Kirk-Othmer Encyclopedia of Chemical Technology.

HYPNOTICS, SEDATIVES, ANTICONVULSANTS, AND ANXIOLYTICS

The clinical effects observed with the variety of therapeutic agents that are used as hypnotics, sedatives, anxiolytics, and anticonvulsants reflect a spectrum of related activities at the cellular level characterized by a series of generalized responses within the central nervous system (CNS) that result in alterations in the dynamic state of brain function. Considerable advances have been made in the elucidation of the molecular events surrounding the activities of these agents and the γ-aminobutyric acid [56-12-2] (GABA)/benzodiazepine (BZ) receptor complex (1). Serotonin [50-67-9] (2), ion channel(s), and purinergic (3) recognition sites have been implicated in the mechanism of action of a variety of anxiolytics, hypnotics, sedatives, and anticonvulsants, but the molecular targets for many of these agents, both in terms of efficacy and side effect liabilities, remain unknown. Recombinant deoxyribonucleic acid (DNA) technology is being employed to determine the receptor subclasses and novel molecular targets within the CNS (4).

Hypnotic agents depress the CNS and are able to induce sleep when given at appropriate doses. Such agents typically act either by enhancing inhibitory neurotransmitter actions, eg, GABA, in the CNS or by inhibiting the actions of excitatory neurotransmitters, eg, glutamate (see Neuroregulators). At lower doses, this class of compound can be sedating and can also have a calming or anxiolytic action. At higher doses, the traditional hypnotic agents, but not the BZs, can produce coma, a degree of anesthesia, and eventually death.

Anticonvulsants or antiepileptics are agents that prevent epileptic seizures or modulate the convulsant episodes elicited by seizure activity. Certain of these agents, eg, the BZs, are also hypnotics, anxiolytics, and sedatives, reinforcing the possibility of a common focus of action at the molecular level (1).

Anxiolytics are compounds that act primarily to relieve the symptoms of anxiety although such agents can also be used as anticonvulsants, sedatives, hypnotics, and anesthetic agents (see Anesthetics). The principal class of anxiolytics, the BZs, shows dependence liability (5) whereas newer agents such as buspirone [36505-84-7] and ritanserine [8705-43-2] produce antianxiety effects via central serotoninergic systems (6).

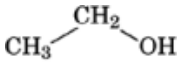
1. Hypnotics and Sedatives

Sleep disturbance or insomnia has become an increasingly prevalent condition in modern society. It is associated with a variety of mental states including chronic anxiety, depression, various dementias, stress, overwork, and aging. The condition is manifest by difficulty in falling asleep, a disturbed sleep cycle, awakening without any feeling of refreshment, and a general malaise. Whereas some chronic sleep disturbances may be attributable to viral infections, causes are generally asymptomatic and result in a poor quality of life. Superimposed on everyday stress factors that have the potential to interfere with sleep is the phenomenon of transcontinental and international jet travel that alters the circadian and ultradian mechanisms involved in sleep (7).

As a therapeutic class, hypnotics are nonselective CNS depressants that elicit drowsiness and a natural sleep state from which the individual can be aroused. The effects of hypnotics are generally dose-dependent.

2. Alcohols

Ethanol [64-17-5], C_2H_5OH (**1**) is a potent sleep inducing agent that in the form of wine (qv), liquor (see Beverage spirits, distilled), and beer (qv) has been in recreational use since prehistory. Ethanol (qv) is a sedative, anxiolytic, and hypnotic agent. It can prove fatal in excess both acutely, owing to CNS depressive actions, and chronically as the result of progressive alcohol-induced tissue atrophy, most notably cirrhosis of the liver and neurological damage. Whereas ethanol is typically viewed as a CNS stimulant, this perceived effect results from a depression of tonic inhibitory neurotransmission processes. Chlorinated alcohols such as ethchlorvynol [113-18-8], C_7H_9ClO (**2**) and chloral hydrate [302-17-0], $C_2H_3Cl_3O_2$ (**3**) are also useful hypnotics. The latter compound also possesses anticonvulsant and muscle relaxant activities. Both ethanol derivatives are associated with nausea, vomiting, dizziness at high doses and a typical hangover effect reflecting a residual depression of the CNS. Chloral hydrate irritates the gastrointestinal tract and can cause ataxia, nightmares, and allergic reactions. Ethchlorvynol has many properties in common with chloral hydrate and in addition has hypotensive actions.



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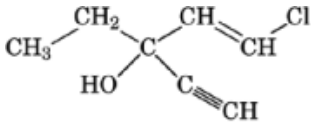

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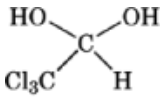
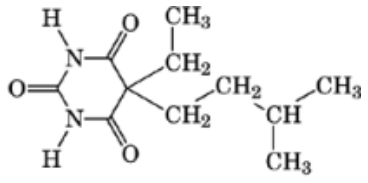


(**3**)

3. Barbiturates

The barbiturates represent a seminal class of hypnotic agents that have been largely replaced in clinical use by the benzodiazepines (BZs). The latter have a wider therapeutic index in terms of respiratory depression and residual depression and less abuse potential than the barbiturates. In addition, the BZs lack the spectrum of drug interactions that are seen with barbiturates. As a class, barbiturates have a broad spectrum of CNS depressant activity from mild sedation to general anesthesia. Representative compounds include amobarbital [57-43-2], $C_{11}H_{18}N_2O_3$ (**4**), pentobarbital [76-74-4], $C_{11}H_{18}N_2O_3$ (**5**), phenobarbital [50-06-6], $C_{12}H_{12}N_2O_3$ (**6**), and the 5-allyl-5-(1-methylbutyl) analogue, secobarbital [76-73-3], $C_{12}H_{17}N_2O_3$ (**7**). The barbiturates decrease sleep latency, decrease the number of awakenings and REM sleep period, and decrease body movement. With chronic use, the effects of the barbiturates can decrease by up to 50% within two weeks. The 5-phenyl substituted

barbiturates, eg (**6**), are selective as anticonvulsant agents. Phenobarbital (**6**) is used in emergency rooms for the treatment of convulsions, whereas shorter-acting barbiturates are used as intravenous anesthetics.



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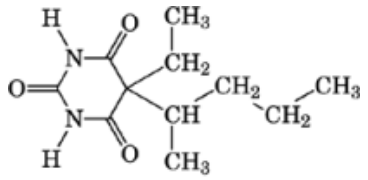

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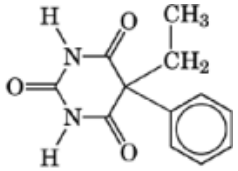

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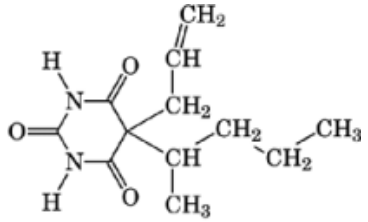


(**7**)

Mechanistically, the barbiturates interact with the $GABA_A$/BZ receptor complex to indirectly facilitate GABAergic neurotransmission (1). Hypnotic doses of barbiturates result in a hangover like that from usage of ethanol and the chlorinated alcohols. Barbiturate poisoning is a significant clinical problem resulting from deliberate or accidental overdosing.

3.1. Benzodiazepines

Many of the 1,4-BZs are routinely used as hypnotics. Examples include chlordiazepoxide [58-25-3], $C_{21}H_{14}Cl_2N_3O$ 1, clorazepate [57109-90-7], $C_{16}H_{13}ClN_2O_4$ 1, diazepam [439-14-5], $C_{16}H_{13}ClN_2O$ 1, flurazepam [17617-23-1], $C_{21}H_{23}ClFN_3O$ 1, lorazepam [846-49-1], $C_{15}H_{10}Cl_2N_2O$ 1, triazolam [28911-01-5], $C_{17}H_{12}Cl_2N_4$ 1, estazolam [29975-16-4], $C_{16}H_{11}ClN_4$ 1, quazepam [36735-22-5], $C_{17}H_{11}ClF_4N_2S$ 1, and temazepam [846-50-4],

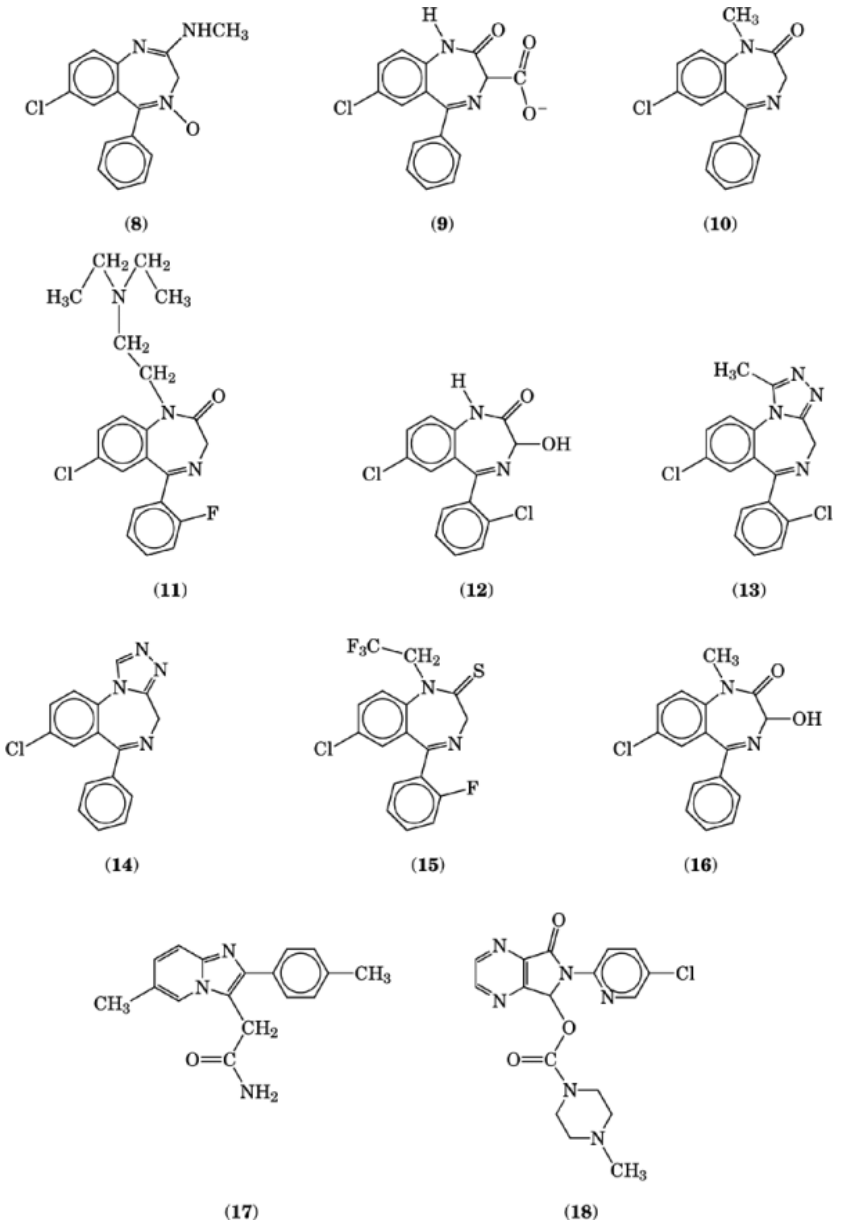


Fig. 1. Structures of 1,4-benzodiazepines and the newer non-BZ pharmacophores used as hypnotics. See text.

$C_{16}H_{13}ClN_2O_2$ 1, all shown in Figure 1. Unlike the barbiturates, the BZs are not general CNS depressants and are generally considered to be the safest available as hypnotics. As a class, BZs are also muscle relaxants and interact with alcohol (1). These last properties in addition to dependence liability (5) and amnesia limit their usefulness in the clinical setting.

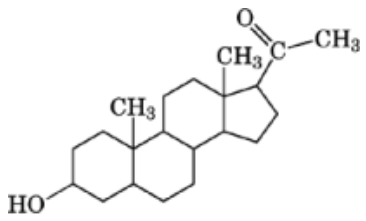
Extensive research into the BZs stimulated by the identification of the $GABA_A$/BZ receptor complex (1) resulted in the identification of a number of non-BZ pharmacophores that interact with the central BZ/GABA

receptor complex having a reduced incidence of the side effects seen with classical BZs. Zolpidem [82626-48-0], $C_{19}H_{21}N_3O$ 1 and zopiclone [43200-80-2], $C_{17}H_{17}ClN_6O_3$ 1 are sedative–hypnotics lacking anticonvulsant and anxiolytic activity that are thought to selectively interact with a BZ receptor subtype termed the ω1 or BZ1. Activation of the ω2 BZ or BZ2 receptor is responsible for the side effects of the BZs which include dependence liability, muscle relaxation, and alcohol and barbiturate potentiation. Rebound insomnia is a significant problem associated with the BZ hypnotics (8) that may be alleviated with the use of compounds like zolpidem and zopiclone.

3.2. Miscellaneous Agents

Compounds having sedative–hypnotic properties include the phenothiazines (Fig. 2), methotrimeprazine [60-99-1], $C_{19}H_{24}N_2OS$ 2 and promethazine [60-87-7], $C_{17}H_{20}N_{20}S$ 2, methyprylon [125-64-4], $C_{10}H_{17}NO_2$ 2, glutethemide [77-21-4], $C_{13}H_{15}NO_2$ 2, methaqualone [72-44-6], $C_{16}H_{14}N_2O$ 2, meprobamate [57-53-4], $C_9H_{18}N_2O_4$ 2, carbromal [77-65-6], $C_7H_{13}BrN_2O_2$ 2, bromoisovalum [496-67-3], $C_6H_{11}BrN_2O_2$ 2, ethinamate [126-52-3], $C_9H_{13}NO_2$ 2, etomidate [33125-97-2], $C_{14}H_{16}N_2O_2$ 2, and paraldehyde [123-63-7], $C_6H_{12}O_3$ 2. Of these, glutethimide is addicting and shows little advantage in use as compared to the BZs or barbiturates whereas meprobamate is the most clinically useful.

A newer class of hypnotic at the preclinical stage as of this writing (ca 1993) are the neurosteroids, also known as the epalons and represented by (**30**) (9), $C_{21}H_{34}O_2$. These also interact with the $GABA_A$/BZ receptor complex, have shown interesting activity in preclinical models (10), and are undergoing clinical trials.



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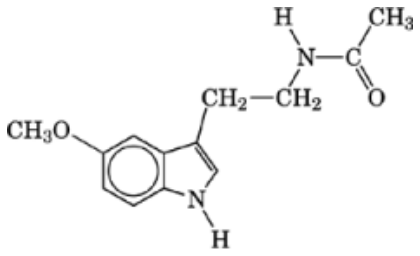

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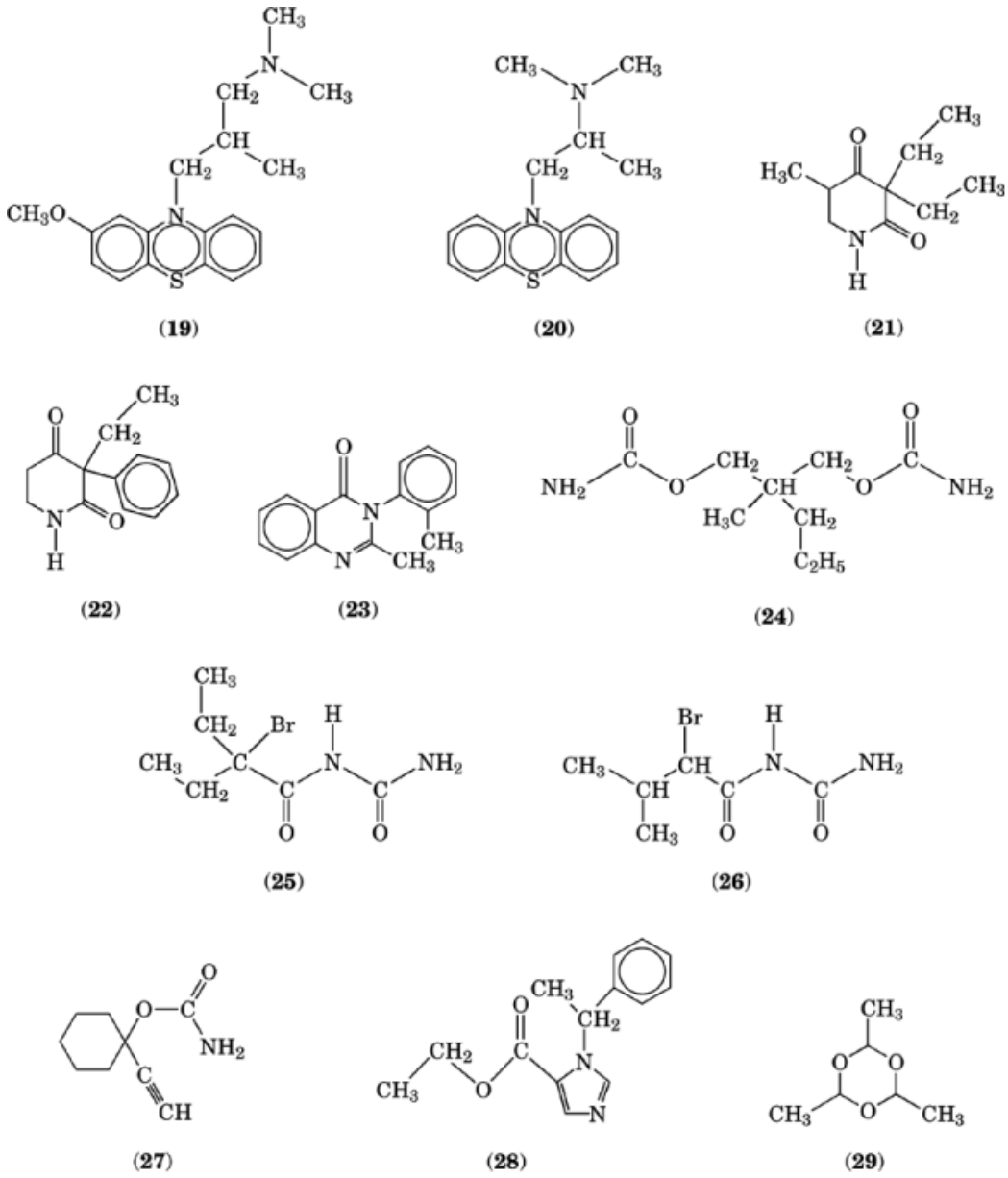
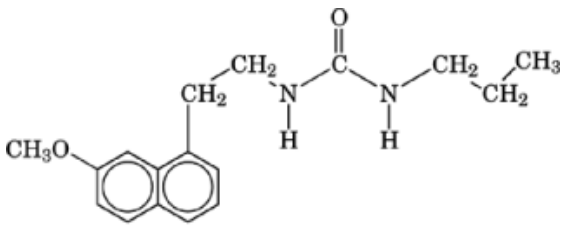
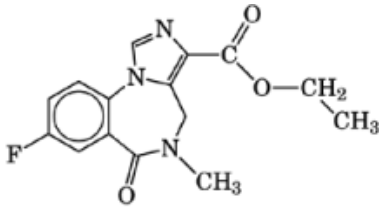


Fig. 2. Structures of phenothiazines having sedative–hypnotic properties. See text.



Melatonin [73-31-4], $C_{13}H_{16}N_2O_2$ (**31**) has marked effects on circadian rhythm (11). Novel ligands for melatonin receptors such as (**32**) (12), $C_{17}H_{16}N_2O_2$, have affinities in the range of $10^{-13}\ M$, and have potential use as therapeutic agents in the treatment of the sleep disorders associated with jet lag. Such agents may also be useful in the treatment of seasonal affective disorder (SAD), the depression associated with the winter months. Histamine (see Histamine and histamine antagonists), adenosine (see Nucleic acids), and neuropeptides such as corticotropin-like intermediate lobe peptide (CLIP) and vasoactive intestinal polypeptide (VIP) have also been reported to have sedative–hypnotic activities (7).

BZ analogues that can act as antagonists or inverse agonists of the classical anxiolytic agonist, diazepam [439-14-5], have also been discovered as the result of the intensive effort following the discovery of the GABA/BZ receptor complex. Flumazenil [78755-81-4], $C_{15}H_{14}FN_3O_3$ (**33**), an imidazoBZ, is in clinical use as an analeptic. It is used in reversing the sedation associated with the BZs, specifically in terms of outpatient anesthesia (1).



(**33**)

4. Anticonvulsants

The neurological CNS disorder known as epilepsy encompasses a group of disorders associated with seizures and convulsions (13). Primary or idiopathic epilepsy refers to situations in which there is no apparent cause for seizures; secondary or symptomatic epilepsy can be traced to infections, adverse drug reactions, trauma, neoplasm, developmental abnormalities, or cerebrovascular disease. Convulsive seizures are associated with a generalized disturbance in cerebral function that may result from the abnormal discharge of a localized group of neurons in response to ill-defined endogenous or exogenous stimuli. Partial seizures may be ascribed to different lobes of the cerebral cortex.

Seizures are classified in terms of clinical manifestations into either partial or generalized according to guidelines established by the Commission on Classification and Terminology of the International League Against Epilepsy (14). The partial seizure category includes simple partial and complex partial seizures; the generalized seizure category includes absence seizures, atypical absence seizures, myoclonic, clonic, tonic, tonic–clonic (grand mal), and atonic seizures (13–15).

Simple partial seizures are characterized by convulsions confined to a specific muscle group, ie, sensory disturbances but no loss of consciousness. Complex partial seizures involve atypical electroencephalogram (EEG) activity, confused behavior, abnormalities in anterior temporal lobe function, and loss of consciousness. Absence or petit mal seizures are associated with a brief loss of consciousness associated with high voltage, synchronous, spike, and wave EEG patterns with clonic motor manifestations. Atypical absence seizures are slower in onset than absence seizures having a heterogenous EEG profile. Myoclonic seizures involve isolated clonic jerks associated with multiple EEG spiking, whereas clonic seizures involve a rhythmic contraction of all muscles, autonomic features, and loss of consciousness. Tonic seizures have similar manifestations to clonic seizures except that these are marked by opisthotonus, spasm of the back muscles, that causes the head and limbs to arch backward and the trunk forward, ie, the classical manifestation of an epileptic episode. Tonic–clonic or grand mal seizures involve major convulsive episodes with tonic, then clonic contractions of the

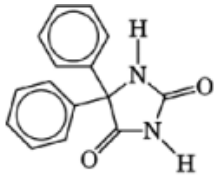
muscles in the limbs, trunk, and head. Such attacks last 2–5 min. Atonic seizures are associated with a loss of postural tone.

The majority of patients experience only one type of seizure, although some individuals can have two or more seizure types (13). Considerable experience is required to determine the various seizure nuances in affected patients and assign medication accordingly. *Status epilepticus* describes the situation where seizures occur with no intervening periods of consciousness.

There are many classes of anticonvulsant agent in use, many associated with side effect liabilities of unknown etiology. Despite many years of clinical use, the mechanism of action of many anticonvulsant drugs, with the exception of the BZs, remains unclear and may reflect multiple effects on different systems, the summation of which results in the anticonvulsant activity. The pharmacophore structures involved are diverse and as of this writing there is little evidence for a common mechanism of action. Some consensus is evolving, however, in regard to effects on sodium and potassium channels (16) to reduce CNS excitation owing to convulsive episodes.

4.1. Barbiturates

Whereas the barbiturates, eg, phenobarbital (**6**), and bromides, were used as antiepileptic agents in the nineteenth century, the discovery and introduction of phenytoin [57-41-0], $C_{15}H_{12}N_2O_2$ (**34**), in the mid-1930s represented a significant therapeutic advance. Phenytoin is used in the treatment of all types of seizure except absence and is the drug of choice in *status epilepticus.* This drug is not very useful, however, in treating myoclonic or atonic seizures. Phenytoin exerts its anticonvulsant effects without causing a general depression of the CNS. Its mechanism of action has been linked to alterations in $Na^+ - K^+$-adenosine triphosphatase (ATPase) activity and sodium channel conductance that result in a stabilization of excitation threshold (17, 18). Overdosing with phenytoin generally leads to increased excitability of the CNS that can exacerbate epileptic symptoms and on a chronic basis leads to intellectual deterioration, memory impairment, and peripheral neuropathy and in some instances megablastic anemia (13). Phenytoin, like other anticonvulsants, is counterindicated in pregnancy owing to tetratogenic effects characterized as fetal anticonvulsant syndrome (19). Mephenytoin [50-12-4], $C_{12}H_{14}N_2O_2$ (**35**) and ethotoin [86-35-1], $C_{11}H_{12}N_2O_2$ (**36**) are other hydantoin anticonvulsant agents (see Hydantoin and derivatives).



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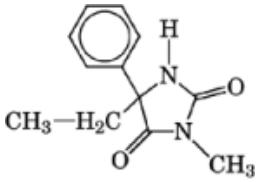

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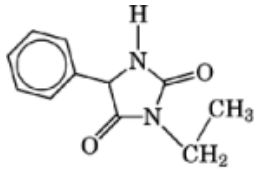
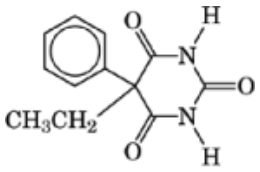


(**36**)

The barbiturate phenobarbital (**6**) is a long-acting anticonvulsant used against generalized and partial seizures but it is ineffective in absence seizures (13). The compound is thought to produce its effects via the $GABA_A$/BZ receptor complex resulting in an enhancement of inhibitory GABAergic transmission that results in an increased threshold to electrical and chemical convulsant stimuli. A concomitant depression of excitatory glutamatergic transmission is also produced by phenobarbital. Phenobarbital is sedating and, like phenytoin, has adverse effects on CNS function including ataxia and learning deficits (13). Unlike phenytoin, phenobarbital produces physical dependence and impotence. Methylphenobarbital [115-38-8], $C_7H_{15}N_2O_3$ (**37**) and metharbital [50-11-3], $C_9H_{14}N_2O_3$ (**38**) are *N*-methyl derivatives of phenobarbital that are also used as anticonvulsants.



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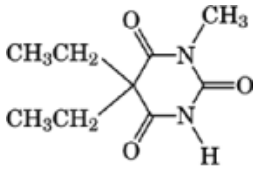

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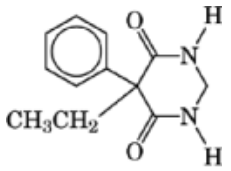

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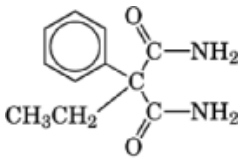
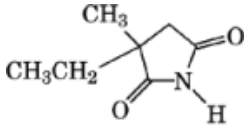


(**40**)

Primidone [125-33-7], $C_{12}H_{14}N_2O_2$ (**39**) is an analogue of phenobarbital that is used for the treatment of generalized tonic-clonic seizures. It is metabolized in humans to phenobarbital (**6**) and phenylethylmalondiamide [7206-76-0], $C_{11}H_{14}N_2O_2$ (**40**) and these metabolites are probably responsible for its anticonvulsant actions. Primidone has many of the side effect liabilities seen with phenobarbital.

4.2. Succinimides

Ethosuximide [77-67-8], $C_7H_{11}NO_2$ (**41**) and the related succinimide, methsuximide [77-41-8], $C_{12}H_{13}NO_2$ (**42**) are used in absence seizure treatment. Like the other anticonvulsants discussed, the mechanism of action of the succinimides is unclear. Effects on T-type calcium channels and $Na^+ - K^+$-ATPase activity have been reported (20). Ethosuximide has significant CNS and gastrointestinal (GI) side effect liabilities (13).



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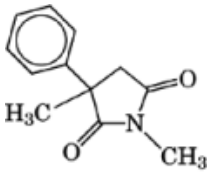
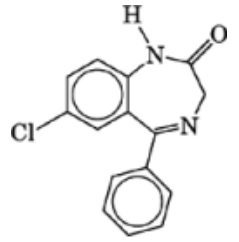


(**42**)

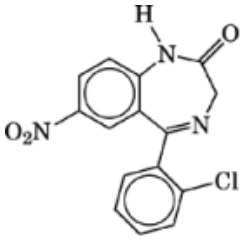
4.3. Benzodiazepines

Several BZs have anticonvulsant activity and are used for the treatment of epilepsy producing their anticonvulsant actions via interactions with the $GABA_A$/BZ receptor complex to enhance inhibitory GABAergic transmission (1). The anticonvulsant actions of the BZs tend to tolerate upon chronic usage in six months, and BZs also lead to withdrawal symptomatology. Other side effects include sedation, ataxia, and cognitive impairment.

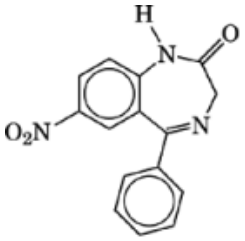
Clorazepate 1 is a prodrug of the antiepileptic agent, desmethyldiazepam [1088-11-5], $C_{15}H_{11}ClN_2O$ (**43**) that can also be formed from chlordiazepoxide and diazepam. Clorazepate is used in the treatment of generalized or partial seizures. It appears to tolerate to a lesser extent than other BZs. Diazepam and lorazepam are used in the treatment of *status epilepticus.* Clonazepam [1622-61-3], $C_{15}H_{10}ClN_3O_3$ (**44**) is effective in the treatment of absence seizures. Nitrazepam [145-22-5], $C_{15}H_{11}N_3O_3$ (**45**), which was used through the 1970s for the generalized treatment of epilepsy, is primarily used for the treatment of infantile myoclonic seizures and spasms. Clobazam [22316-47-8], $C_{16}H_{13}ClN_2O_2$ (**46**) is a 1,5-BZ having broad-spectrum antiepileptic activity.



(**43**)



(**44**)



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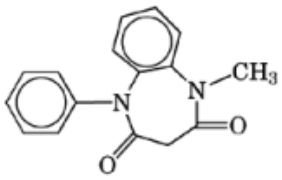
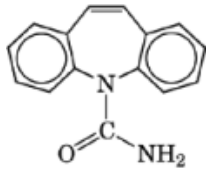


(**46**)

4.4. Miscellaneous

The iminostilbene carbamazepine [294-46-4], $C_{15}H_{12}N_2$-O (**47**) is a congener of the tricyclic antidepressant, imipramine. Initially used in the treatment of trigeminal neuralgia, (**47**) is effective against all types of epilepsy except absence. Predominant usage is in generalized tonic, tonic-clonic, and partial seizures. Like phenytoin, carbamazepine is active in enhancing neuronal sodium channel activity. Several lines of evidence (3, 21) indicate that carbamazepine has additional sites of action that distinguish this anticonvulsant from the barbiturates and phenytoin. Among these are weak interactions with CNS adenosine receptors. Carbamazepine has CNS side effects and produces nausea and respiratory depression. Oxcarbazepine [28721-07-5], $C_{15}H_{12}N_2O_2$ (**48**) is

better tolerated than carbamazepine. The latter compound has also been found to have utility in the treatment of manic depressive disorders and potentially, migraine.



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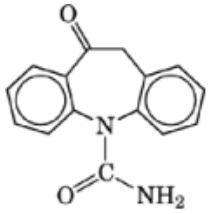
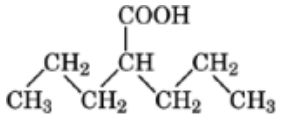


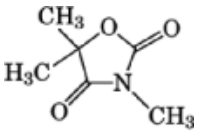
(48)

Unlike the heterocyclic anticonvulsants, valproate [99-66-1], $C_8H_{16}O_2$ (**49**) is a branched chain carboxylic acid. It is thought to interact with neuronal sodium channels and appears to enhance GABAergic tone by increasing GABA levels via inhibition of GABA transaminase and stimulation of glutamic acid decarboxylase (GAD), the enzyme responsible for the formation of GABA. The compound has minimal sedative and CNS side effects and is indicated for use in a wide variety of seizure types (22) including tonic-clonic and absence seizures. Side effects associated with the use of valproate include nausea, transient drowsiness and neutropenia, and fetal anticonvulsant syndrome (22). Like carbamazepine, valproate may have potential use in the treatment of manic depressive illness and migraine.

The oxazolidinedione trimethadione [127-48-0], $C_6H_9NO_3$ **(50)**, at one time the drug of choice for the treatment of absence seizures, has been replaced by ethosuximide (**41**) and valproate (**49**). (**50**) has a distinct profile from that of phenytoin but causes photophobia and night blindness in approximately 30% of the patients taking it and has the CNS and sedative properties seen for other anticonvulsants together with moderate neutropenia, hepatitis, and skin rashes (13). Trimethadione does not appear to produce its effects via modulation of GABA-mediated responses.



(49)



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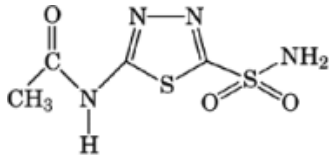
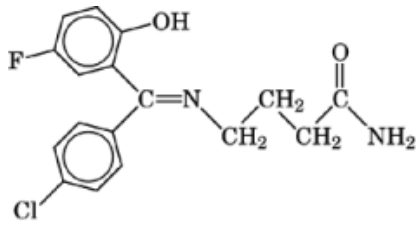


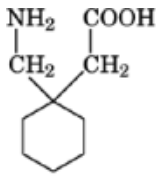
(**51**)

Acetazolamide [59-66-5], $C_4H_6N_4O_3S_2$ (**51**) is a sulfonamide having antiepileptic activity. The effects of this agent are thought to occur from inhibition of the enzyme carbonic anhydrase, which can lead to localized increases in CO_2 although not all carbonic anhydrase inhibitors have anticonvulsant activity. The anticonvulsant actions of acetazolamide are, however, rapidly tolerated. Paraldehyde 2 has been used in the treatment of *status epilepticus* but has been replaced by the BZs. Its mechanism of action remains unknown.

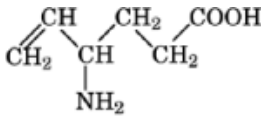
Given the potential focus of action of the BZs and valproate on enhancing GABAergic function in the CNS, a number of alternative approaches to enhancing GABAergic function have undergone evaluation in more recent years. These include GABAmimetics and inhibitors of GABA uptake (23). Progabide [62666-20-0], $C_{17}H_{16}ClFN_2O_2$ (**52**) is a GABA receptor agonist that interacts with both $GABA_A$ and $GABA_B$ receptor subtypes and is used for the treatment of complex partial seizures, generalized tonic-clonic, atonic, and myoclonic seizures as both mono- and cotherapy. Its principal side effect is hepatotoxicity. Gabapentin [60142-96-3] $C_9H_{17}NO_2$ (**53**), an analogue of GABA, has anticonvulsant activity yet is not a GABAmimetic because its actions in preclinical epileptic models are not blocked by the $GABA_A$ receptor antagonist bicuculline [485-49-4]. Vigabatrin [60643-86-9] $C_6H_{11}N_2O_2$ (**54**) is the γ-vinyl analogue of GABA that acts as an irreversible inhibitor of the enzyme GABA transaminase (GABA-T) thus acting to increase synaptic GABA levels, in turn facilitating inhibitory GABAergic transmission. CI 966 [110283-66-4], $C_{23}H_{21}F_6NO_3$ (**55**), SKF 89976A [85375-15-1], $C_{22}H_{25}NO_2$ (**56**), and tiagabine [115103-54-3], $C_{20}H_{25}NO_2S_2$ (**57**) are GABA uptake blockers, the latter of which is in Phase III clinical trials.



(**52**)



(**53**)



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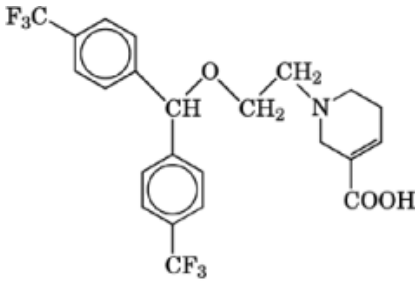

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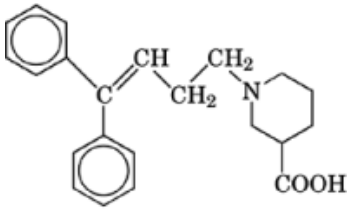
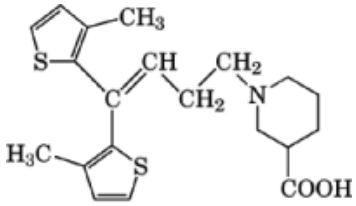
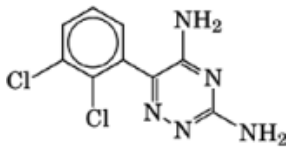


(**56**)

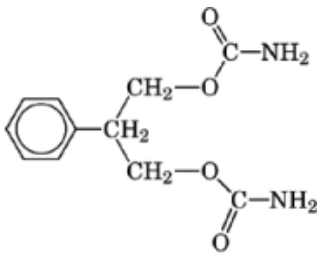


(**57**)

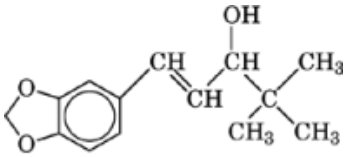
Lamotrigine [84057-84-1], $C_9H_7Cl_2N_5$ (**58**) was approved for use as an anticonvulsant in 1992 (23) and is thought to act by inhibiting the release of the excitatory neurotransmitter, glutamate (25). Felbamate [25451-15-4], $C_{11}H_{14}N_2O_4$ (**59**) is a newer anticonvulsant also approved by the FDA at the end of 1992. It has a relatively milder side effect profile than other anticonvulsant agents (23) and appears to produce its effects through a weak interaction with the glycine site associated with the *N*-methyl-D-aspartic acid (NMDA) receptor complex (26). Stiripentol [49763-96-4], $C_{14}H_{18}O_3$ (**60**) is an older agent that may produce its anticonvulsant actions via a direct or indirect GABAergic mechanism (27).



(58)



(59)



(60)

Zonisamide [68291-97-4], $C_8H_8N_2O_3S$ 3 is a broad-spectrum anticonvulsant that was approved in Japan in 1989 and as of this writing is in Phase III clinical trials in the United States (23). Remacemide [128298-28-2], $C_{17}H_{20}N_2O$ 3 is a prodrug of an *N*-methyl-D-aspartate antagonist having anticonvulsant activity in preclinical animal models that is being evaluated clinically for complex partial seizures (28). Topiramate [97240-79-4], $C_{12}H_{21}NO_8S$ 3 is another potential anticonvulsant agent currently in Phase III clinical trials (23). The purine, BW A78U, $C_{14}H_{164}N_6$ 3 and mioflazine [79467-23-5], $C_{29}H_{30}Cl_2F_2N_4O_2$ 3, an inhibitor of adenosine transport, are also active in animal models of epilepsy and are noteworthy given the potential role of the neuromodulator, adenosine, as an endogenous anticonvulsant (29). The neurosteroids, eg (**31**), represent an additional class of compound interacting with the $GABA_A$/BZ receptor complex that have anticonvulsant potential. Antagonists of the *N*-methyl-D-aspartate glutamate receptor subclass, which include the direct antagonist CGS 19755 [110347-85-8], $C_7H_{14}N_2O_5P$ 3 and the uncompetitive antagonist MK 801, dizocilpine [77086-21-6], $C_{16}H_{15}N$ 3 have reported anticonvulsant activity in preclinical models (30). The structures of these compounds are shown in Figure 3.

5. Anxiolytics

Anxiety is a fearful anticipation of an unpleasant event in the future (31) the cause of which may be unjustified by external activities. Anxiety disorders may be classified into four principal classes (32): (*1*) generalized anxiety disorder (GAD), an unrealistic or excessive anxiety and worry (apprehensive expectation) about two or more life circumstances that cannot readily be ascribed to any other mood, psychotic, or organic disorder that is manifested by motor tension, autonomic hyperactivity, and vigilance/scanning behavior paradigms;

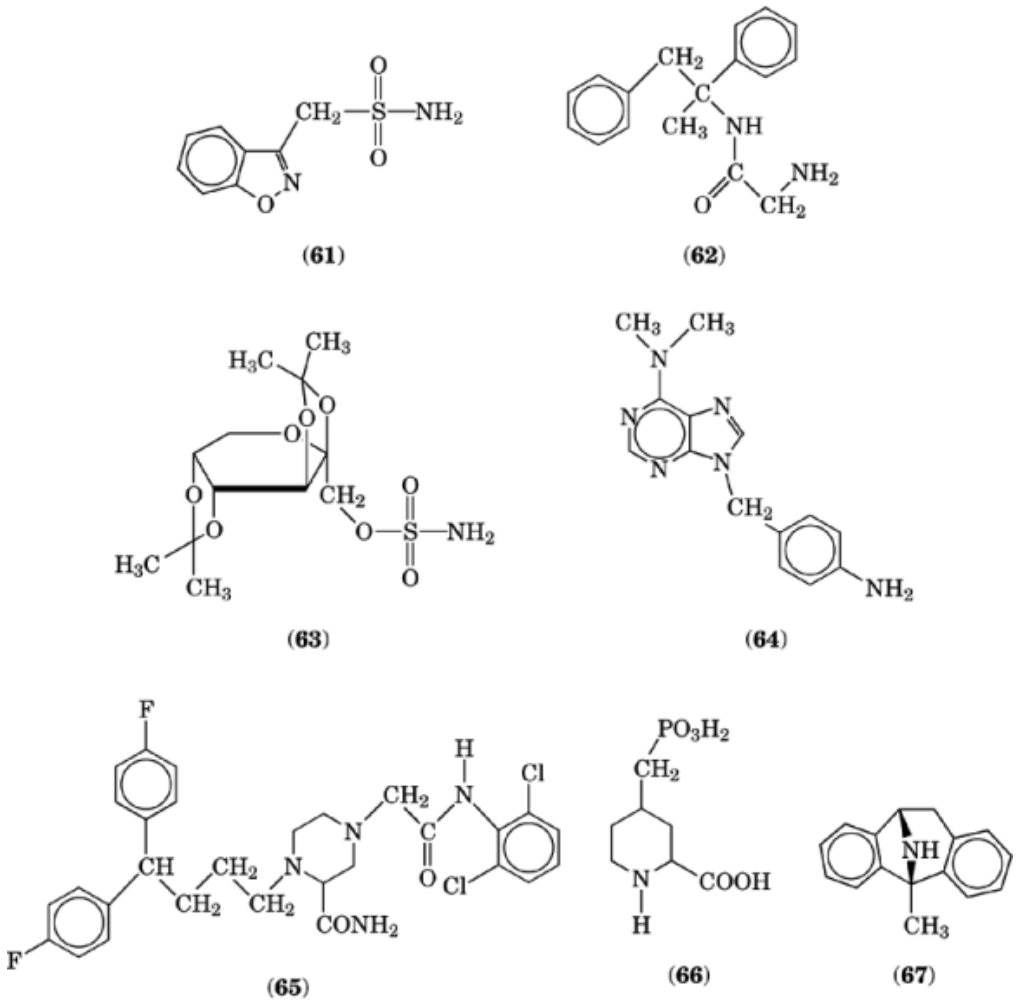
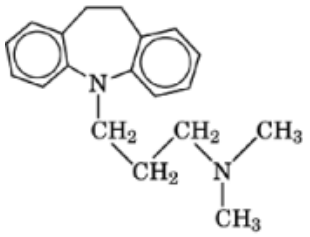


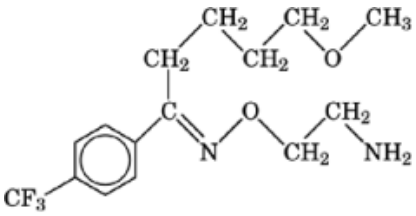
Fig. 3. Miscellaneous anticonvulsants. See text.

(*2*) panic disorders which involve discrete periods of intense fear or discomfort in the absence of appropriate external stimuli. One such disorder is agoraphobia that involves a fear of open, public places or being in a crowd; (*3*) phobic disorders, which are characterized by a persistent fear of a circumscribed stimulus, an object, or a situation, other than panic attacks. An example of a phobic disorder is being in situations that are potentially difficult or embarrassing which may involve a fear of eating in public or a fear of blushing (erythrophobia); (*4*) obsessive compulsive disorder (OCD) syndrome which involves the persistent intrusion of intense, unwanted, senseless thought (obsessions) often accompanied by repetitive, ritualistic behaviors (compulsions), perform(ed) in order to reduce the obsessional distress (32). Such compulsions include repetitive washing to remove imaginary contamination, checking, cognitive rituals, obsessional slowness and the pure obsessions that include intrusive thoughts that may be sexual and/or aggressive in nature. It is only since the late 1980s when various serotonin [50-67-9] (5HT) uptake blockers were identified, ie, cloimipramine [303-49-1], $C_{19}H_{23}ClN_2$ (**68**), fluvoxamine [54739-18-3], $C_{15}H_{21}F_3N_2O_2$ (**69**), and fluoxetine [54910-89-3], $C_{17}H_{18}F_3NO$

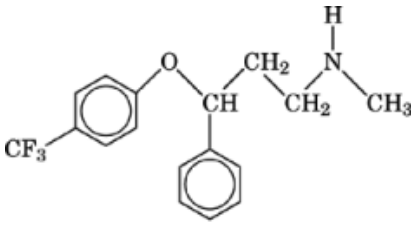
(**70**) (2, 33), that patients who subjectively ascribed their disorder to character deficits could be effectively treated.



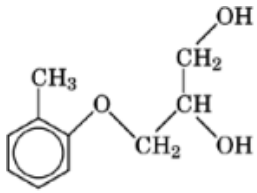
(**68**)



(**69**)



(**70**)



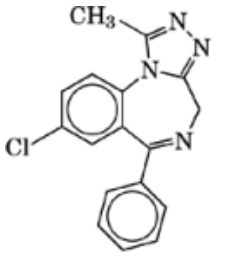
(**71**)

Ethanol (**1**) is the most widely used antianxiety agent. In the 1950s, the pioneering work of Berger on the muscle relaxant mephenesin [59-47-1], $C_{10}H_{14}O_3$ (**71**), led to the identification of meprobamate 2 as an effective agent for the treatment of anxiety.

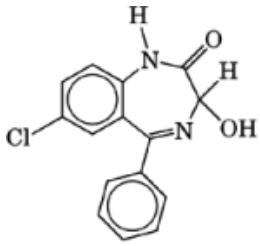
5.1. Benzodiazepines

The breakthrough in antianxiety therapy occurred in 1958 when the BZ chloradiazepoxide 1, was discovered. This compound was the first of a series of antianxiety or anxiolytic agents having significant efficacy and a

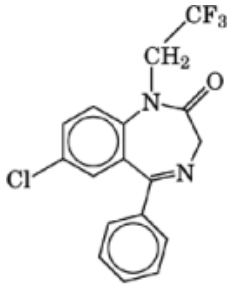
relatively safe profile despite side effects of sedation, muscle relaxation, alcohol potentiation, and dependence liability (1, 5). Other BZ anxiolytic agents include clorazepate 1, diazepam 1, lorazepam 1, alprazolam [28981-97-7], $C_{17}H_{13}ClN_4$ (**72**), oxazepam [604-75-1], $C_{15}H_{11}ClN_2O_2$ (**73**), halazepam [23092-17-3], $C_{17}H_{12}ClF_3N_2O$ (**74**), and prazepam [2955-38-6], $C_{19}H_{17}ClN_2O$ (**75**). Several of these BZ anxiolytics are also effective anticonvulsant agents.



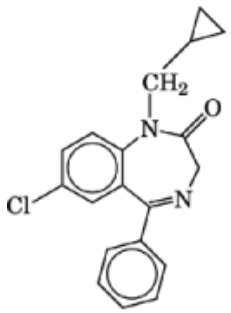
(**72**)



(**73**)



(**74**)



(75)

5.2. Nonbenzodiazepine Benzodiazepine Receptor Ligands

The simultaneous discovery of the molecular target for the BZs, the $GABA_A$/BZ receptor complex, by two teams of workers (34, 35) resulted in the identification of a number of atypical or anxioselective anxiolytics that, whereas not having the BZ pharmacophore, interacted directly with the central BZ receptor. The anxioselective nature of such agents was considered to be related to the ability to interact with proposed subclasses of the $GABA_A$/BZ receptor complex (1). The $GABA_A$/BZ receptor is a multimeric ligand-gated ion channel, the pentameric subunit composition of which offers the potential, in terms of molecular structure, of over 1000 subclasses (36) few of which have been identified *in situ* let alone functionally characterized.

The triazolopyridazine, CL 218872, $C_{13}H_9F_3N_4$ 4 and the pyrazolo [4,3-*c*] pyridine, CGS 9896, $C_{16}H_{10}ClN_3O$ 4, were the prototypic agents of this type although neither proceeded beyond early clinical trials. CL 218872 (37) was shown to have an increased affinity for BZ receptors in the cerebellum, originally designated as the BZ1 subclass and thought to be the anxioselective receptor and now known as the ω1 receptor. CGS 20625 [111205-55-1], $C_{18}H_{19}N_3O_2$ 4 (38) is a pyrazolopyridine related to CGS 9896 that is an effective anxiolytic lacking the sedative, muscle relaxant, and alcohol potentiating actions associated with the BZs. It is in Phase II clinical trials. Compound $C_{17}H_{13}N_3O_2$ 4 is an imidazoquinoxalinone related to the pyrazolopyridines (39). Another anxioselective anxiolytic is the β-carboline, abecarnil [111841-85-1], $C_{24}H_{24}N_2O_4$ 4 (40). The structures of these compounds are shown in Figure 4.

5.3. Serotonin Receptor Anxiolytics

Concomitant with the characterization of the anxioselective anxiolytics, the arylpiperazine buspirone [36505-84-7], $C_{21}H_{31}N_5O_2$ 5 (33) was the first of a series of partial agonists active at the $5HT_{1A}$ receptor that include ipsapirone [95847-70-4], $C_{19}H_{23}N_5O_3S$ 5 and tandospirone [112457-95-1], $C_{21}H_{29}N_5O_2$ 5. These compounds are shown in Figure 5. Buspirone was introduced into the clinic as a antipsychotic and subsequently found to have antianxiety actions. This effect is apparently manifest as an attenuation of 5HT neurotransmission, buspirone acting as a full agonist at presynaptic 5HT receptors in the dorsal raphe to limit 5HT release and as an antagonist at post-synaptic sites. Other putative anxiolytics acting through the 5HT receptor class of receptor include the serenic eltoprazine [98224-03-4], $C_{12}H_{16}N_2O_2$ 5, which also has activity at the $5HT_{1A}$ receptor (41); the $5HT_2$ receptor antagonist ritanserin [87051-43-2], $C_{27}H_{25}F_2N_3OS$, 5, and the $5HT_3$ receptor antagonist, ondansetron [116002-70-1], $C_{18}H_{19}N_3O$ 5.

Newer experimental approaches to anxiety therapy include ligands interacting with the ligand-gated ion channels that are selectively activated by nicotine, $C_{10}H_{14}N_2$ (**87**), the well-known active ingredient of cigarettes which has anxiolytic actions (42). Cholecystokinin B receptor ligands, specifically the dipeptoid, CI-988 [130404-91-0], $C_{35}H_{42}N_4O_6$ (**88**) have demonstrated anxiolytic activity in preclinical models (43).

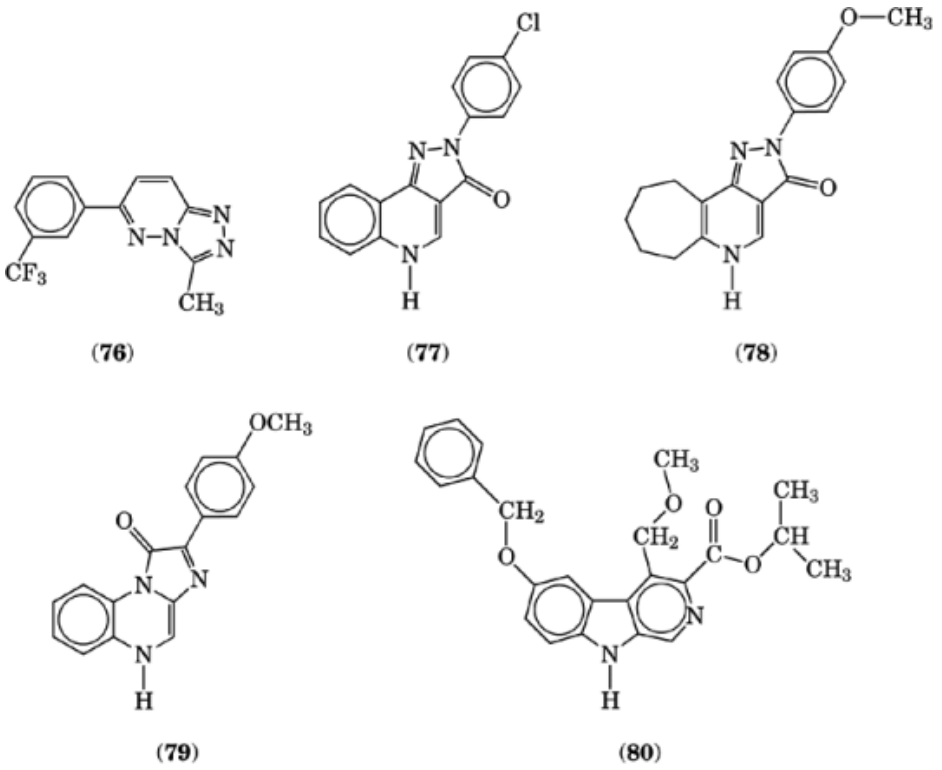
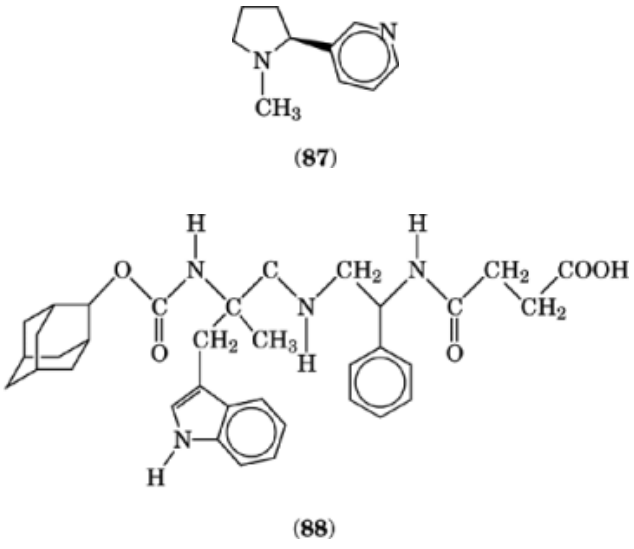


Fig. 4. Nonbenzodiazepine benzodiazepine receptor ligands.



A newer, highly experimental approach to anxiety therapy is the use of antisense oligonucleotides to the anxiogenic peptide, NPY (44).

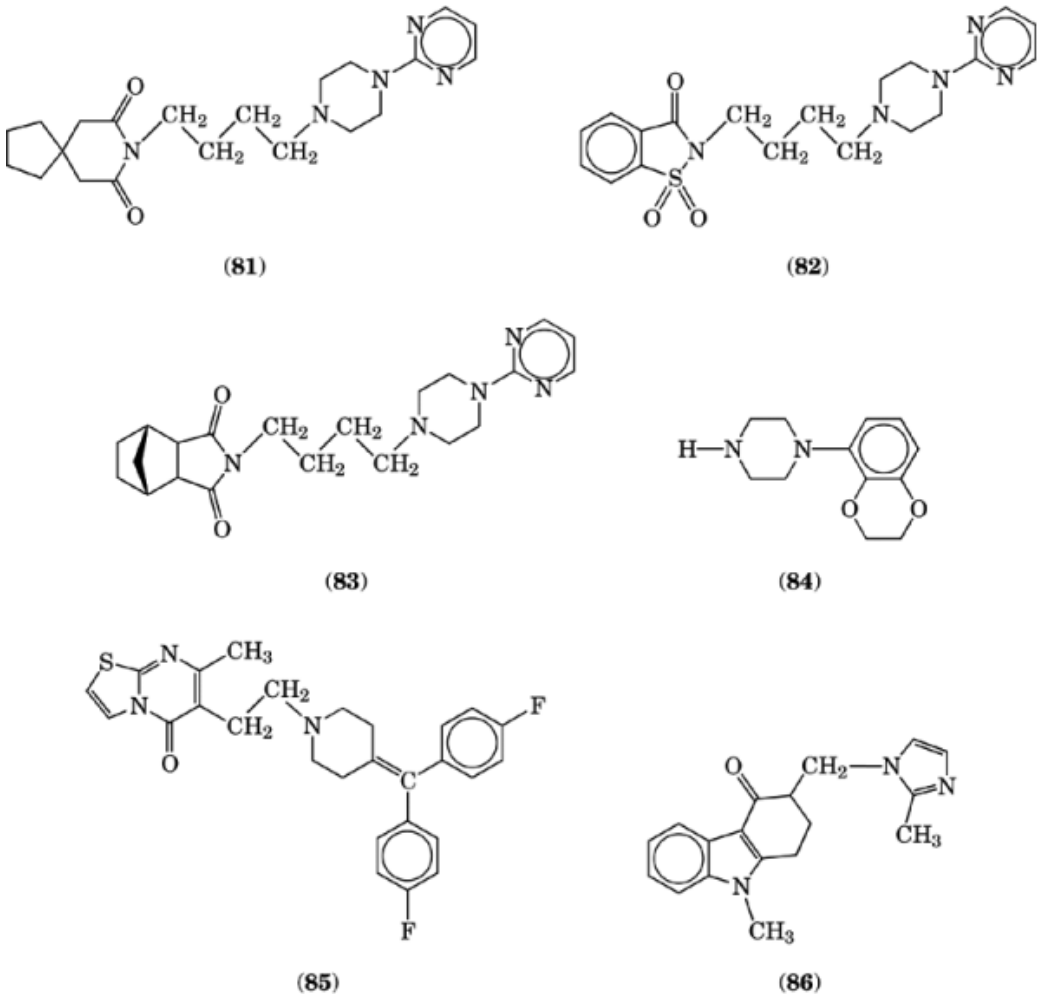


Fig. 5. Serotonergic receptor anxiolytics. See text.

6. Economic Aspects

Sales for hypnotic–sedative agents in the United States for 1993 were estimated to be $139,000,000. Anticonvulsant sales for 1993 were estimated at $525,000,000. U.S. sales of antianxiety agents including both the BZs and buspirone-like agents for 1993 were estimated at $1,046,000,000.

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