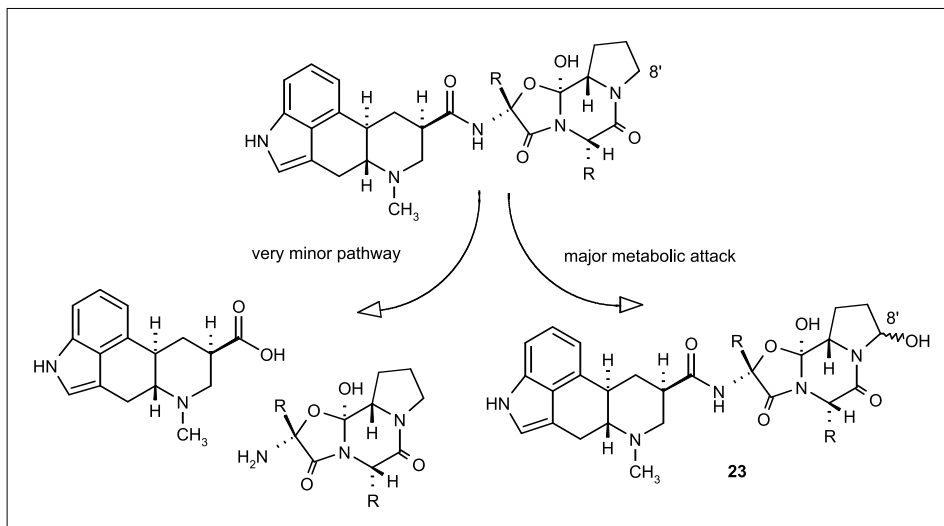


Fig. 14. Major and minor biotransformation pathways of ergot peptide alkaloids

It is also interesting to note that the indole moiety of ergot peptide alkaloids seems to be protected toward metabolic attack. Apparently the presence of the tricyclic peptide part is able to prevent biotransformation of the lysergic acid moiety by providing a major and a minor site for metabolic transformation (Fig. 14). In fact the high first pass effect in the liver produces a large amount of the 8'-hydroxy metabolites (23) [9][11][12] beside cleavage of the amide bridge. Fortunately the 8'-hydroxy-metabolites usually show a profile of action very similar to their parent compounds contributing therefore to the high biological activity of these drugs. This biotransformation is once more a desirable property since apparently it ensures the maintenance of the spectrum of action of the parent compound and avoids potential complications due to biotransformations.

### Serotonergic Ergot Compounds

Following the hypothesis that serotonin (Fig. 12) might be involved in inflammatory processes and migraine, A. Cerletti observed a potent effect of another lysergic acid derivative prepared by Hofmann: methysergide (24) (Fig. 15). This compound was introduced under the name of Deseril® for migraine prophylaxis. It was one the first pharmacologically specific serotonin antagonists. It found application for treatment of carcinoid syndrome.

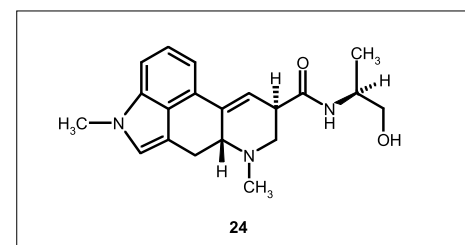


Fig. 15. Methysergide (24) (Deseril®)

### New Development Compounds Based on the Ergoline Partial Structure

In the 1980s the tetracyclic ergoline moiety of ergot alkaloids inspired chemists to prepare and to derivatise a number of novel scaffolds, seeking to obtain more selective dopaminergic agents (Fig. 16) [2]. This allowed a better understanding of the structure-activity relationships, however no real breakthrough with respect to a new drug could be accomplished.

### Indole Derivatives as New Drugs

In the 1958 Hofman elucidated the chemical structure of psilocybin (25), a

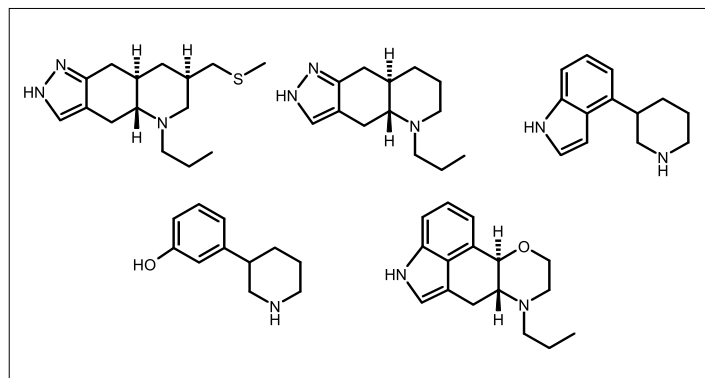


Fig. 16. Development compounds whose scaffold contains portions of the tetracyclic ergoline skeleton and close derivatives thereof

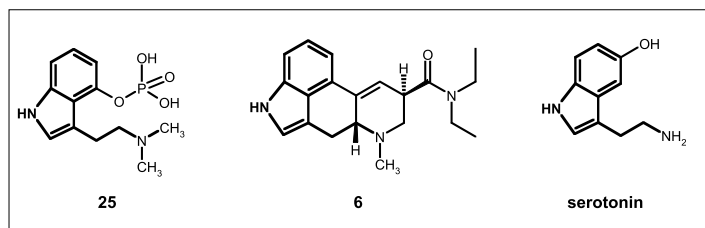


Fig. 17. Structure similarity between psilocybin (**25**), LSD (**6**), and serotonin

psychoactive principle isolated from the mushroom *Psilocybe Mexicana* which has the indole moiety in common with LSD (**6**) (Fig. 17).

This result initiated a shift in the focus of Hofmann's interest, away from the ergot alkaloids and structurally complex derivatives of lysergic acids towards simpler indole derivatives. These compounds produced remarkable biological effects on account of their structural similarities to the neurotransmitter serotonin. F. Troxler, an associate of A. Hofmann, had succeeded in preparing the psilocybin precursor 4-hydroxy-indole (**26**) when in 1960 the first potent beta-blocker propranolol (Inderal<sup>®</sup>) (**27**) was described by the British pharmacologist James Black. In 1965 F. Troxler combined the 4-hydroxy-indole with the side chain of propranolol and obtained pindolol (Visken<sup>®</sup>) (**28**) (Fig. 18).

The indole moiety was also incorporated in compounds that were introduced onto the market in later years, such as tropisetron (**29**) (Fig. 19). In fact toward the end of the 1970s, Sandoz once again turned its attention to the pharmacology of serotonin, with the aim of developing a new small-molecule drug for the treatment of migraine.

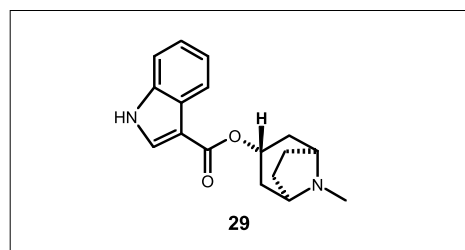


Fig. 19. Tropisetron (Navoban<sup>®</sup>) (**29**)

As serotonin (Fig. 17) plays a key role in migraine attacks and particularly in the pain phase, efforts were made to find a serotonin antagonist through derivatization of the indole moiety. In 1982 P. Stadler, an associate of Hofmann's research group, synthesized tropisetron (**29**). Despite the fact that this agent was not effective against migraine, it was the first highly selective antagonist on neuronally located serotonin receptors. It was pharmacologically described by B.P. Richardson, P. Donatsch, G. Engel, P.A. Stadler [13]. In 1995 tropisetron (**29**) was introduced as a very potent antiemetic drug for patients with chemotherapy-induced nausea and vomiting under the trade name of Navoban<sup>®</sup>.

Through the development of Navoban<sup>®</sup> (**29**), the company had built up considerable expertise in the area of serotonin pharmacology. In 1986 K.-H. Buchheit launched a project with the aim of discovering non-classical serotonin receptor agonists for curing disorders of the gastro-intestinal tract, in particular gastrointestinal motility disorders. In 1988 R. Giger and H. Mattes achieved the goal by delivering tegaserod (**30**) (Fig. 20) to the pharmacologists K.-H. Buchheit, R. Gamse and H.-J. Pfannkuche.

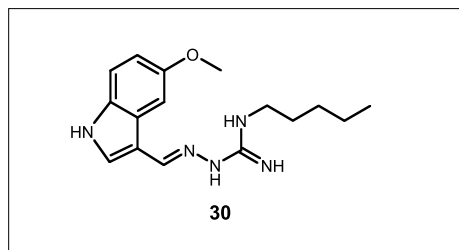


Fig. 20. Tegaserod (Zelmac<sup>®</sup>/Zelnorm<sup>®</sup>) (**30**)

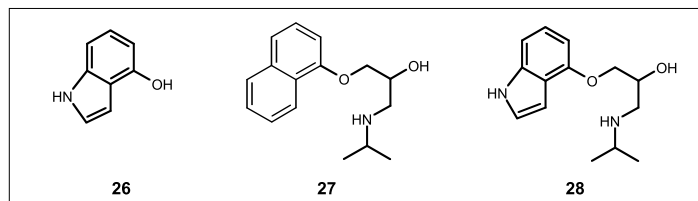


Fig. 18. 4-Hydroxy-indole (**26**), propranolol (Inderal<sup>®</sup>) (**27**), and pindolol (Visken<sup>®</sup>) (**28**)

Tegaserod (**30**) was approved in 2001/02 for the indication irritable bowel syndrome with the trade name Zelmac<sup>®</sup>/Zelnorm<sup>®</sup>.

In summary the ergot alkaloids have been for long time not only a real treasure house for valuable medicines but also a source of inspiration for many chemists and pharmacologists in their search for innovative drugs as demonstrated by Dr. Albert Hofmann and his associates for more than half a century.

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