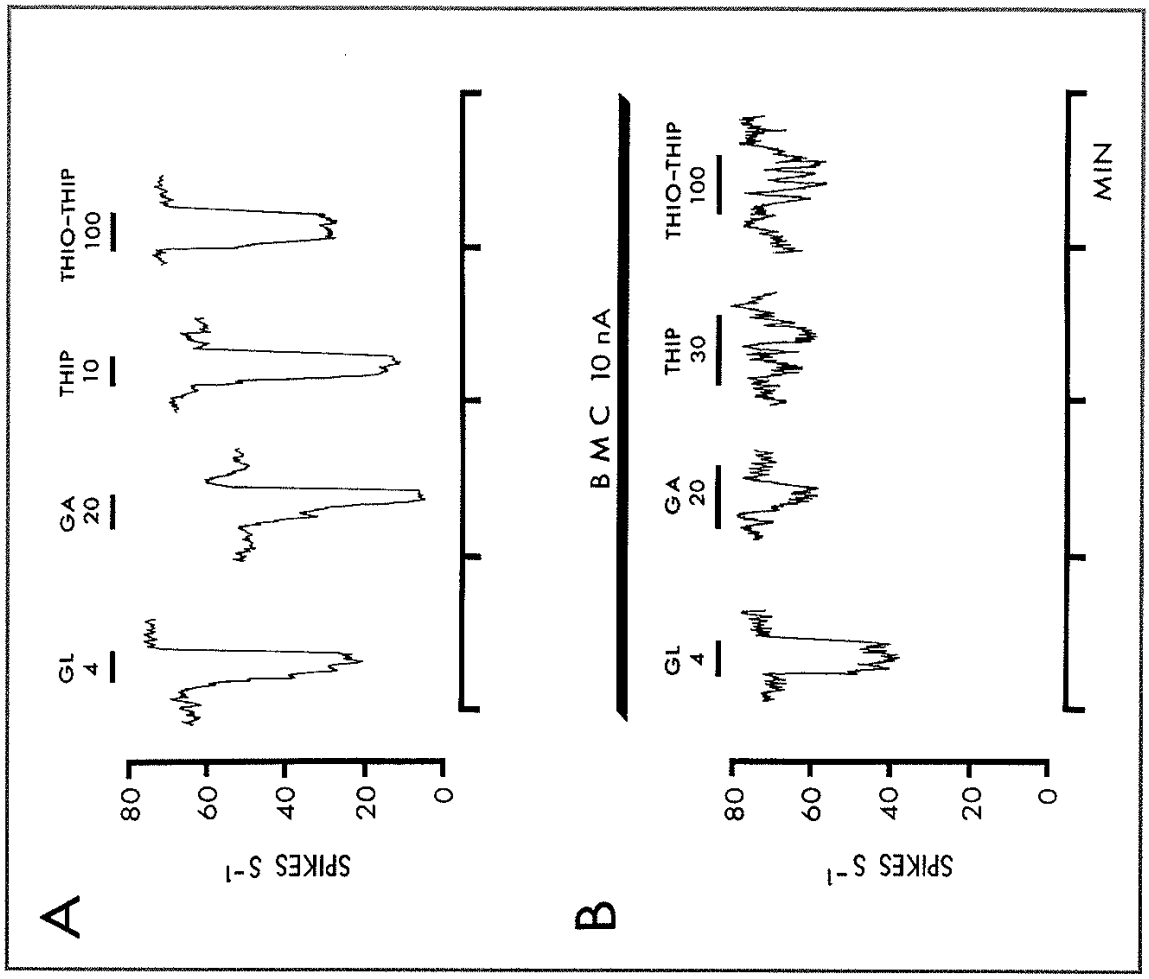


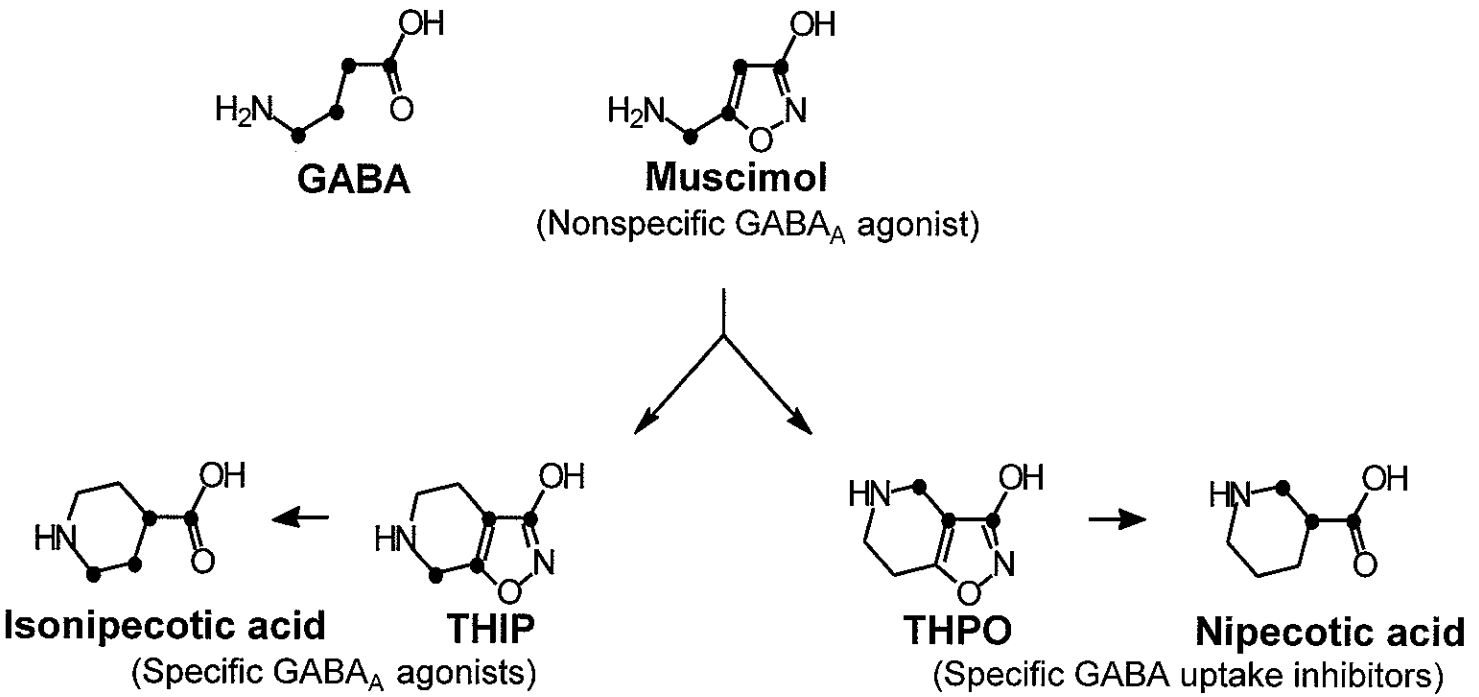
Professor, dr.pharm. Povl Krogsgaard-Larsen

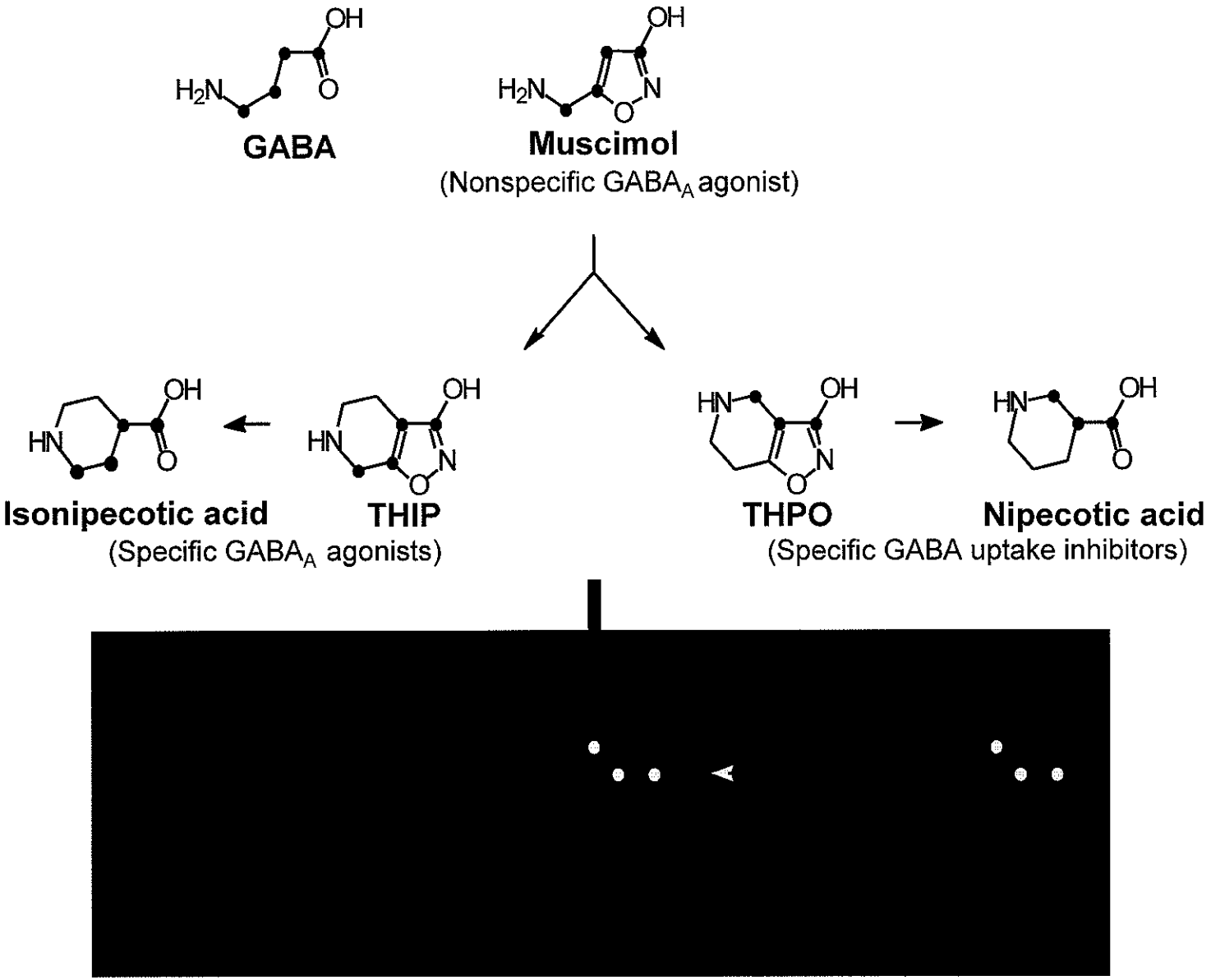
Nature **1977**, *268*, 53–55

A New Class of GABA Agonist

P. Krogsgaard-Larsen, G. A. R. Johnston, D. Lodge and D. R. Curtis

Professor, dr.pharm. Povl Krogsgaard-Larsen


GABA
Muscimol
(Nonspecific GABA$_A$ agonist)
Isonipecotic acid
THIP
(Specific GABA$_A$ agonists)
THPO
Nipecotic acid
(Specific GABA uptake inhibitors)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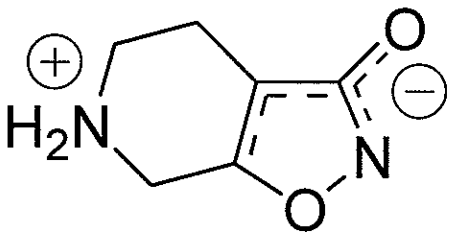
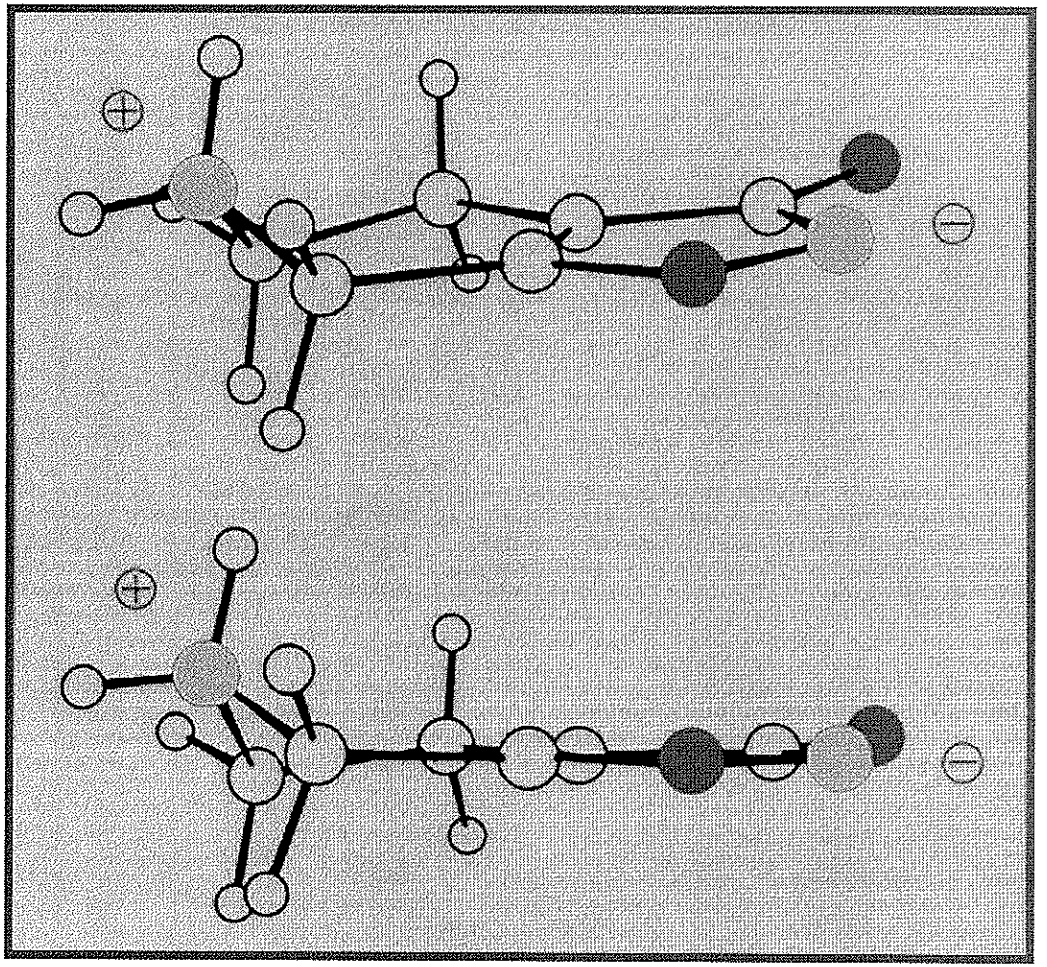


THIP

(Gaboxadol)



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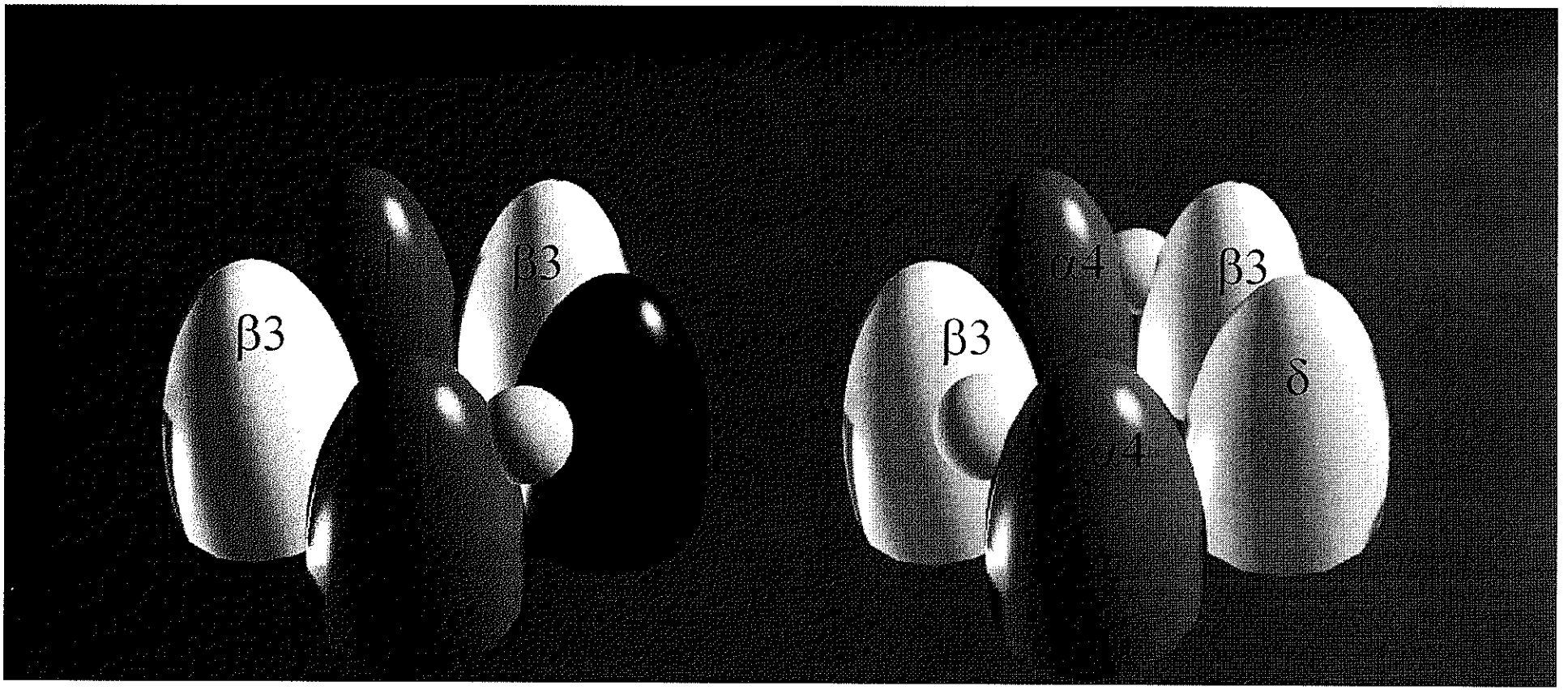
Functional selectivity

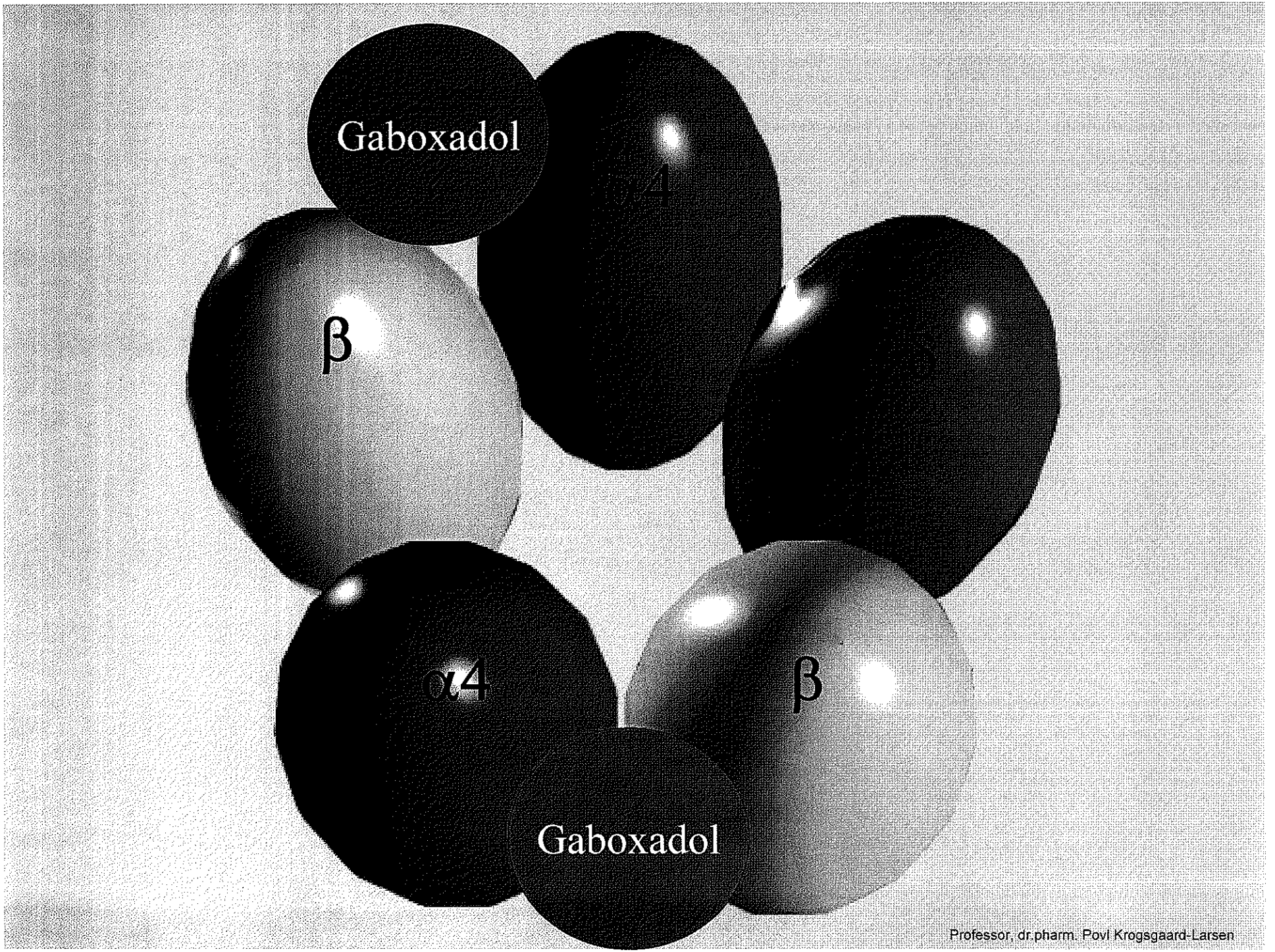
Synaptic

Extra Synaptic



Benzodiazepine Receptor Agonists

Gaboxadol



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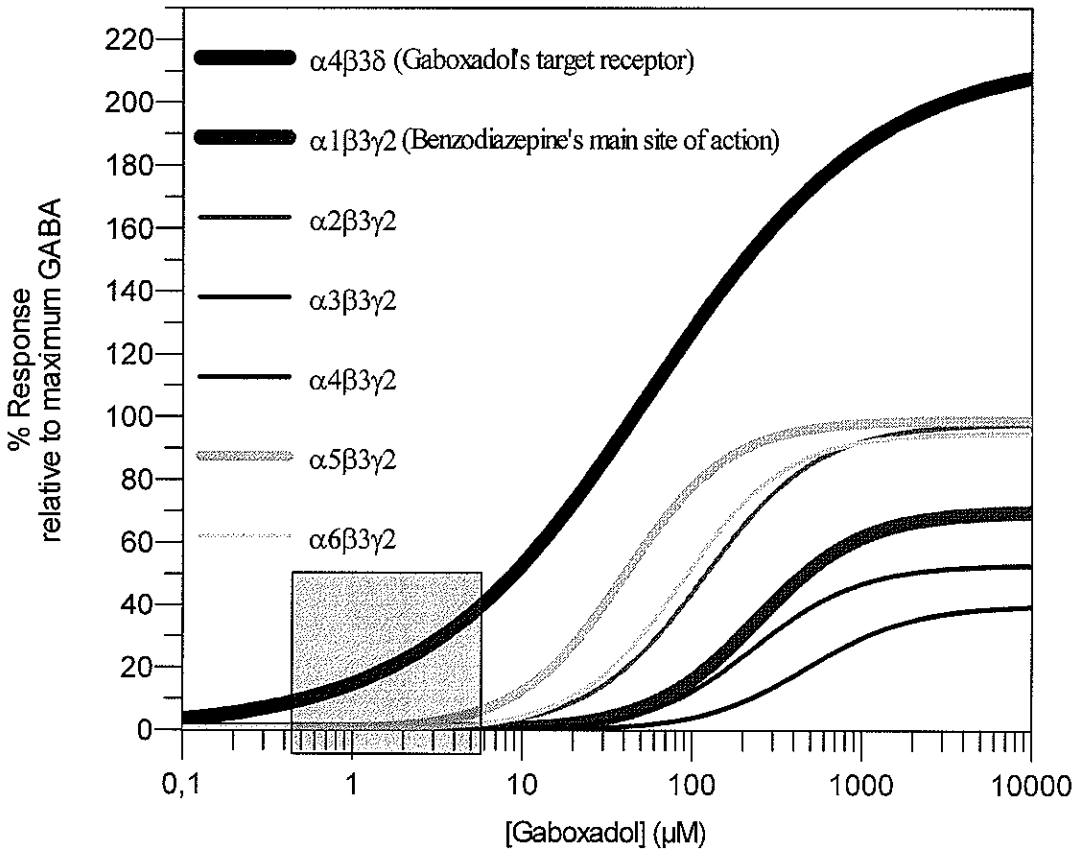
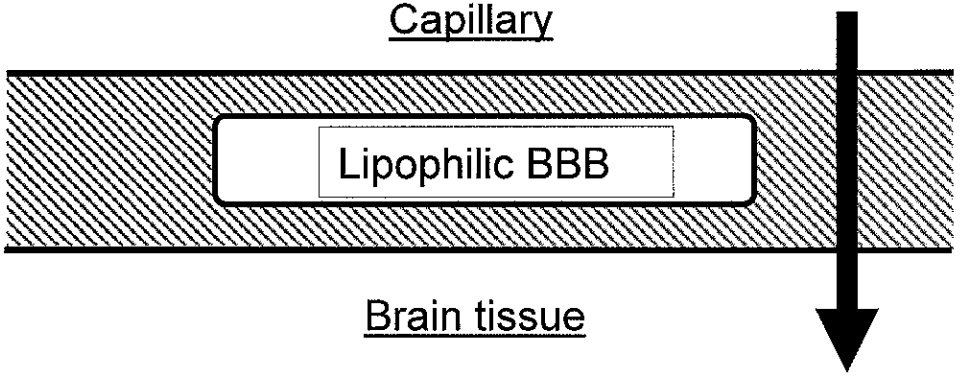
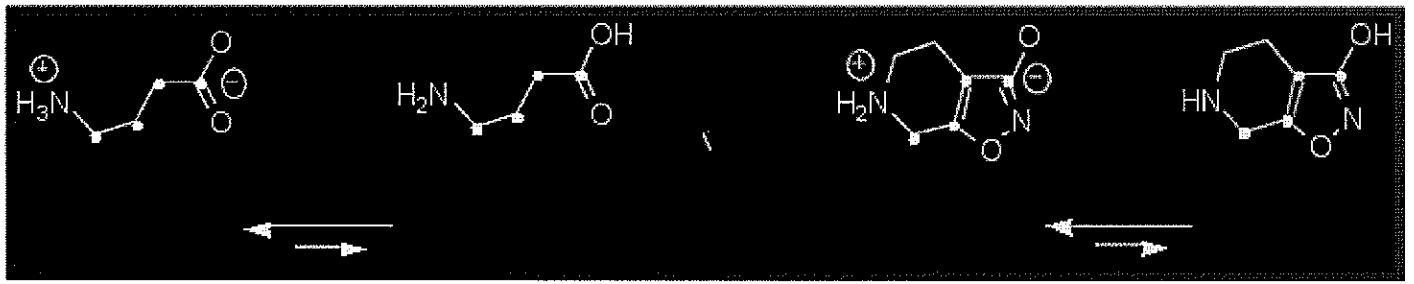
Gaboxadol is selective for $\alpha_4\beta\delta$ receptors



Physiologically relevant concentration





GABA

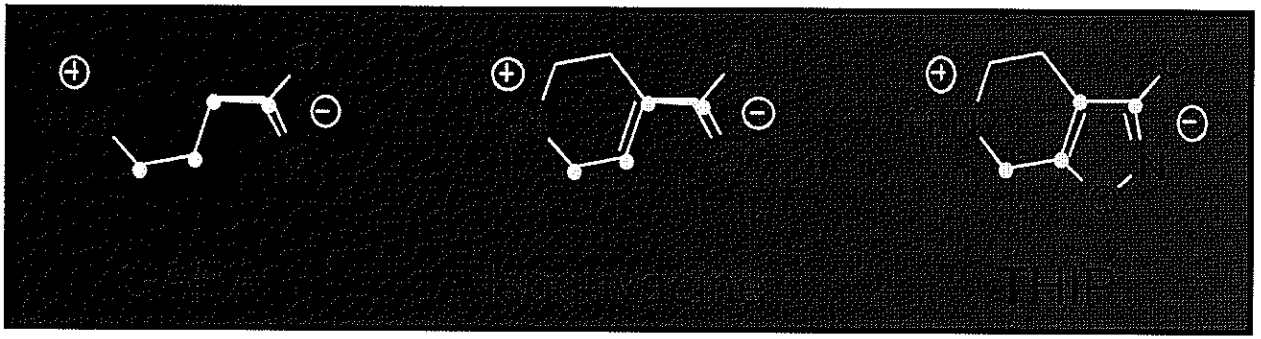
0.00001 %

pKa 4.0; 10.7
I/U Ratio 800,000
No penetration of BBB

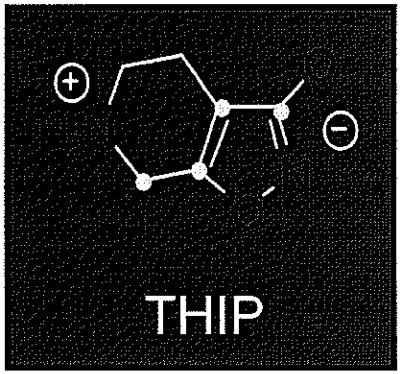
THIP

0.1 %

pKa 4.4; 8.5
I/U Ratio 1,000
Penetration of BBB

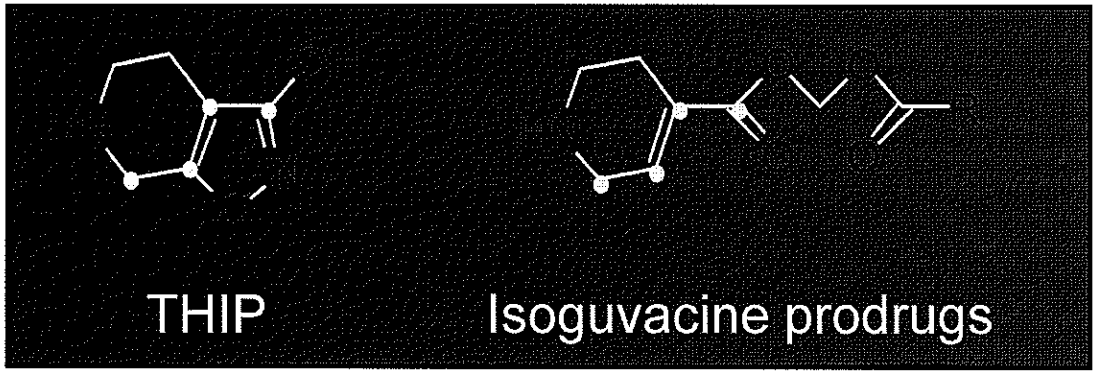


- THIP (4,5,6,7-tetrahydroisoxazolo[5,4-*c*]pyridin-3-ol) was synthesized in 1975-1976.
- Isoguvacine was synthesized in 1976.
- THIP and isoguvacine were shown to be potent and specific $GABA_A$ receptor agonists *in vitro* and *in vivo* in 1977.
- THIP and isoguvacine represented a novel structural class of $GABA_A$ agonists.
- In agreement with the results of calculations, **THIP** was shown to be **capable of penetrating the blood-brain barrier** in spite of zwitterionic structure (1977).
- In agreement with the results of calculations, **isoguvacine** was shown **not to penetrate** the blood-brain barrier (1977).



- On the basis of the *in vitro* and *in vivo* (non-behavioural) pharmacology of THIP it was decided to patent this "difficult-to-synthesize" bicyclic $GABA_A$ agonist.

- **Problems:**
  - Two articles describing the chemistry and pharmacology of THIP (and isoguvacine) were *in press* in international journals and were expected to be published 3-4 weeks after decision to submit patent application.
  - Preparation of patent application.
  - Financing of patent application.



- In addition to a general grant supporting a basic drug design project in the GABA neurotransmitter field, the Danish MRC (now SSVF) supported the above patenting work in the form of six supplementary grants:

• June	1977	15,000 DKK
• July	1977	13,200 -
• September	1978	131,930 -
• September	1979	12,879 -
• June	1980	26,924 -
• September	1980	3,343 - .
	Total	203,276 DKK

THIP
Clinical Evaluation

1981 – 1984

Anticonvulsant in animal models –
but only marginal antiepileptic effects in man

No significant effects (positive or negative) in Alzheimer patients

Non-opioid analgesic effects in man (0.2 – 0.5 mg/kg, p.o.) approximately equipotent with morphine

"Sedative effects"

Clinical studies terminated

1999 –

"Sedative effects" in animals and man identified as hypnotic effects (M. Lancel)

Fast onset hypnotic effects in man

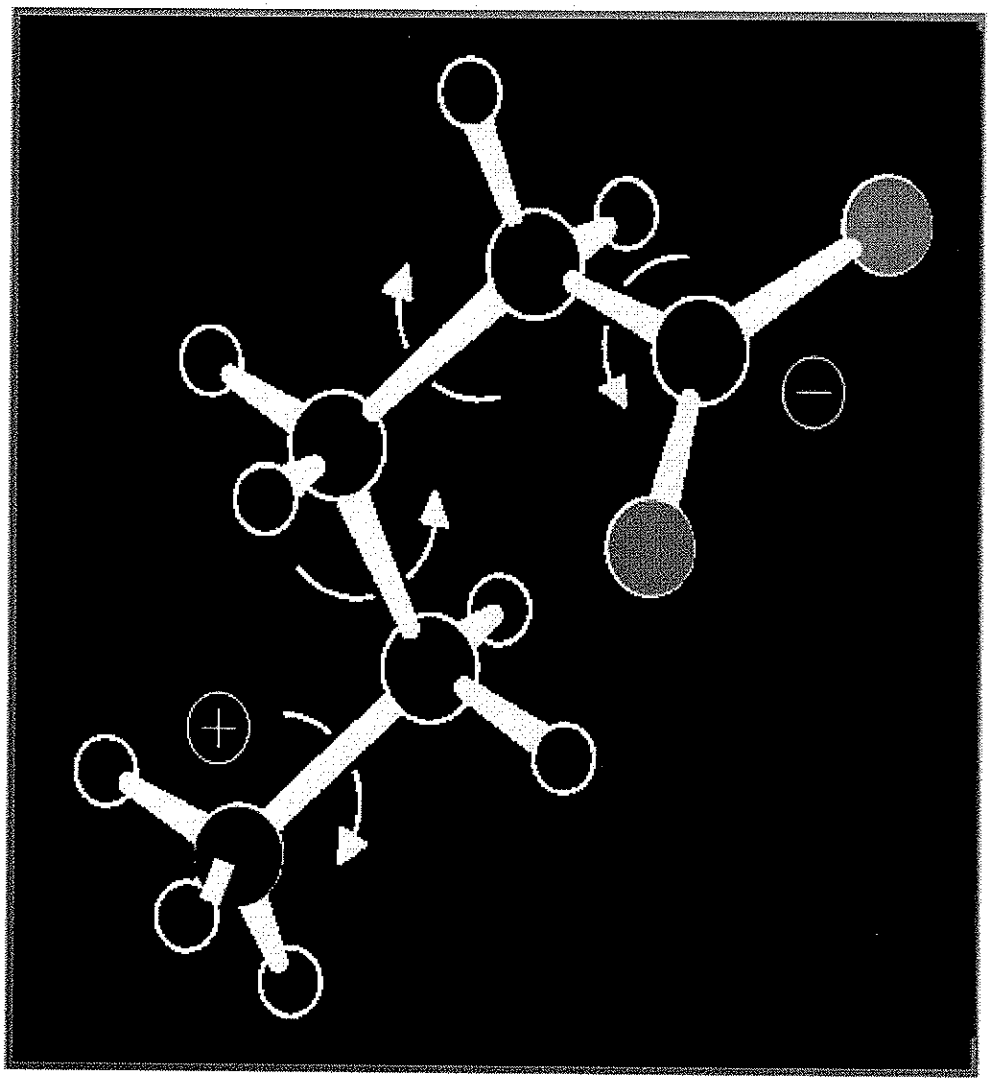
Unique modification of sleep pattern ("re-structuring of normal sleep architecture")

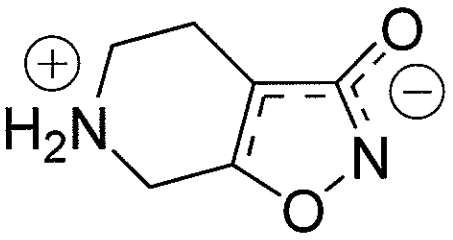
Hypnotic effect different from those of benzodiazepines

Combination of hypnotic and analgesic effects of clinical interest

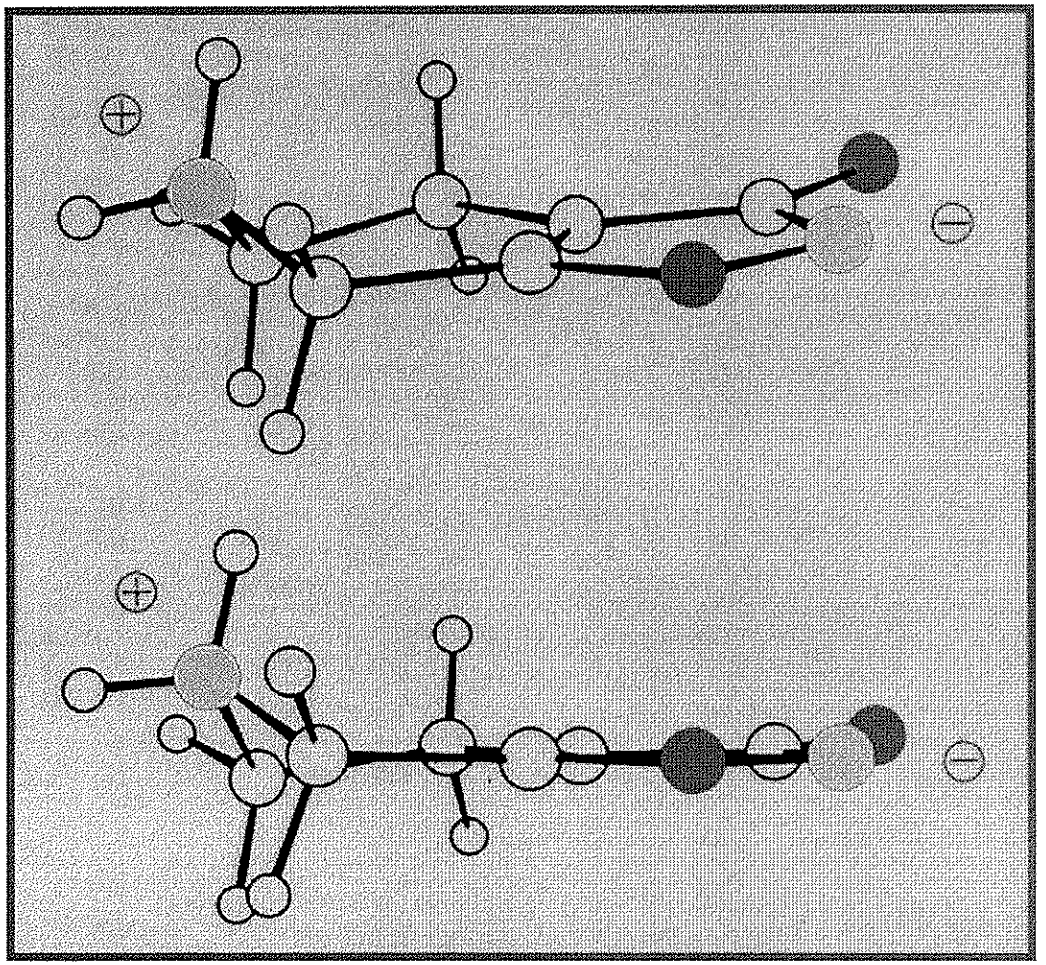
THIP (Gaboxadol) is at present in advanced Phase III clinical trials as a hypnotic capable of re-establishing a normal sleep architecture and showing non-opioid analgesic activity.

GABA

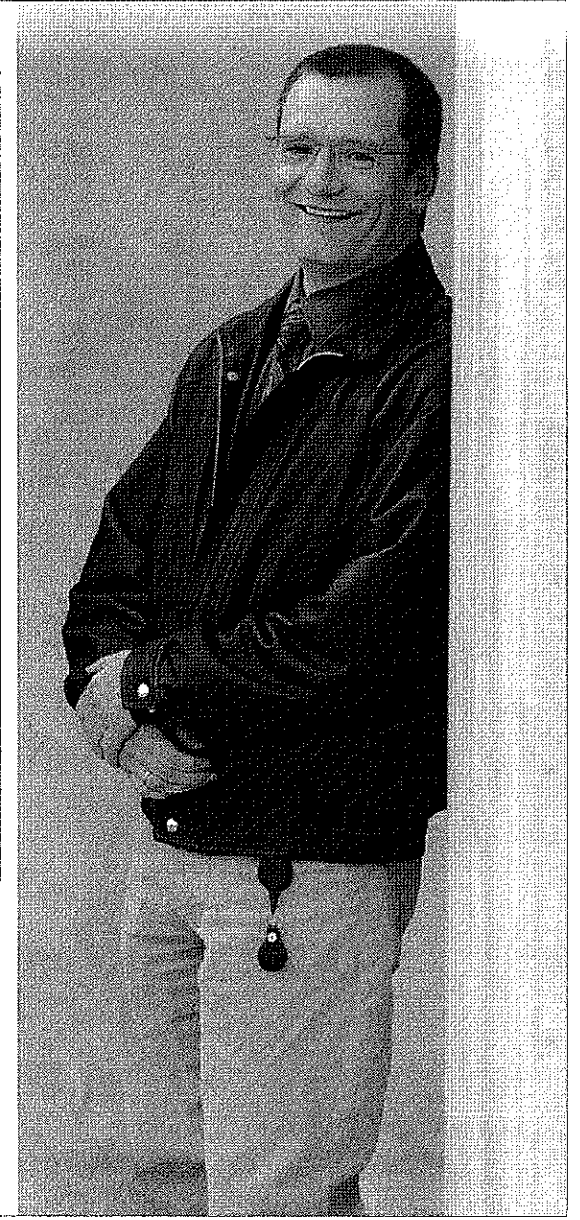


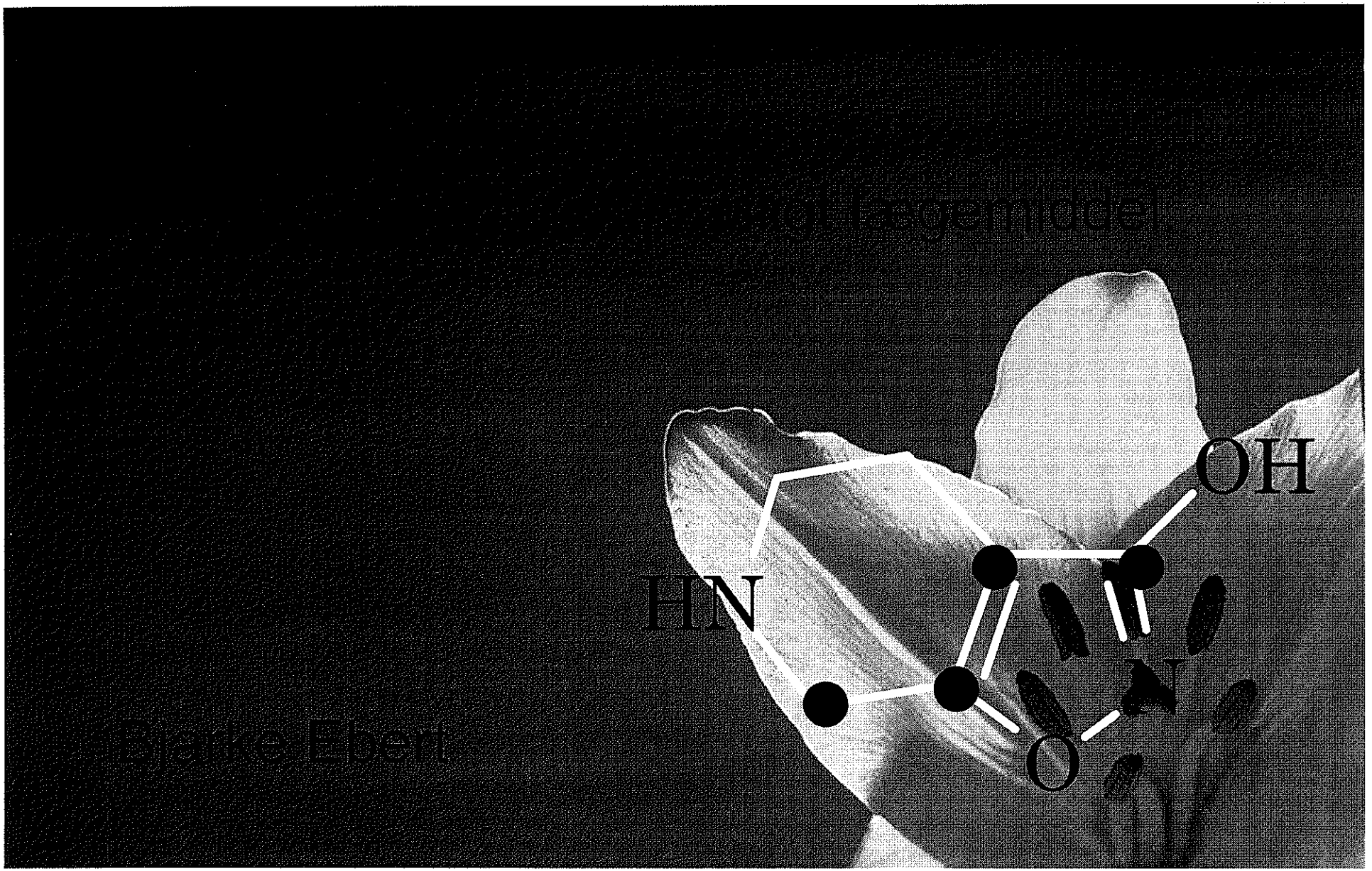


THIP
(Gaboxadol)



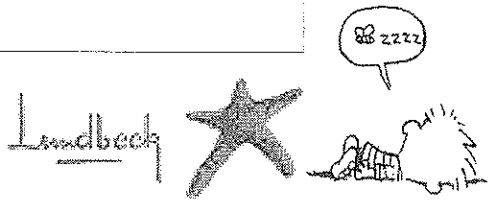
- 46 år
- Cand & Lic Pharm.
- Dr disputats antaget til forsvar
- Tidligere lektor på Farmaceutisk Højskole
- Forsket i GABA i 16 år
- Pt Senior Pricincipal Scientist & Adjungeret Professor
- >100 Publikationer i internationale tidsskrifter
- Ansvarlig for forskningen med Gaboxadol





H. Lundbeck A/S

- At udvikle lægemidler er det mest ophidsende der findes
- Desværre tager det 12 år
- Målet: at hjælpe mennesker bliver derfor det bærende perspektiv
- Mit håb:
- Ved at behandle søvnproblemer på den rette måde, kan man hjælpe patienter med stress og depression langt bedre end vi kan idag.



Fremtidighed

- Grundvidenskabligt samarbejde over hele verden
- Ændring af paradigmer
- Ny forståelse af virkning
- Helt ny terapeutisk effekt
- Udfordring for Lundbeck og myndigheder.