# Chapter 3 Anti-Anxiety Agents, Anticonvulsants and Sedative-Hypnotics

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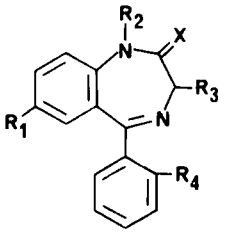
## Benzodiazepines and Related Compounds

General — A specific benzodiazepine receptor has been found in rat and human brain cells that may mediate their pharmacological activities.[1, 2a] Binding sites in the rat are unevenly distributed throughout the brain and a loose parallel between the pharmacological potency and receptor affinity was found. The cerebral and cerebellar cortical regions of the human brain contain the highest density of binding sites and the receptors are very similar to those of rat brain.[1,2a] The proposal that benzodiazepines act on the glycine or GABA receptor now seems unlikely since neither glycine or its antagonist strychnine displaced $^3$H-diazepam binding on the benzodiazepine receptor[1] and chronic administration of diazepam (1a) to mice led to tolerance of anti-strychnine and anti-bicuculline, but not anti-pentylenetetrazole activity.[2b]

Animal studies indicate that the pharmacological actions of benzodiazepines are derived at least in part from activating effects on the 5-HT receptor in the brain[3,4,5] and are probably mediated by several neurotransmitters.[6] The CNS pharmacological activities of benzodiazepines were correlated with some calculated physical parameters[7, 8] and the quantitative SAR in the minor tranquilizer series of benzodiazepinooxazoles (2) was studied.[9]

Changes in the plasma binding of benzodiazepines can be correlated with the lipophilic nature of the ring substituents[10] and diazepam (1a) binding to human serum albumin has been reported.[11]



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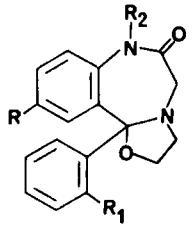

2

2a, R = Cl, $R_1$ = F, $R_2$ = $CH_2CH_2OH$

| | $R_1$ | $R_2$ | $R_3$ | $R_4$ | X |
|---|---|---|---|---|---|
| 1a | Cl | $CH_3$ | H | H | O |
| 1b | Cl | $CH_2POMe_2$ | H | H | O |
| 1c | Cl | $CH_3$ | OH | H | O |
| 1d | Cl | H | OH | H | O |
| 1e | Cl | $CH_2CH_2NEt_2$ | H | F | O |
| 1f | Cl | $CH_2C{\equiv}CH$ | H | H | O |
| 1g | Cl | H | OH | Cl | O |
| 1h | $NO_2$ | $CH_3$ | H | H | O |
| 1i | $NO_2$ | H | H | Cl | O |
| 1j | Cl | $CH_2$-cyclopropyl | H | H | O |
| 1k | Cl | $CH_3$ | $OCONMe_2$ | H | O |
| 1l | Cl | $CH_3$ | H | F | O |
| 1m | Cl | $CH_2CF_3$ | H | H | O |
| 1n | Cl | $CH_3$ | H | H | $H_2$ |
| 1o | Cl | H | H | Cl | O |
| 1p | Cl | $CH_3$ | H | H | S |
| 1q | $NO_2$ | $CH_3$ | H | F | O |
| 1r | Cl | $CH_2CF_3$ | H | F | S |

The behavioral[12] and neural[13] mechanisms of benzodiazepines were reviewed and the monkey behavioral studies of fosazepam[14] (1b), diazepam, temazepam (1c) and oxazepam (1d) were reported.[15]


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Metabolic studies of diazepam in patients with liver diseases[16], flurazepam (1e) in human portal and hepatic systems[17] and the in vitro liver microsomal metabolism of diazepam and pinazepam (1f) in rat, dog and guinea pig[18] and several desmethyldiazepines[19] in rats are reported.

The clinical pharmacokinetics of a number of benzodiazepines has been reviewed.[20,21,22] Additional pharmacokinetic studies of lorazepam (1g) intramuscular in humans,[23] oral triazolam (3a) in humans,[24] oxazepam (1d) in man and dog[25] and diazepam, temazepam (1c) and oxazepam (1d) in macca mulatto monkeys[15] have appeared. Hydrolysis kinetics of diazepam, oxazepam,[26] nitrazepam[27] (1h), ripazepam (4) and other pyrazoloazepinones[28] are reported. A specific radioimmunoassay for determining clonazepam (1i) in human plasma[29] and gas liquid chromatography procedures for separating a variety of benzodiazepines are given.[30]

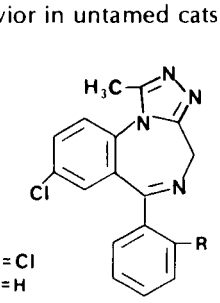
Acute overdosages with benzodiazepines,[31] toxicity of high dose flurazepam (1e) in hospitalized elderly patients[32] and the use of benzodiazepines in nonpsychiatric medical practice[33] are reviewed.

Dietary administration of diazepam (1a), flurazepam (1e), nitrazepam (1h), oxazepam (1d), and prazepam (1j) at subneurotoxic doses to Swiss-Webster mice led to reduced postnatal survival of off-spring.[34]

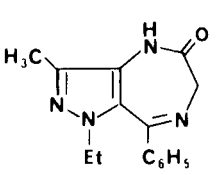
Three cases of acute psychotic illness following sudden withdrawal[35] and disorganization of thought as manifested in speech[36] are reported with benzodiazepine therapy.

Anti-Anxiety Agents — Alprazolam (U31, 889, 3b) at 1.5-3.0 mg daily gave moderate to marked improvement in patients suffering from anxiety and tension after alcohol withdrawal.[37] Camazepam[38] (SB 5883, 1k) at 30 mg, fludiazepam[39] (1l) at 7 mg, halazepam[40] (1m) at 120 mg, lorazepam[41,42] (1g) at 3-6 mg, medazepam[43] (1n) at 16 mg and clobazam[44,45] (HR 376, 5) at 20-40 mg daily doses were useful for relieving anxiety in adult patients. Chlordesmethyldiazepam (1o) at 6 mg daily was effective in female neurotic patients.[46] Chlordiazepoxide at 30 mg daily in anxious patients induced increases in verbal interpersonal hostility following frustration.[47]

The imidazobenzodiazepine[48] 6, ethoxy benzodiazepine[49] 7 and the as-triazinobenzodiazepine[50] 8 all have potent minor tranquillizer activity in mice. Triazobenzodiazepine[51] 9 and RGH-3331[52] (10) gave anxiolytic activity in rats. The pyrolobenzodiazepine 11 was more potent than diazepam in reducing anxiety in rats and is used in veterinary medicine as an animal anesthetic.[53] Agressive behavior in untamed cats was markedly inhibited by MS 4101[54] (2a).




3a R=Cl
3b R=H

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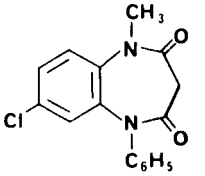


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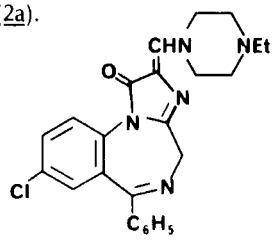


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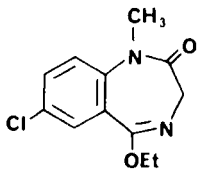


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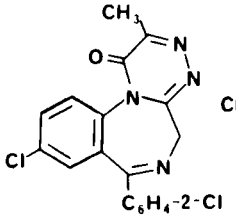


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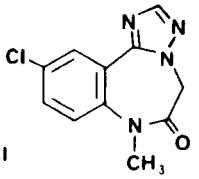


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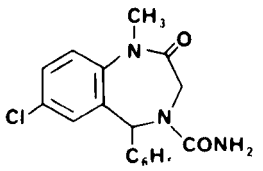
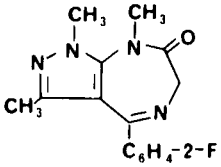



10

Anticonvulsant Agents — Clonazepam (1i) was clinically useful in the treatment of tonic-clonic convulsions,[55] photosensitive epilepsy,[55] focal epilepsy,[55,56] and the stiff-man syndrome[57] caused by diazepam. Studies in dogs, mice and rats indicate that the anticonvulsant activity of clonazepam is partially due to the inhibition of synaptic recovery and the enhancement of presynaptic inhibition.[58]

The benzodiazepine 12 showed anticonvulsant activity greater than diazepam in mice.[59] Sulazepam (1p) was active against corazol induced convulsions,[60] the benzodiazepine 13 against metrazole convulsions[61] and the pyrolodiazepine 14 against pentylenetetrazole convulsions.[62]

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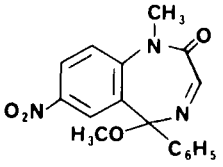


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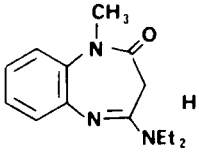


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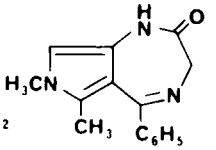


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Sedative-Hypnotics — Triazolam (3a) at 0.25-0.5 mg was an effective sleep inducer devoid of significant side effects,[63] showed no evidence of toleration,[64-66] but caused increased thought disorders, and congnitive-intellectual impairment.[67]

Flunitrazepam (1q) at 1 mg in normal subjects[68] and at 2 mg in sleep disorder[69,70] or minor gynecological surgery patients[71] was effective in inducing sleep. Hangover and rebound phenomena was found with flurazepam (1e), flunitrazepam (1q) and nitrazepam (1h) in healthy subjects.[72]

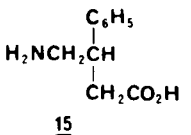
Temazepam (1c) at 10-30 mg is a useful hypnotic in general practice with no hangover effects.[73] Chlordesmethyldiazepam (1o) at 2 mg induced sleep in long lasting severe insomniacs[74] but caused behavioral performance impairment at the same dose.[75] Useful sleep induction was given by Sch 16134 (1r) at 50 mg.[76]

## Non-Benzodiazepine Compounds

Anti-Anxiety Agents — Several clinical strategies,[41,77] a new anxiolytic rating scale[78] and an intensive design analysis[79] for evaluating anxiolytic agents were reported. The joint use of antidepressant and anxiolytic therapy for the alleviation of anxiety was indicated.[80] A social isolation syndrome in monkeys was proposed as a model for human psychoses.[81]

The tranquilizer phenigam (15) potentiates sedation.[82] Compound 16 was active in monkeys and rodents[83] as an anti-anxiety agent, and 17 appears similar in mice i.p. to chlordiazepoxide.[84]

Based on an increased NE turnover in rats and no effect on DA turnover, it was anticipated that pyrroxan (18) would display anti-anxiety action together with sedation and tranquilizing effects.[85]

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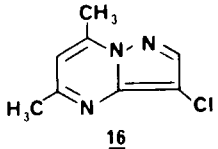


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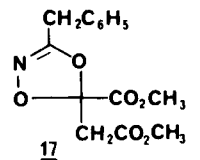


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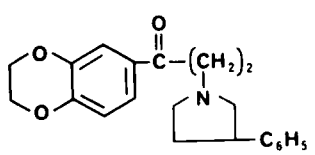


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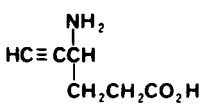


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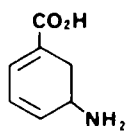



20

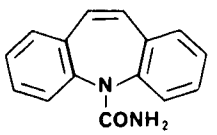
Anticonvulsants — The drug interaction of antiepileptic agents,[86] drugs in common use to control clinical seizures,[87] indications for determining serum levels of antiepileptic agents[88] and the metabolic correlation between epilepsy and transmitters[89] are reviewed. A theory was postulated which might explain the relationship between psychosis and epilepsy that occurs in a subgroup of schizophrenic patients.[90] New rodent models for status epilepticus[91] and petit mal epilepsy[92] were reported. The teratogenic activity of several antiepileptic drugs in mice is compared[93] and the teratogenesis of phenytoin is postulated to result from the covalent binding of phenytoin epoxide to constituents of the gestational tissues.[94]

Intracerebroventricular administration of GABA to mice inhibited electrically or pentylenetetrazole induced convulsions.[95] The role played by the transmitter pool of GABA in the convulsant action of chemoconvulsants and in the anticonvulsant effect of antiepileptics clinically used in petit mal epilesy was suggested.[96]

GAG (RMI 71675, 19) produces a sustained elevation of brain GABA concentration, protected against electroshock, thiosemicarbazide and strychnine seizures.[97] Gabaculine (20), a potent inhibitor of GABA transaminase, given i.v. or i.p., elevated brain GABA content and prevented picrotoxin and thiosemicarbazide, but not electroshock induced convulsions.[98]

Carbamazepine (21) produced qualitative control of focal seizures and reduced intracortical spike propagation,[99] and caused less side effects than phenytoin,[100] with no hematotoxic complications. It is less likely to interfere with mental functions in children than equivalent doses of sedative anticonvulsants.[101]

Mephenytoin (22a) was effective against seizures of focal origin, but was of little value in other seizures.[102] The binding of pentobarbital (23a) and diphenylhydantoin (22b) to blood cells was found to be independent of total drug concentration within therapeutic levels.[103]



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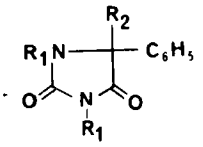
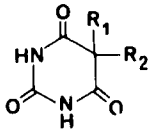
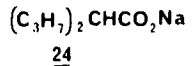


22a, $R_1$=Me, $R_2$=Et

22b, $R_1$=H, $R_2$=$C_6H_5$



| | $R_1$ | $R_2$ |
|---|---|---|
| 23a | CHMeEt | Et |
| 23b | Ph | Et |
| 23c | CHMeEt | allyl |



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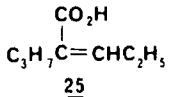


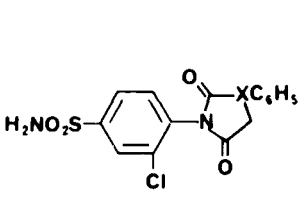
25

Sodium valproate (24) at 600-1200 mg daily was useful in the treatment of grand mal seizures and atonic attacks.[104,105] The bioavalibility,[106] therapeutic efficacy in epilepsy and the mechanism of action[107] of sodium valproate are reviewed. The related pentenoic acid 25 exhibited anxiolytic action by inhibiting 2-oxoglutarate transaminase in animals.[108]

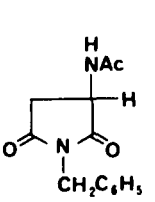
The structure activity correlation between inhibition of tetrazole seizures and partition coefficients of various thiobarbiturates[109] and hydantoins[110] were studied. GS 223 (26a) was the most

active member of a series protecting rodents against MES and pentylenetetrazole seizures.[111a] The related succinimide PB 385 (26b) has been proposed for clinical studies as an anticonvulsant agent.[111b]

Glutarimides, (R)-27,[112] 28,[113] and 29[114] protected against MES and tetrazole induced seizures in mice. X-ray studies of phenacetamide (30) support the concept that the stereochemical features confer anticonvulsant action against grand mal epilepsy.[115]



26a X=N
26b X=CH



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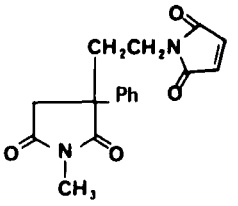

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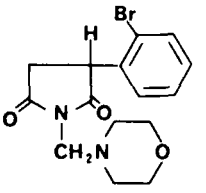
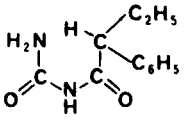


29

Thiocarbamate 31[116] and mercaptotriazole 32[117] protected mice against pentylenetetrazole induced convulsions. Other ureas providing protection in mice against MES or pentylenetetrazole induced convulsions include 33,[118] 34,[119] 35,[120] 36,[121] and 37.[122]



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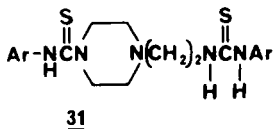
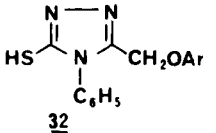


31

Ar=4C$_2$H$_5$OC$_6$H$_4$



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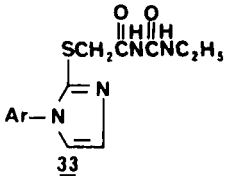
Ar= 2,6-(CH$_3$)$_2$C$_6$H$_4$



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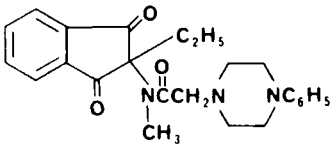
Ar=4-CH$_3$C$_6$H$_4$



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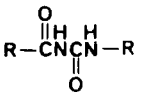
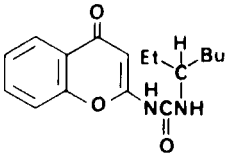
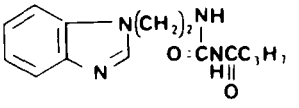


35

R=CH(C$_6$H$_5$)$_2$



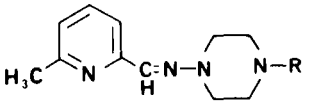
36



37

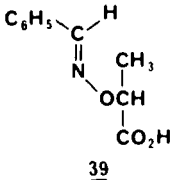
Piperazinimine SC 13504 (38) was shown to be a very selective anticonvulsant when fixed interval operant responses were used to compare behavioral toxicities.[123] Benzylideneaminoxypropionic acid 39 prevented convulsions induced by aminoxyacetic acid.[124]

p-Chlorophenylalanine (40) caused a marked reduction in the susceptibility of inbred mice to audiogenic seizures.[125] Compounds 41a,[126] 42,[127] and 43[128] were active against MES induced convulsions in mice.

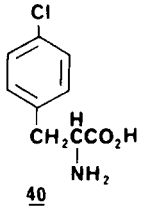


38

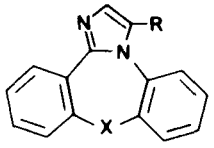
R= CH(C$_6$H$_5$)$_2$



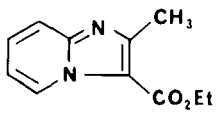
39



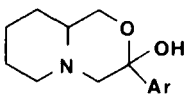
40



41a R=H, X=NH
41b R=CH$_3$, X=O

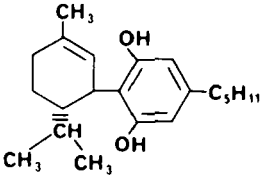


42

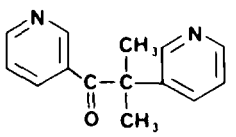


43

Ar = 3-$CF_3C_6H_4$



44

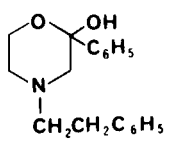


45

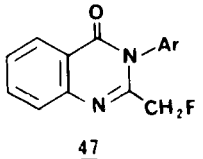
Cannabidiol (44) in rats protected against MES and audiogenic seizures indicating its effectiveness against major rather than minor seizures.[129]

In mice metyrapone (45) prevented both the onset of seizures and the long term accumulation of cerebral glycogen.[130] Morpholine 46,[131] quinazolone 47[132] as well as compound 48[133] provided protection against tetrazole convulsions.

Diphenylsilanediol (49) was shown to be orally active in the mouse electroshock model and idiopathic epileptic dogs refractory to seizure control by several anticonvulsants.[134] Swertiamarin (50) was effective against MES and pentylenetetrazole.[135] Glycine choline ester 51[136] was effective in mice and taurine[137] (52) caused a disappearance of the chemical manifestation of seizures in the chronically epileptic cat.

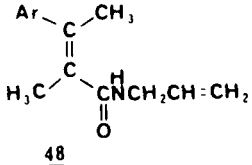


46



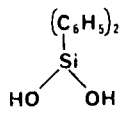
47

Ar = 2-$CH_3C_6H_4$

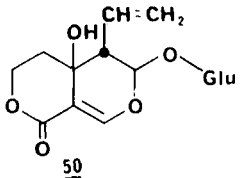


48

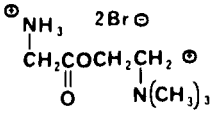
Ar = 4-$FC_6H_4$



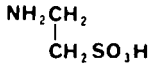
49



50



51

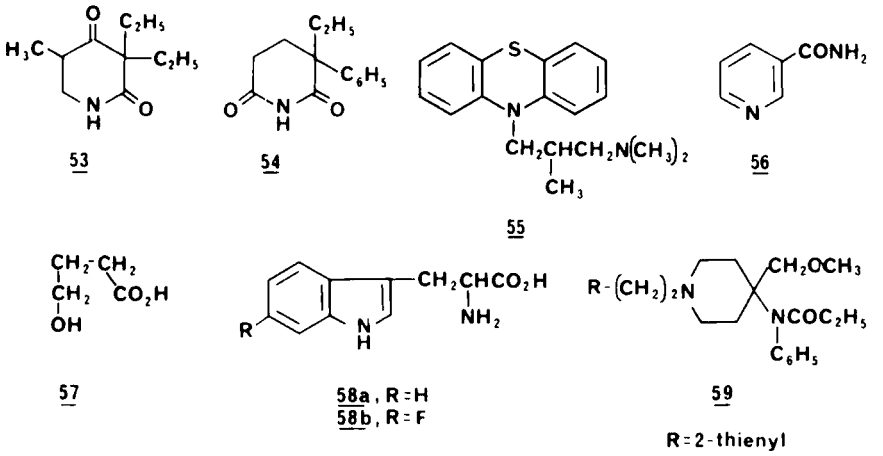


52

Sedative-Hypnotics — A standard protocol was reported to study hypnotic drugs in separate sleep laboratories.[138] Stress induced insomnia in rats was reported to be a reliable model for screening potential hypnotic agents[139] and several laboratory screens for detecting thalidomide-like hypnotic activity were described.[140] The metabolism of phenobarbital[141] (23b) and secobarbital[142] (23c) and the pharmacokinetics of glutethimide[143] (54) were reported.

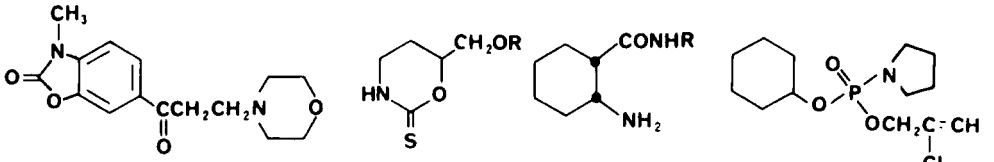
Methyprylon (53) was found more frequently superior to placebo than pentobarbital (22a) and glutethimide (54) when assessed using both subjective and objective techniques with chronic insomniacs.[144]

The antihistamine trimeprazine (55) acts as a sleep inducer, increasing both REM and slow wave sleep with no REM rebound after withdrawal.[145] It was shown that large doses of nicotinamide (56) result in an increased brain 5-HT level and consequently an increase in REM sleep.[146]



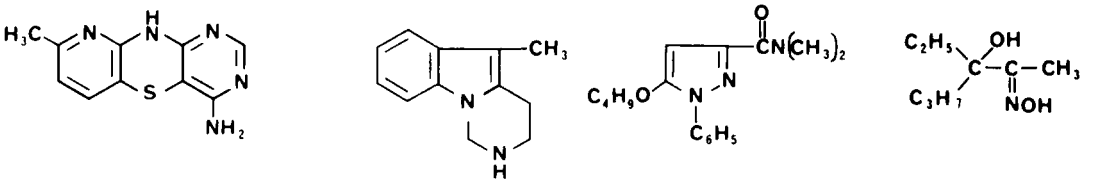
53 54 55 56 57 58a, R=H 58b, R=F 59 R=2-thienyl

While only lasting 2-3 hrs., γ-hydroxybutyric acid (57) induced a sleep indistinguishable from natural sleep by subjective, behavioral and EEG criteria.[147] In humans, ℓ-tryptophan (58a) reduced sleep latency without distorting sleep physiology, both on long term administration and after drug withdrawal[148] and sufentanil (59) had greater hypnotic activity than ten fold higher doses of fentanyl.[149]



60 61 R=4-FC6H4 62 63

Several peptide fragments related to bradykinin injected intracerebrally in mice prolonged pentobarbital sleeping times[150] and the isolation and pharmacology of the controversial rabbit δ -EEG enhancing nonapeptide were reported.[151] Compound 41b[126] caused sedation in rats while 60,[152] 61,[153] 62,[154] and 63[155] were active in mice. In rats, ip., 6-flurotryptophan (58b) produce a significant reduction is sleep latency, but an increase in the number of awakenings.[156] In mice, compound 64[157] and 65[158] potentiated the effects of barbiturates. Pyrazole 66[159] and oxime 67[160] were the most active sedative-hypnotics of their respective series.



64 65 66 67

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