Kirk-Othmer Encyclopedia of Chemical Technology.

NEUROREGULATORS

Molecular regulation of tissue function and cellular homeostasis provides an organism, from mollusk to human, with the ability to adapt and react to a changing environment. A critical element in such adaptation and reaction is the nervous system. This not only acts to control muscles, organs, and behavior, but is itself regulated by sections of the cardiovascular, endocrine, and immune systems. Signaling within the nervous system may be acute, eg, cell depolarization, or may involve longer term regulatory functions, eg, gene expression. Thus the term neuroregulator encompasses a diversity of chemical substances involved in signaling: (*1*) between neurons; (*2*) between neurons and glia; (*3*) from neuron to effector target such as skeletal muscle, cardiac and smooth muscle, endocrine cell, or immunocompetent cell; and (*4*) from these diverse cell types to the neuron.

Two specialties of the nervous system are speed and localization, accomplished using highly developed electrical signaling and close cellular apposition. At specialized points of communication, such as the synapse and the neuromuscular junction, the cells are separated by a nanometer or less. For the purposes herein, synapse also is used to describe the neuromuscular junction. The neuron uses electrical signals, such as the action potential, to transmit from one end of the cell to the other, from the cell body to the synapse, whether the distance is relatively short as for interneurons, or relatively long as for the motor neuron which carries action potentials from the spinal cord to skeletal muscle. Transmission between cells, however, is mediated chemically in the majority of instances. Classically, these signaling molecules are known as neurotransmitters or neuromodulators, the latter term reflecting agents having longer term effects than those of the former. The neuron synthesizes and stores neurotransmitters in specialized areas of the cell, known as nerve terminals when they occur at the end of an axon, or varicosities when they occur as swellings arranged serially along the axon. Electrical impulses arriving in these areas depolarize the plasma membrane, causing voltage-dependent Ca^{2+} channels to open. This leads to a rapid influx of Ca^{2+} that triggers neurotransmitter release into the synapase. The neurotransmitter diffuses across the synapse, acting upon discrete recognition sites known as receptors in the plasma membrane of the post-synaptic cell. The neurotransmitter–receptor interaction then results in the depolarization or hyperpolarization of the post-synaptic membrane. The transmitter is removed from the synaptic milieu by metabolism, re-uptake, and/or diffusion, thus terminating its action as an intercellular messenger (Fig. 1). The integration of many such signals at the post-synaptic cell determines the response, for example, elicitation of an action potential or muscle contraction. The entire process occurs within milliseconds.

The concept of discrete neurotransmitter recognition sites or receptors on nerve cells was based on work on systems physiology and drug action (1). It was not until 1921 however, that it was shown that information could be transferred between neurons via a chemical, in this instance acetylcholine [51-84-3] (ACh), $C_7H_{16}NO_2$ **(1)**.

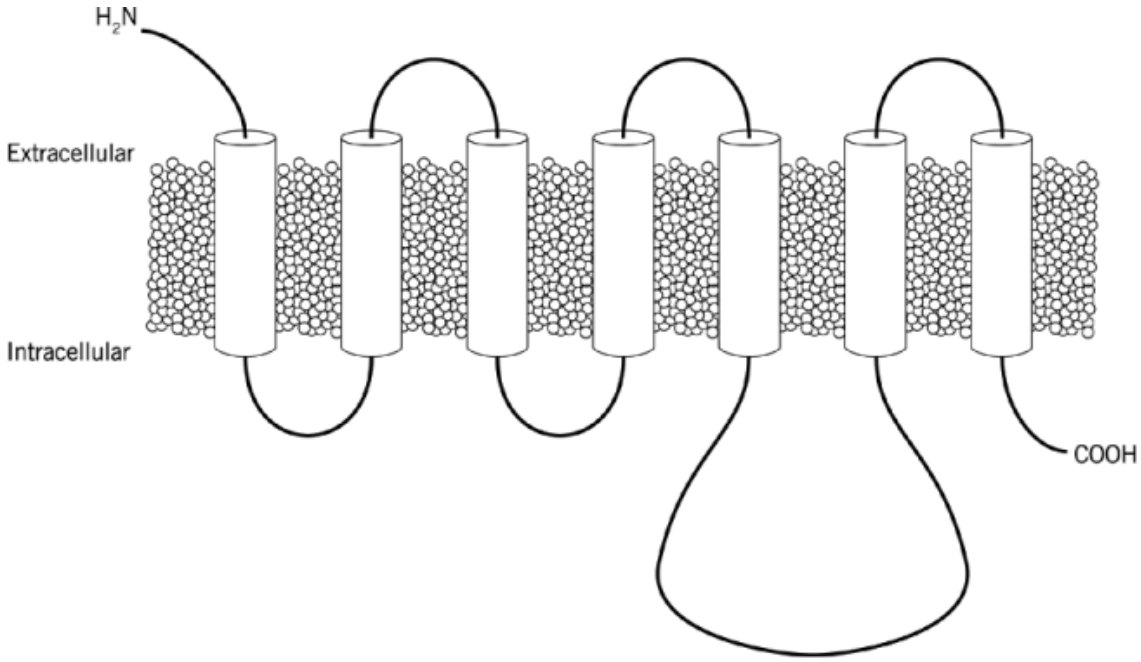
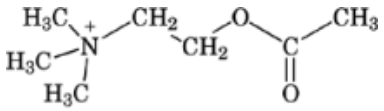


Fig. 1. Model of a ligand gated ion channel (LGIC) where (**a**) is the structure of a generic LGIC subunit showing the two cysteine (Cys) residues common to all LGIC subunits, and (**b**) shows the arrangement of five such subunits as a pentamer having psuedo-cyclic symmetry delineating a gated, fluid-filled pathway for ions.



(**1**)

The fundamental concept of synaptic transmission has, to a large extent, been based on cholinergic transmission in skeletal muscle, heart, and the autonomic nervous system. This classical form of transmission clearly is important in the central as well the peripheral nervous system. However, numerous substances can act as important modulators and regulators, filtering, adjusting the gain, and even triggering agents that may lead to modification of the neuronal circuiting.

Classical rapidly acting neurotransmitter receptors are represented by ligand–gated ion channels (LGICs), which are multimeric protein complexes surrounding an ion channel (Fig. 1) that typically mediate fast responses. The neurotransmitter, eg, ACh, γ-aminobutyric acid (GABA), glutamate, and adenosine triphosphate (ATP), activate the receptor, probably through a conformational change, such that the ion channel is opened to specific ion permeation. LGICs can have a multiplicity of ligand recognition sites allowing modulation of the action of the primary neurotransmitter. For example, benzodiazepines like diazepam are positive modulators of the effects of GABA on the chloride channel associated with the $GABA_A$ receptor (2).

Another receptor class is the G-protein coupled receptors (GPCRs), which constitute the majority of receptors characterized to date. These have seven transmembrane helical structures connected by extracellular and intracellular loops (Fig. 2). The G-protein subunits act as transducer systems to couple receptor activation to membranous and intracellular actions. The latter usually involves a hierarchy of enzymes including

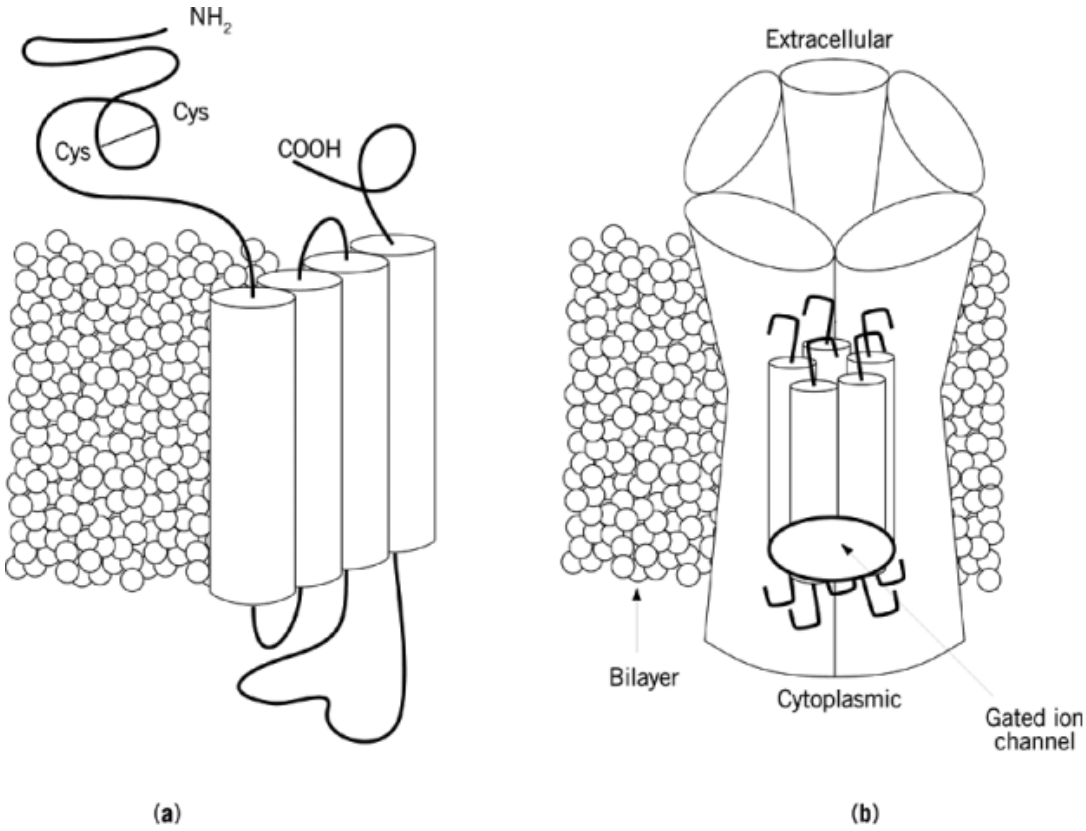


Fig. 2. Schematic of the G-protein coupled receptor (GPCR). The seven α-helical hydrophobic regions spanning the membrane are joined by extracellular and intracellular loops. The amino terminal is located extracellularly and the carboxy terminal intracellularly.

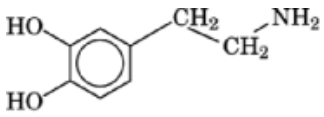
adenylate cyclase, the various enzymes involved in phospholipid metabolism, and various protein kinases and phosphatases. Activation of GPCRs also can lead to early response gene induction. Thus ligands that activate GPCRs have the potential to mediate long-term modulatory and regulatory functions as well as synaptic neurotransmission.

1. Neurotransmitter Criteria

A number of general characteristics can be defined that permit the definition of criteria for classifying an endogenous agent as a neurotransmitter (3, 4).

The neurotransmitter must be present in presynaptic nerve terminals; and the precursors and enzymes necessary for its synthesis must be present in the neuron. For example, ACh is stored in vesicles specifically in cholinergic nerve terminals. It is synthesized from choline and acetyl-coenzyme A (acetyl-CoA) by the enzyme, choline acetyltransferase. Choline is taken up by a high affinity transporter specific to cholinergic nerve terminals. Choline uptake appears to be the rate-limiting step in ACh synthesis, and is regulated to keep pace with demands for the neurotransmitter. Dopamine [51-61-6] **(2)** is synthesized from tyrosine by tyrosine

hydroxylase, which converts tyrosine to L-dopa (3,4-dihydroxy-L-phenylalanine) **(3)**, and dopa decarboxylase, which converts L-dopa to dopamine.



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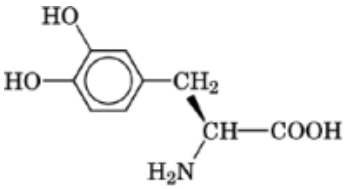


(3)

The dopamine is then concentrated in storage vesicles via an ATP-dependent process. Here the rate-limiting step appears not to be precursor uptake, under normal conditions, but tyrosine hydroxylase activity. This is regulated by protein phosphorylation and by *de novo* enzyme synthesis. The enzyme requires oxygen, ferrous iron, and tetrahydrobiopterin (BH_4). The enzymatic conversion of the precursor to the active agent and its subsequent storage in a vesicle are energy-dependent processes.

Stimulation of the neuron leading to electrical activation of the nerve terminal in a physiologically relevant manner should elicit a calcium-dependent release of the neurotransmitter. Although release is dependent on extracellular calcium, intracellular calcium homeostasis may also modulate the process. Neurotransmitter release that is independent of extracellular calcium is usually artifactual, or in some cases may represent release from a non-neuronal sources such as glia (3).

Neurotransmitter activation of a discrete receptor on the post-synaptic membrane should alter post-synaptic events in a concentration- or dose-dependent manner. Many neurotransmitter receptors are known to exist in a number of subtypes. For example, there are at least five subtypes of dopamine receptor, defined by molecular biological, pharmacological, and functional criteria. Pharmacological distinction depends on the discovery of potent ligands, synthetic or from natural sources, that are selective for specific subtypes. The processes of receptor characterization and ligand identification and characterization are frequently parallel events. The observation that new chemical entities elicit unusual responses in tissue and whole animal preparations can lead to the identification of new receptors or receptor subtypes. Identification of multiple receptor subtypes using recombinant DNA techniques provides a basis for interpretation of pharmacological results (see Biotechnology).

Agonists are receptor ligands that act like the endogenous neurotransmitter and include the neurotransmitter itself as well as analogues and mimics that may have greater or lesser potency, efficacy, and/or receptor selectivity. A full agonist is one that produces a functional response identical to that seen with the endogenous transmitter or neuroeffector. Partial agonists are substances that mimic receptor activation but do not have full efficacy, eg, are not capable of producing the maximal response observed with a full agonist. Antagonists are receptor ligands that block the actions of agonists acting on the same receptor. By definition antagonists have zero efficacy and elicit no effect on their own (1). Although some antagonists are competitive in nature, interacting at the same site to which the agonist ligand binds to produce its effects, other antagonists are non-competitive or uncompetitive in nature reflecting their ability to antagonize agonist actions by binding to sites distinct from the agonist binding site. Because full agonists have full efficacy, usually referred to as intrinsic

activity of unity, and antagonists have zero efficacy, the range for efficacy for a partial agonist can extend from 0 to 1. Thus a partial agonist having an efficacy of 0.5 not only has half the efficacy of a full agonist, but also has intrinsic antagonist activity. Some receptors are subject to more complex ligand-mediated regulatory processes, such as the GABA–benzodiazepine LGIC receptor complex, which has numerous allosteric modulator sites (2). Studies of these receptors have resulted in identification of a more diversified group of ligands. These include the inverse agonists which are ligands that elicit an effect opposite to that elicited by agonists and consequently have negative efficacy, eg, -1.0. Inverse agonist effects at serotonin receptors have been described (5).

The neurotransmitter receptor should respond to pharmacological manipulation in a predictable manner. Direct application of the neurotransmitter should produce electrophysiological and/or biochemical responses identical to responses observed following presynaptic neuron stimulation. Neurotransmitter receptor antagonists should block the action of the neurotransmitter and related agonists. Agonists known to be selective for other receptors should not act as neurotransmitter mimics when applied at relevant concentrations. Antagonists known to be selective for other receptors likewise should not block the neurotransmitter or related agonists when present at relevant concentrations.

There should be specific, saturable binding to the receptor, accompanied by pharmacological characteristics appropriate to the functional effects, demonstrable using a radioactive, eg, tritium or iodine-125, ligand to label the receptor. Radioligand binding assays (1, 6) have become a significant means by which to identify and characterize receptors and enzymes (see Immunoassays; Radioactive tracers). Isolation of the receptor or expression of the receptor in another cell, eg, an oocyte can be used to confirm the existence of a discrete entity.

Specific systems, such as enzymatic inactivation or neurotransmitter re-uptake, should exist to terminate the physiological actions of the neurotransmitter. Synaptic neurotransmission is a rapid and highly localized process, requiring that the effect of released neurotransmitter be terminated rapidly and prevented from affecting a widespread area. Thus diffusion of a typical chemical neurotransmitter is insufficient to terminate its actions. In the case of ACh, the neurotransmitter is rapidly hydrolyzed by acetylcholinesterase to the relatively inactive products, choline and acetate. About 50% of this choline is recaptured by the nerve terminal for resynthesis of acetylcholine. The effects of many neurotransmitters are terminated principally by active high affinity transporter systems that help to recapture a portion of the transmitter for subsequent release. Uptake processes in glia and catabolism of the neurotransmitter in neurons and glia also help to terminate and localize the neurotransmitter action. In Parkinson's disease, a neurodegenerative disorder resulting from a loss of certain dopaminergic neurons and presynaptic dopamine stores, the precursor, L-dopa can be used to increase brain levels of dopamine as long as presynaptic mechanisms are available to convert L-dopa to dopamine. Alternatively, inhibitors of catabolism or transport can augment dopamine availability or its synaptic concentration, provided some degree of dopaminergic neuronal function remains intact.

Numerous processes modulate neurotransmitter synthesis, presynaptic excitability, neurotransmitter release, post-synaptic receptors, and post-synaptic excitability.

The distinction between neuromodulator and neurotransmitter is sometimes difficult to define (7, 8). Generally, however, the primary function of a neurotransmitter is thought to be the rapid transmission of impulses eliciting a brief depolarization or hyperpolarization of the post-synaptic cell. Summation of neurotransmitter signals lead either to electrical excitation or electrical blockade of excitation. Neuromodulators regulate these processes, and may or may not produce an electrical signal themselves. The same molecule may function as neurotransmitter or neuromodulator, depending on the receptors present. For example, ACh acts as a neurotransmitter via nicotinic receptors, although it can act as a neuromodulator via muscarinic receptors that regulate its release and post-synaptic excitability. Some substances such as steroids (qv) may act as neuromodulators, or may produce longer term effects through hormonal regulation.

Some of the neurotransmitter criteria may or may not apply to a particular neuromodulator. The source of the neuromodulator is not restricted to the nerve terminal. The neuromodulator may be stored in a form other than its released form; it may be released extrasynaptically, and it may or may not be metabo lized or taken up particularly rapidly to terminate its action. However, neuromodulators are subject to agonist/antagonist

pharmacological criteria. GPCRs are involved in many neuromodulatory functions. Other neuromodulators may act through receptive sites that are not typically considered receptors. For example, nitric oxide [10102-43-9], NO, a neuromodulator implicated in learning and memory (long-term potentiation) and cytotoxic phenomena, acts directly on the enzyme guanylate cyclase to increase activity (9, 10).

Drug receptors represent another type of receptor family. The central nervous system (CNS) effects of the anxiolytic, diazepam, and the psychotropic actions of the cannabinoids and phencyclidine have resulted in the identification of specific receptors for these molecules. This has resulted in the search for an endogenous ligand for these receptors. Thus, in these situations, the pharmacological action has preceded the discovery of the receptor which, in turn, has provided clues in several instances to the endogenous ligand.

Another category of neuroregulator includes substances that do not directly regulate depolarization or hyperpolarization and may or may not be released from neurons, but do affect cellular function in neurons. These include trophic factors, growth factors, cytokines, and hormones (qv) that regulate neuronal morphology, synapse formation, or function through longer term effects on neurotransmitter synthesis, receptor expression, or ion channel expression.

Receptors for the thyroid hormone–retinoic acid (RA) superfamily, including steroid receptors, act through cell surface recognition sites (10). Ligands for this class of receptor are internalized and then interact with promoter regions on DNA, known as hormone responsive elements (HREs), to affect transcription processes in the target cell. This class of receptor is characterized by the presence of a zinc finger region. A class of intracellular drug targets that has yet to be exploited is represented by the G-protein transduction elements involved in coupling receptor events to activation of adenylate and guanylate cyclase as well as other enzyme systems and ion channels within the cell (11).

Another class of receptor that has been described is typified by receptors for cytokines such as tumor necrosis factor-α (TNF-α). Activation of this class of receptor leads to changes in intracellular target proteins including the so called receptor-activated factors of transcription (RAFTs), also known as signal transducers and activators of transcription (STATs), that include AP-1 and NFκB. These STATs can modulate the DNA transcription processes thought to be involved in cellular inflammatory responses and mechanisms related to apoptosis in the peripheral and central nervous systems. Cytokines have profound effects on target cell function including neurons and glia and may be involved in many disease states involving an inflammatory mediator component, eg, AIDS and Alzheimer's disease.

A newer receptor class, still being characterized, is that known as orphan receptors. These are receptors identified by cloning homology to GPCR and other receptors using a process known as receptor trolling. Whereas these receptors have the characteristic seven transmembrane (7TM) helical regions associated with the GPCR superfamily, they do not show sequence homology with other known receptors of this class. These are receptors in search of a ligand. The intracellular chicken ovalbumin upstream promotor transcription factor (COUP-TF) receptor is an orphan receptor (12), activation of which requires dopamine-dependent phosphorylation. An endogenous ligand has yet to be identified. Another orphan receptor for which the ligand has been isolated is thrombopoetin (13).

A subset of ion channels not gated by traditional neurotransmitters represents another receptor class. These include potassium, calcium, sodium, and cyclic adenosine monophosphate (cAMP)-gated channels (14–16) for which a large number of synthetic molecules exist that alter cellular function.

Despite quantal advances in technology in the twentieth century, the receptor–neurotransmitter concept remains the foundation of neuroregulator action and disease pathophysiology understanding. The drug discovery process typically has focused on neurotransmitter receptors, catabolic enzymes for neurotransmitters, and neurotransmitter transporters. Alterations in the process of chemical neurotransmission, either an over- or under-stimulation of the target receptor, occurring as a result of changes in the availability of the neurotransmitter or an alteration in the responsiveness of the signal transduction processes in the target cell, are thought to represent the molecular defects involved in many disease states. The physiology and pharmacology of such systems can be defined according to clear criteria, and often there is a pharmacological specificity that may

be missing from more ubiquitous regulatory systems. Neurotransmission can be attenuated by post-synaptic receptor antagonists, including desensitizing agonists, or by activation of feedback inhibition processes. Augmentation of neurotransmitter–neuroregulator function can be effected by limiting feedback inhibition or the inactivation processes, catabolism or re-uptake. However, exogenous neurotransmitter agonists are unlikely to mimic the millisecond and micrometer resolution of the physiological system; this can be explained by considerations related to chaos theory (17). There have been many advances made in drug therapeutics and progress continues to be made. As of this writing (ca 1995), however, most approaches are more or less palliative. Transgenic animals that overexpress the β_2-adrenoceptor have been developed that reflect the potential for receptor replacement therapy (18). These animals show enhanced atrial contractility and increased left ventricular function even in the presence of β_2-adrenoceptor antagonists.

An increased focus on those processes that regulate neurotransmission and cellular functions both of neurons and of the other half of the brain, the glial cell family, is expected.

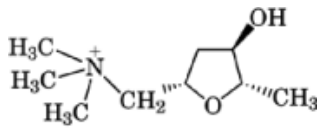
2. Neurotransmitters and Receptors

In general the receptor nomenclature used is consistent with the recommendations of the various International Union of Pharmacology (IUPHAR) Committee on receptor nomenclature (19, 20). In some cases the human receptor has been cloned. By convention, pharmacologically defined receptors are shown in capital letters; cloned receptors in lower case letters.

The grouping of receptors on the basis of sequence homology has been easiest in the case of those receptor classes where pharmacological tools have enabled the elucidation of function consistent with structure.

2.1. Acetylcholine

Acetylcholine (ACh) **(1)** is a crystalline material that is very soluble in water and alcohol. ACh, synthesized by the enzyme choline acetyltransferase (3), interacts with two main classes of receptor in mammals: muscarinic (mAChR), defined on the basis of the agonist activity of the alkaloid muscarine **(4)**, and nicotinic (nAChR), based on the agonist activity of nicotine **(5)** (Table 1). mAChRs are GPCRs (21); nAChRs are LGICs (22).



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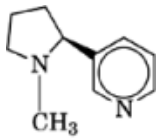


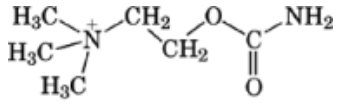
(5)

mAChRs are divided into five subclasses, M_1–M_5. Carbachol **(6)** and oxotremorine-M **(7)** are prototypic agonists for all five classes. McN-A343 **(8)** is a selective agonist for the M_1 receptor; pirenzepine **(9)** is a selective antagonist for the M_1 receptor. Methoctramine **(10)** and himbacine **(11)** are selective M_2 receptor antagonists. Hexahydrosiladifendiol **(12)** and tropicamide **(13)** are selective antagonists for the M_3 and M_4 mAChR,

Table 1. Agonists and Antagonists of Acetylcholine and Receptors

Agonist/antagonist	CAS Registry Number	Molecular formula	Structure number
	Muscarinic receptors		
muscarine	[300-54-9]	$C_9H_{20}NO_2$	**(4)**
carbachol	[51-83-2]	$C_6H_{15}ClN_2O_2$	**(6)**
oxotremorine-M	[63939-65-1]	$C_{11}H_{19}N_2O$	**(7)**
McN-A343		$C_{14}H_{18}ClN_2O_2$	**(8)**
pirenzepine	[28797-61-7]	$C_{19}H_{21}N_5O_2$	**(9)**
methoctramine	[104807-46-7]	$C_{36}M_{62}N_4O_2$	**(10)**
himbacine	[6879-74-9]	$C_{22}H_{35}NO_2$	**(11)**
hexahydrosiladifendiol	[98299-40-2]	$C_{20}H_{33}NOSi$	**(12)**
tropicamide	[1508-75-4]	$C_{17}H_{20}N_2O_2$	**(13)**
4-diphenylacetoxy-*N*-methylpiperidium	[106458-69-9]	$C_{21}H_{26}NO_2$	**(14)**
	Nicotinic receptors		
nicotine	[54-11-5]	$C_{10}H_{14}N_2$	**(5)**
phenyltrimethyl-ammonium	[3426-74-2]	$C_9H_{14}N$	**(15)**
1,1-dimethyl-4-phenyl-piperazinium	[54-77-3]	$C_{12}H_{19}N_2$	**(18)**
cytisine	[485-35-8]	$C_{11}H_{14}N_2O$	**(21)**
ABT-418	[147402-53-7]	$C_9H_{14}N_2O$	**(22)**
methylcarbamylcholine	[14721-69-8]	$C_7H_{17}N_2O_2$	**(23)**
GTS 21	[148372-04-7]	$C_{19}H_{20}N_2O_2$	**(24)**
(±)-epibatidine	[140111-52-0]	$C_{11}H_{13}ClN_2$	**(25)**
d-tubocurarine	[57-95-4]	$C_{37}H_{41}N_2O_6$	**(16)**
α-bungarotoxin	[11032-79-4]	$C_{338}H_{529}N_{97}O_{105}S_{11}$	**(17)**
trimethaphan	[7187-66-8]	$C_{22}H_{25}N_2OS$	**(19)**
hexamethonium	[60-26-4]	$C_{12}H_{30}N_2$	**(20)**
dihydro-β-erythroidine	[23255-54-1]	$C_{16}H_2NO_3$	**(26)**
mecamylamine	[60-40-2]	$C_{11}H_{21}N$	**(27)**
methyllycaconitine	[21019-30-7]	$C_{37}H_{50}N_2O_{10}$	**(28)**

respectively. 4-Diphenylacetoxy-*N*-methylpiperidium (4-DAMP) **(14)** is an antagonist for the M_5 receptor (Table 1).



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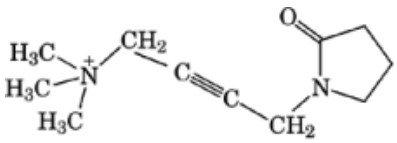

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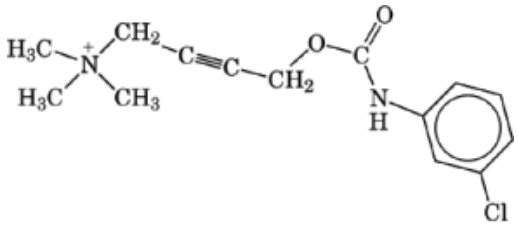

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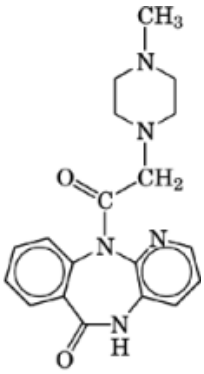

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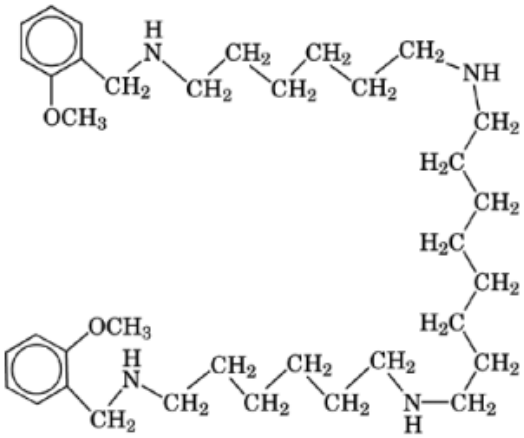

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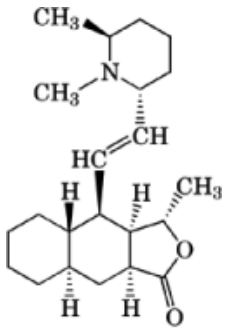

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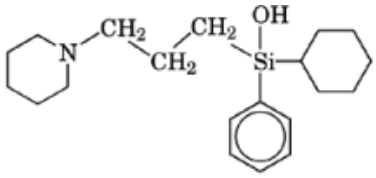

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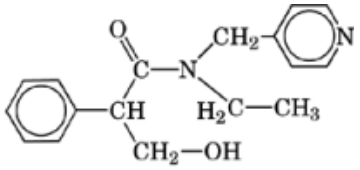

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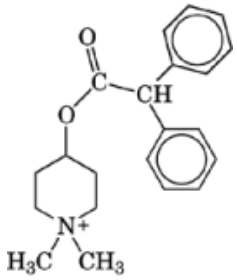


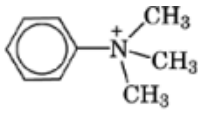
(14)

Selective M_1 receptor ligands have been targeted for therapeutic use in Alzheimer's disease and related dementias. There has been little success because of side effect liabilities (see Memory-enhancing drugs). M_2 antagonists may act as autoreceptor antagonists also promoting the release of ACh. Muscarinic receptor ligands have also been targeted for use in cardiovascular, gastrointestinal, and pulmonary disorders.

nAChRs are pentameric LGICs composed of α, β, γ, δ, and ϵ subunits, the composition of which is dependent on the tissue of origin. Eleven neuronal gene products ($\alpha 2$–$\alpha 9$; $\beta 2$–$\beta 4$) have been identified from the cloning of rat, chick, and human brain and sensory tissue cDNAs. At least eight combinations form putative neuronal nAChR subtypes (23).

A systematic nomenclature for nAChRs has yet to evolve. An N nomenclature describes receptors present in muscle as N_1. These are activated by phenyltrimethylammonium (PTMA) **(15)** and blocked by *d*-tubocurarine **(16)** and α-bungarotoxin (α-BgT) **(17)**. N_2 receptors are present in ganglia and are activated by 1,1-dimethyl-4-phenylpiperazinium (DMPP) **(18)** and blocked by trimethaphan **(19)** and bis-quaternary agents, with hexamethonium **(20)** being the most potent.

In the brain, three nAChR subclasses have been identified: those having high affinity ($K_d = 0.5 - 5$ nM) for (−)-nicotine; those having high affinity ($K_d \sim 0.5$ nM) for α-BgT (αBTnAChRs); and a population of receptors that display marked selectivity for neuronal bungarotoxin (n-BgT) (**23**). The distribution of the $\alpha 4\beta 2$ subunit combination coincides somewhat with the distribution of high affinity [^{3}H]nicotine binding sites in rat brain. Agonists for the α-BTX insensitive receptors include nicotine **(5)**, cytisine **(21)**, ABT-418 **(22)**, and methylcarbamylcholine (MCC) **(23)**. The ability of the classical agonist, (−)-nicotine, to act as an agonist or an antagonist is dependent on the β-subunits present. GTS 21 **(24)** is a potent partial agonist at the α-BgT-sensitive α_7 subtype. The novel analgesic, (+)-epibatidine **(25)** is a potent ligand at high affinity [^{3}H]nicotine binding sites and the receptors labeled by n-BgT. Antagonists include dihydro-β-erythroidine (DHβE) **(26)**, mecamylamine **(27)**, hexamethonium **(20)**, and methyllycaconitine (MLA) **(28)**. MLA differentiates between αBgT sensitive sites on neuronal and muscle nAChRs.



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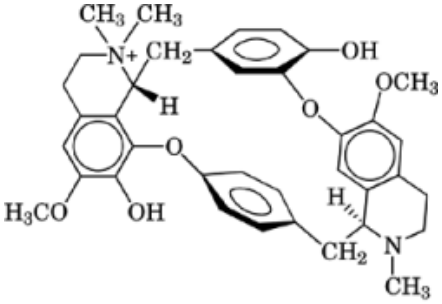

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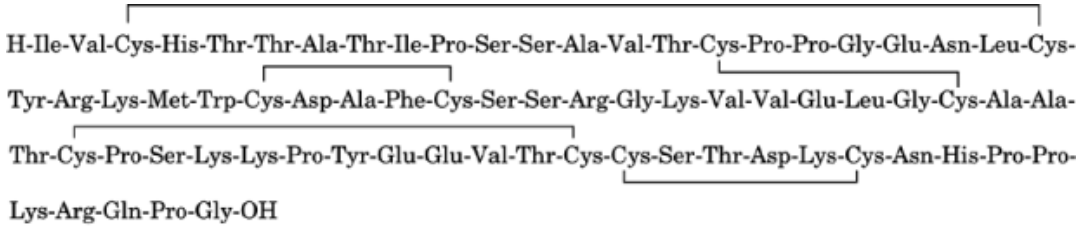

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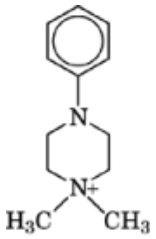

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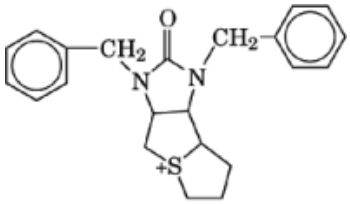

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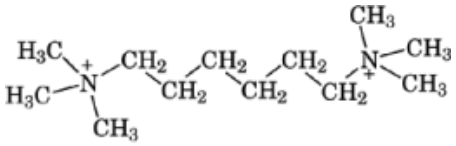

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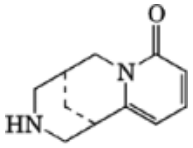

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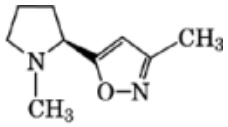

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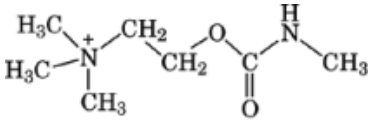

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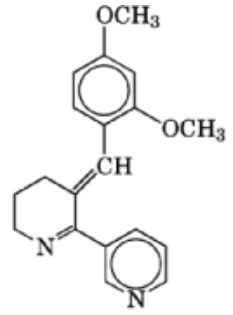

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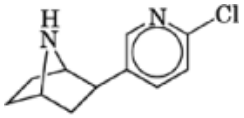

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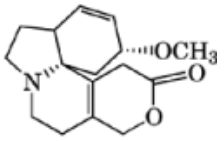

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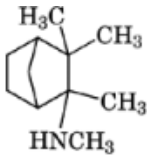

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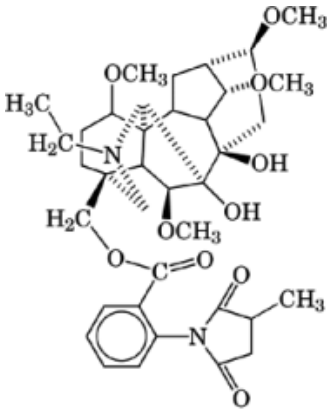
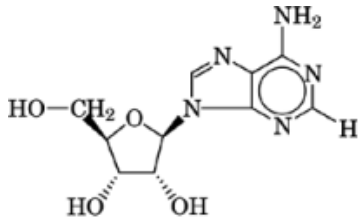


(28)

Like mAChRs, nAChRs have been implicated in the etiology of Alzheimer's disease and related dementias as well as in gastrointestinal and cardiovascular disorders. Nicotine has high abuse potential and is the primary component in reinforcing smoking behaviors. Nicotine patches have been developed for use as aids in smoking cessation, however, the usefulness of nicotine is hampered by dose-limiting side effects. Medicinal chemistry efforts in this emerging area are focused on the development of ligands, eg, ABT-418 and GTS-21, that are selective for nAChR subtypes and thus may have a reduced side effect profile as compared to nicotine. Such agents, collectively termed cholinergic channel modulators (ChCM), may be useful in the treatment of a number of neurological disorders, such as anxiety, schizophrenia, and analgesia.

2.2. Adenosine

Adenosine [58-61-7] (Ado), $C_{10}H_{13}N_5O_4$ **(29)**, a purine nucleoside, is an intracellular constituent acting as both an enzyme cofactor and substrate and also as part of the basic energy cycle in the form of its phosphorylated derivative, ATP **(30)**. Evidence for a role for adenosine as a neuromodulatory agent has accumulated for the better part of the twentieth century (24).



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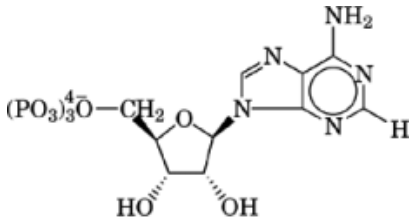

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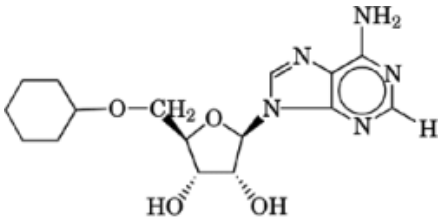
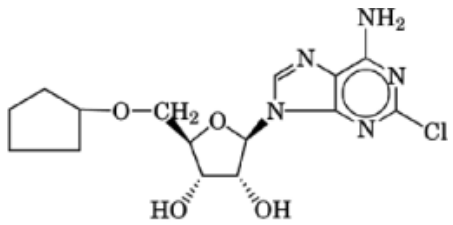


(31)

Table 2. Agonists and Antagonists of Adenosine and Receptors

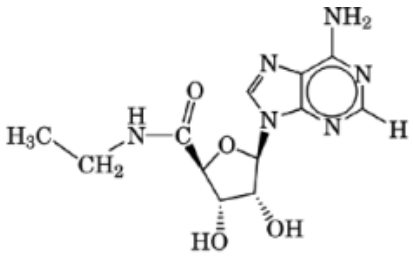
Agonist/antagonist	CAS Registry Number	Molecular formula	Structure number
N^6-cyclohexyladenosine	[36396-99-3]	$C_{16}H_{23}N_5O_4$	**(31)**
2-chloro-N^6-cyclopentyl-adenosine	[37739-05-2]	$C_{15}H_{20}ClN_5O_4$	**(32)**
5′-*N*-ethylcarboxamido-adenosine	[35920-39-9]	$C_{12}H_{16}N_6O_4$	**(33)**
CGS 21680	[120225-54-9]	$C_{23}H_{29}N_7O_6$	**(34)**
DBXRM		$C_{19}H_{29}N_5O_6$	**(35)**
cyclopentylxanthine	[102146-07-6]	$C_{16}H_{24}N_4O_2$	**(36)**
KFM 19	[133058-72-7]	$C_{16}H_{22}N_4O_3$	**(37)**
CGS 15943	[104615-18-1]	$C_{13}H_8ClN_5O$	**(38)**
KF 17837	[141807-96-7]	$C_{22}H_{28}N_4O_4$	**(39)**
AMBP		$C_{17}H_{13}N_3O_2$	**(40)**
I-ABPOX		$C_{23}H_{22}IN_5O_5$	**(41)**



(32)

Adenosine is formed from ATP via a phosphatase cascade that sequentially involves the diphosphate, ADP, and the monophosphate, AMP. The actions of adenosine are terminated by uptake and rephosphorylation via adenosine kinase to AMP or by catabolism via adenosine deaminase to inosine and hypoxanthine.

Adenosine receptors are members of the P_1 purinoceptor GPCR family and can be classified into four subtypes: A_1, A_{2a}, A_{2b}, and A_3. At the A_1 receptor, N^6-substituted analogues of adenosine including N^6-cyclohexyladenosine (CHA) **(31)**, and 2-chloro-N^6-cyclopentyladenosine (CCPA) **(32)** are potent and selective agonists. 5′-*N*-Ethylcarboxamidoadenosine (NECA) **(33)** is a potent agonist (K_i = 15 nM) at A_1, A_{2a}, and A_{2b} receptors. CGS 21680 **(34)** and DBXRM **(35)** are selective agonists for A_{2a} and A_3 receptors, respectively. Antagonists for the A_1 receptor include a large series of eight-substituted xanthines including cyclopentylxanthine (CPX) **(36)** and KFM 19 **(37)**. The triazoloquinazoline, CGS 15943 **(38)** is a potent (K_i = 20 nM) nonselective, nonxanthine adenosine antagonist. The 8-styrylxanthine, KF 17837 **(39)** and the benzopyranopyrazolone, AMBP **(40)** are selective A_{2a} antagonists. The rat A_3 receptor, which is approximately 75% homologous to sheep and human A_3 receptors, is insensitive to xanthine blockade, whereas the sheep and human receptor can be blocked by acidic xanthines such as I-ABPOX **(41)** (Table 2).



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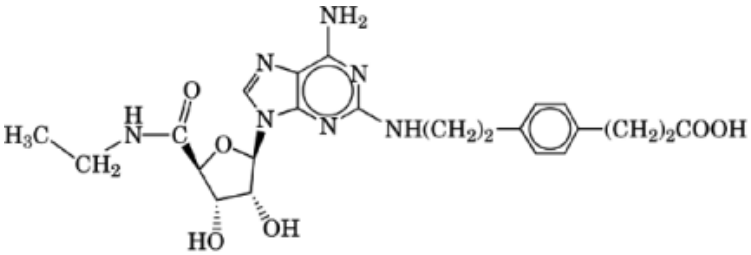

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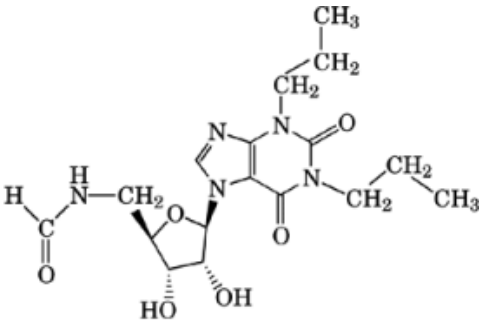

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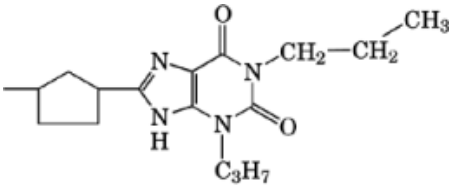

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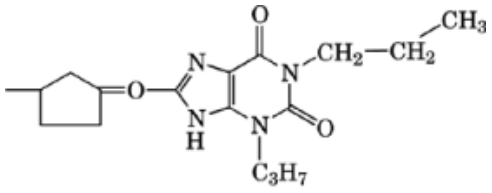

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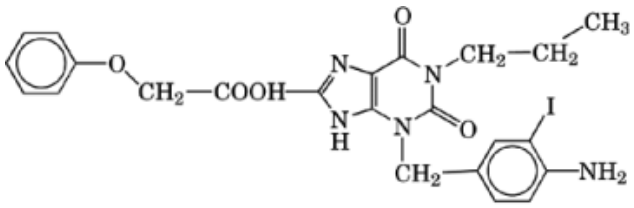

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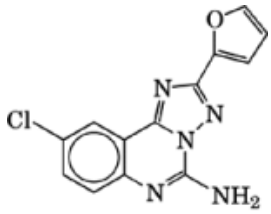

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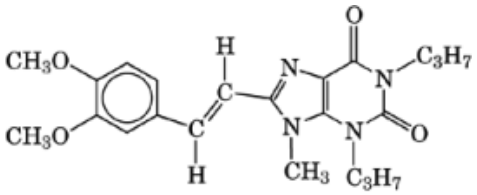

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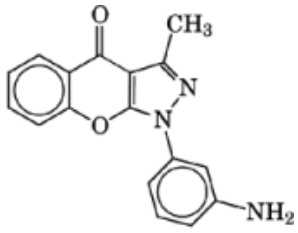


(40)

Adenosine is a ubiquitous neuromodulatory agent that is normally present in the extracellular milieu and functions to maintain tissue homeostasis. This is most evident in the daily intake of caffeine [58-08-2], a weak yet effective adenosine antagonist, that is the most widely used drug. Consumed in various beverages,

Table 3. Agonists and Antagonists of Adenosine Triphosphate and Receptors

Agonist/antagonist	CAS Registry Number	Molecular formula	Structure number
α,β-methylene–ATP	[7292-42-4]	$C_{11}H_{18}N_5O_{12}P_3$	**(42)**
2-(4-nitrophenylethylthio)–ATP		$C_{18}H_{19}N_6O_{15}P_3S$	**(43)**
5-fluorouridine triphosphate	[3828-96-4]	$C_9H_{14}FN_2O_{15}P_3$	**(44)**
2-methylthio–ATP	[43170-89-4]	$C_{11}H_{14}N_5O_{13}P_3S$	**(47)**
uridine triphosphate (UTP)	[63-39-8]	$C_9H_{15}N_2O_{15}P_3$	**(48)**
2-methylthio–ADP	[34983-48-7]	$C_{11}H_{14}N_5Na_3O_{10}P_2S$	**(49)**
Ap4A		$C_{20}H_{28}N_{10}O_{19}P_4$	**(50)**
suramin	[145-63-1]	$C_{51}H_{40}N_6O_{23}S_6$	**(45)**
PPADS		$C_{15}H_{11}N_2O_{12}PS_2$	**(46)**
FPL 67085		$C_{14}H_{18}Cl_2N_5Na_4O_{12}P_3S$	**(51)**

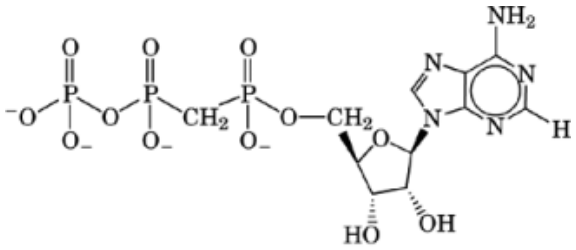
caffeine acts to counteract the sedative actions of adenosine. A side effect of caffeine intake is the diuretic actions produced via the blockade of adenosine receptors in the kidney. More potent analogues of caffeine such as **(37)** are being evaluated for use as cognition enhancers and A_1 receptor agonists have potential use as antiischemic agents, both centrally and peripherally. Adenosine receptor ligands may have therapeutic potential in cardiovascular, pulmonary, renal, and immune system-associated disease states. The human A_3 receptor is implicated in the pathophysiology of asthma (see Antiasthmatic agents).

2.3. Adenosine Triphosphate

Adenosine triphosphate [56-65-5] (ATP), $C_{10}H_{16}N_5O_{13}P_3$ **(30)**, like adenosine, is an important intracellular constituent. Its role as a neuromodulator has been firmly established (24). ATP is formed within the cell by a variety of energy-dependent phosphate exchanges. Co-released with ACh and catecholamines, its actions are terminated by the action of cell surface ectonucleotidases.

ATP receptors, initially classified as P_{2X} and P_{2Y} subtypes, have evolved into a number of subclasses including P_{2T}, P_{2Z}, P_{2U}/P_{2N}, and P_{2D}. Classification of P_2 purinoceptors has been limited by a lack of potent, selective, and bioavailable antagonists. Nonetheless a rational scheme for P_2 purinoceptor nomenclature divides P_2 receptors into two superfamilies: P_{2X}, an LGIC family having four subclasses; and P_{2Y}, a GPCR family having seven subclasses. A third receptor type, designated the P_{2Z}, is a nonselective ion pore.

α,β-Methylene–ATP **(42)** is an agonist at the P_{2X1}, P_{2X2}, P_{2X3}, and P_{2X4} receptors. The P_{2X3} receptor is located in vascular smooth muscle, and the P_{2X4} receptor is differentiated by its tissue location (25). 2-(4-Nitrophenylethylthio)ATP **(43)** is a selective P_{2X1} agonist. 5-Fluorouridine triphosphate (UTP) **(44)** is a selective P_{2X2} agonist. There are no selective agonists for P_{2X3} and P_{2X4} receptors. P_{2X} superfamily antagonists include suramin **(45)** and PPADS **(46)** (see Table 3).



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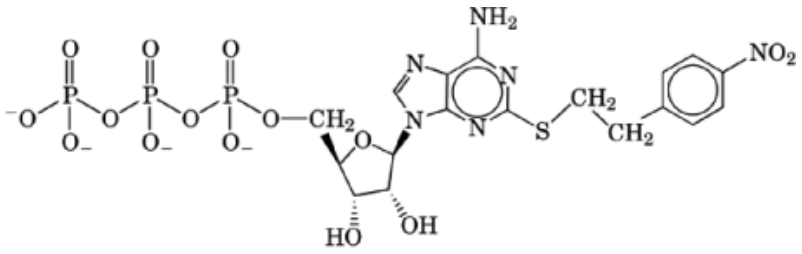

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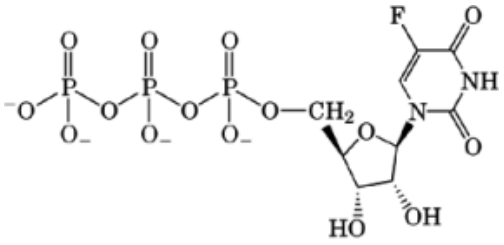

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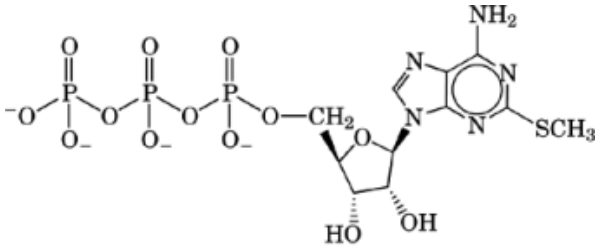

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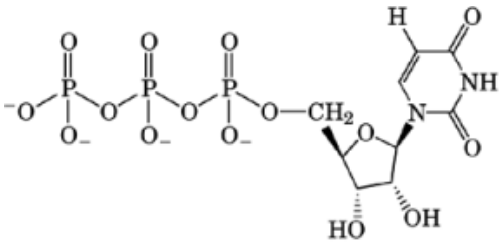

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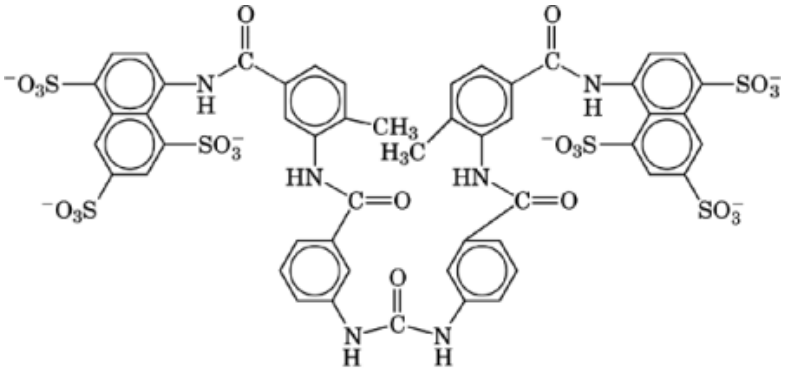

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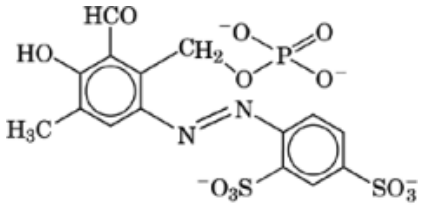
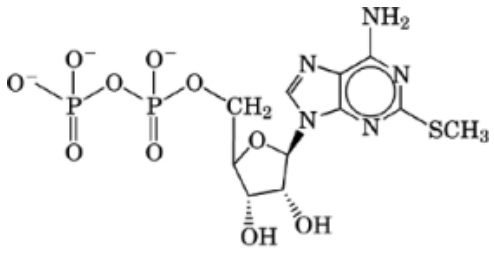


(46)

2-Methylthio-ATP **(47)** is an agonist at P_{2Y1}, P_{2Y4}, P_{2Y5}, and P_{2Y6} receptors. UTP **(48)** is equipotent with ATP at the P_{2Y2} receptor. 2-Methylthio-ADP **(49)** is a selective agonist for the platelet P_{2Y3} receptor. The differentiation between the P_{2Y4}, P_{2Y5}, and P_{2Y6} receptors is by agonist efficacy. **(47)** is much more effective than ATP at P_{2Y4}, and slightly more effective than ATP at P_{2Y5}. 2-(6-Cyanohexylthio)-ATP is an agonist at P_{2Y4}, but inactive at P_{2Y6}; 8-(6-aminohexyl)amino-ATP is an agonist at P_{2Y5} and P_{2Y6}. The P_{2Y7} receptor is sensitive to adenine dinucleotides, specifically Ap4A **(50)** and is involved in transmitter release regulation. ATP is a selective ligand for the P_{2Z} receptor. A UTP-sensitive receptor that does not respond to ATP and is thus distinct from the P_{2Y2} receptor has been described (26). Antagonists for the P_{2Y} family include **(45)** and **(46)**. FPL 67085 **(51)** is a selective antagonist for the P_{2Y3} receptor.



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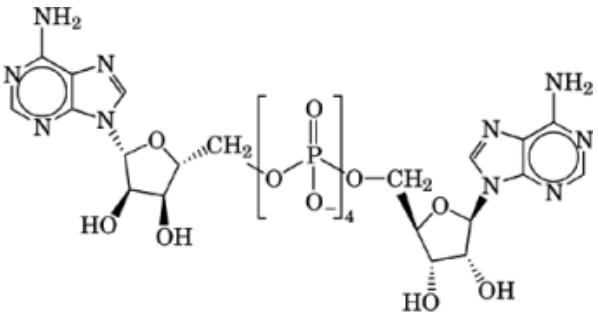

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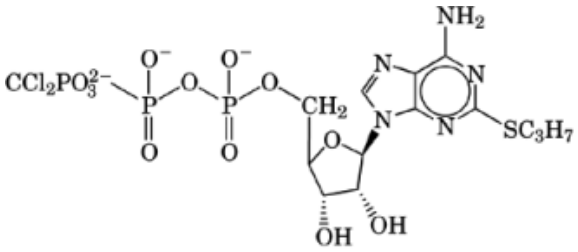


(51)

2.4. Angiotensin

The octapeptide, angiotensin II [4474-91-3, 11128-99-7] (AT-II), H-Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-OH, is the principal mediator of the renin–angiotensin system (RAS) that regulates hemodynamics and water and electrolyte balance (27). The aspartyl protease renin acts on the glycoprotein angiotensinogen to produce the decapeptide angiotensin I that is then cleaved by angiotensin-converting enzyme (ACE) to yield the active pressor agent, AT-II.

Two AT-II receptors, AT_1 and AT_2 are known and show wide distribution (27). The AT_1 receptor has been cloned and predominates in regions involved in the regulation of blood pressure and water and sodium retention, eg, the aorta, liver, adrenal cortex, and in the CNS in the paraventricular nucleus, area postrema, and nucleus of the solitary tract. AT_2 receptors are found primarily in the adrenal medulla, uterus, and in the brain in the locus coeruleus and the medial geniculate nucleus. AT_1 receptors are GCPRs inhibiting adenylate cyclase activity and stimulating phospholipases C, A_2, and D. AT_2 receptors use phosphotyrosine phosphatase as a transduction system.

Nonpeptide biphenyltetrazole AT_1 antagonists include losartan [124750-99-8, 114798-26-4] (DuP 753), $C_{22}H_{23}ClN_6O3$ and SKF 108566 [133040-01-4], $C_{23}H_{24}N_2O_4S$ 3. PD 123177 [114785-12-5], $C_{29}H_{28}N_4O_3$ 3 is a potent and selective nonpeptide AT_2 antagonist (Fig. 3).

AT-II exerts a wide range of physiological effects on the cardiovascular, renal, and endocrine systems, and the peripheral and central nervous systems. The main physiological effects of angiotensin are to increase blood pressure and heart rate and to cause retention of salt and water. The effects derive from a direct vasoconstrictor and myocardial effect of angiotensin, its ability to release other vasoconstrictors from endocrine and neuroendocrine tissues, and its ability to release sodium and water-retaining hormones, primarily aldosterone and vasopressin. In the brain, angiotensin II elicits a diversity of responses including an increase in blood pressure and water intake, stimulation of natriuresis and salt appetite, and secretion of pituitary hormones.

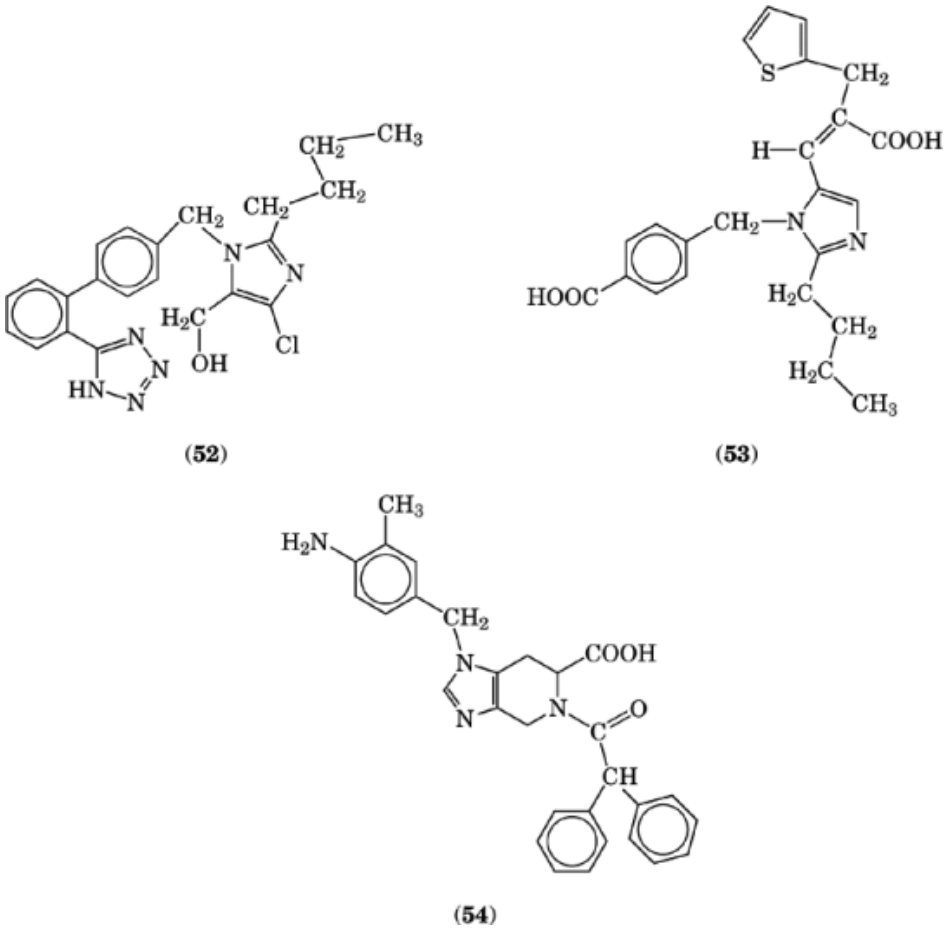
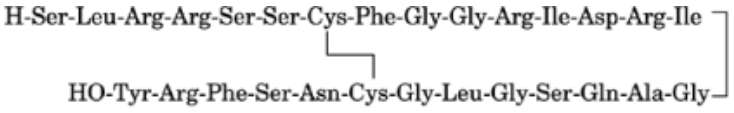


Fig. 3. Structures of angiotensin receptor antagonists.

DuP 753 is an orally active AT_1 receptor antagonist and as of this writing is in clinical trials as an antihypertensive (see Cardiovascular agents). AT-II antagonists affect the brain RAS system to enhance ACh release offering the possibility that these agents may function as cognition enhancers.

2.5. Atrial Natriuretic Peptide

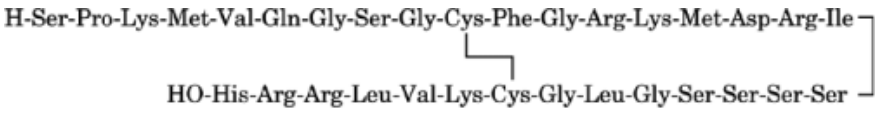
α-Atrial natriuretic peptide [85637-73-6] (ANP) **(55)**, also known as atrial natriuretic factor (ANF), brain natriuretic peptide (BNP) **(56)**, and type C natriuretic peptide (CNP) **(57)** are members of the ANP family (28). These atrial peptides arise from a common 128 amino acid precursor where the active form of ANP is the 28 amino acid peptide at the C terminus.



(55)

Table 4. Benzodiazepines and Related Compounds

Compound	CAS Registry Number	Molecular formula	Structure number
	BZ receptor ligands		
diazepam	[439-14-5]	$C_{16}H_{13}ClN_2O$	**(59)**
chlordiazepoxide	[58-25-3]	$C_{16}H_{14}ClN_3O$	**(60)**
clonazepam	[1622-61-3]	$C_{15}H_{10}ClN_3O_3$	**(61)**
RO 5-4864	[14439-61-3]	$C_{16}H_{12}Cl_2N_2O$	**(62)**
PK 11195	[85532-75-8]	$C_{21}H_{21}ClN_2O$	**(63)**
flumazenil	[78755-81-4]	$C_{15}H_{14}FN_3O_3$	**(64)**
	Peptide receptor ligands		
devazepide	[103420-77-5]	$C_{25}H_{20}N_4O_2$	**(65)**
midazolam	[59467-70-8]	$C_{18}H_{13}ClFN_3$	**(66)**
tifluadom	[83386-35-0]	$C_{22}H_{20}FN_3OS$	**(67)**
BZA-2B		$C_{24}H_{27}N_5O_5S_2$	**(68)**



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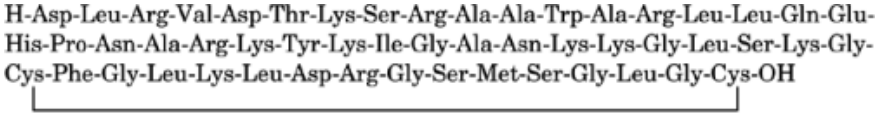
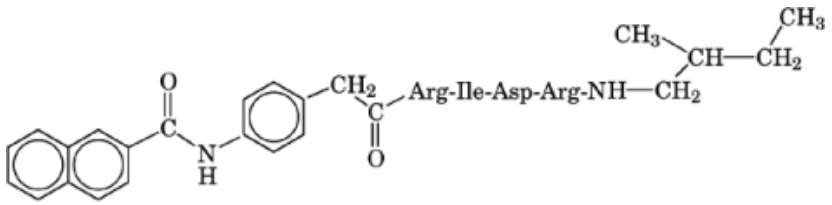


(57)

The ANP receptor exists in two forms, ANP_A and ANP_B, both of which have been cloned. These membrane-bound guanylate cyclases have a single transmembrane domain, an intracellular protein kinase-like domain, and a catalytic cyclase domain, activation of which results in the accumulation of cyclic guanosine monophosphate (cGMP). A third receptor subtype (ANP_C) has been identified that does not have intrinsic guanylate cyclase activity and may play a role in the clearance of ANP.

At low (1–10 n*M*) concentrations ANP activates ANP_A whereas ANP_B appears to be the physiological receptor for CNP. ANP and BNP are inactive at the latter subtype except at high micromolar concentrations. AP 811 [124833-45-0], $C_{46}H_{66}N_{12}O_8$ **(58)** is a selective ANP_C ligand. (L-α-Aminosuberic acid$^{7,23'}$)-*b*-ANP_{7--28} is an ANP_A antagonist.



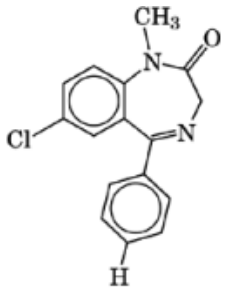
(58)

ANPs play an important role in the maintenance of cardiovascular homeostasis by counterbalancing the renin–angiotensin (RAS) system. ANP, the main circulating form of the natriuretic peptides, effectively relaxes

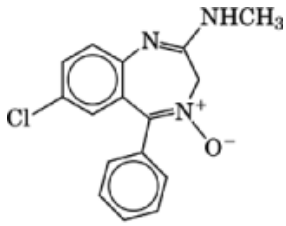
vascular smooth muscle, promotes the excretion of sodium and water, and in the CNS inhibits vasopressin release and antagonizes AT-II induced thirst.

2.6. Benzodiazepines

The benzodiazepines (BZs) are a class of synthetic drugs widely used for the treatment of anxiety and epilepsy and also as muscle relaxants and sedative–hypnotics (see Hypnotics, sedatives, anticonvulsants, and anxiolytics). Diazepam **(59)** and chlordiazepoxide **(60)** (Table 4) were identified as CNS active agents in the early 1960s using empirical animal screening techniques. A unique BZ receptor was identified using classical radioligand binding techniques. A peripheral BZ receptor (PBR) has also been identified (29).



(59)



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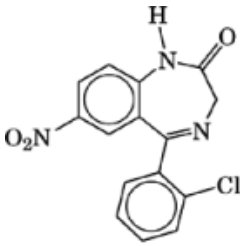
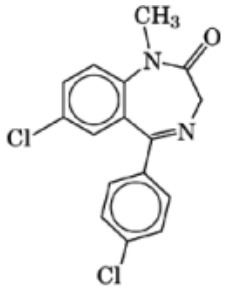
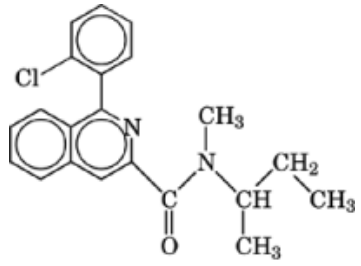


(61)

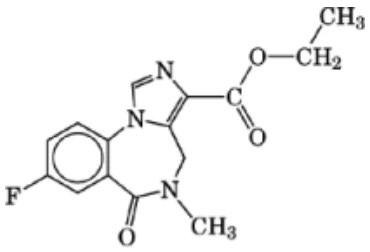


(62)

The endogenous ligand for the central BZ receptor has yet to be identified. Diazepam and clonazepam **(61)** are ligands for the central BZ receptor and Ro 5-4864 **(62)** and PK 11195 **(63)** are selective for the peripheral BZ receptor. Ro 15-1788 (flumazenil) **(64)** is a BZ inverse agonist used as an analeptic. The central BZ receptor is a pentameric LGIC associated with a chloride channel and a $GABA_A$ receptor, BZs acting to modulate the effects of GABA at the latter site. The pentameric structure can be drawn from six α-subunits ($\alpha 1$–$\alpha 6$), three β-subunits ($\beta 1$–$\beta 3$), three γ-subunits ($\gamma 1$–$\gamma 3$), and a δ-subunit. This provides the possibility of over 1000 permutations of the central BZ receptor having potentially different pharmacological and functional properties. However, the subunit stochiometry of endogenous BZ receptors is unknown. The central BZ receptor has several additional binding sites including those for barbiturates, picrotoxin, the avermectins, neurosteroids, etc. Compounds active at these sites modulate the effects of the BZs and GABA on chloride channel function.



(63)

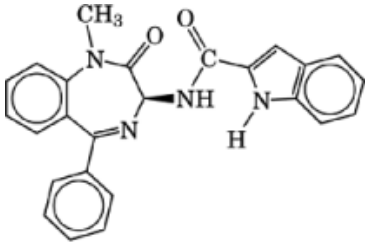


(64)

The PBR is distinct from the central BZ receptor although both can be present in the same tissues in differing ratios. PBRs are predominately localized on the outer mitochondrial membrane and are thus intracellular BZ recognition sites. The PBR is composed of three subunits: an 18,000 mol wt subunit that binds isoquinoline carboxamide derivatives; a 30,000 mol wt subunit that binds BZs; and a 32,000 mol wt

voltage-dependent anion channel subunit. The porphyrins may be endogenous ligands for the PBR. PBRs are involved in the control of cell proliferation and differentiation and steroidogenesis.

The BZ structure also has provided a molecular scaffold for a number of peptide receptor ligands (26). Antagonists for the cholecystokinin (CCK-A) receptor, eg, devazepide **(65)**, the thyrotropin-releasing hormone (TRH) receptor, eg, midazolam **(66)**, and the κ-opiate receptor, eg, tifluadom **(67)**, as well as a series of ras farnyl transferase inhibitors, eg, BZA-2B **(68)** (30) have been identified (Table 4).



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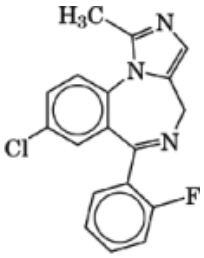
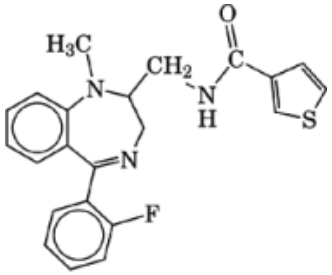


(66)



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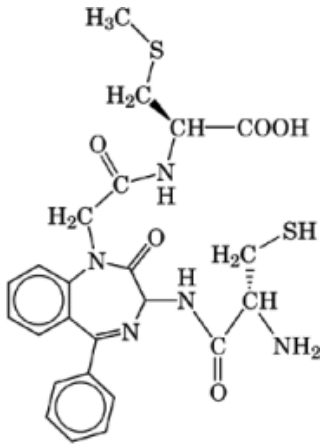


(68)

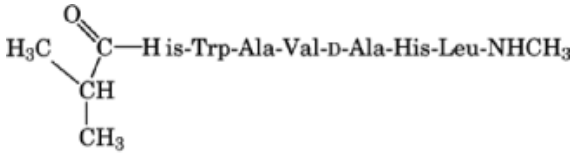
2.7. Bombesin

Bombesin [31362-50-2], *p*-Glu-Gln-Arg-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2, is a tetradecapeptide isolated from the skin of the frog *Bombina bombina* (31). There are two mammalian bombesin-like peptides, the 27-amino acid gastrin-releasing peptide [80043-53-4], (GRP) (69), and the decapeptide, neuromedin B [87096-84-2] (NMB), H-Gly-Asn-Leu-Trp-Ala-Thr-Gly-His-Phe-Met-NH_2. These elicit a wide range of pharmacological activities including thermoregulation, smooth muscle contraction, stimulation of the release of numerous gastrointestinal (GI) peptides, and the regulation and maintenance of circadian rhythms in the suprachiasmatic nucleus. Two bombesin receptor subtypes have been identified, a receptor with high affinity (K_i = 3 nM) and 30-fold selectivity for NMB (BB_1) and one with high affinity (K_i = 2 nM) and 20-fold selectivity for GRP (BB_2). Both are GPCRs, utilizing IP_3/DAG for their transduction mechanisms, and are widely distributed in the central and peripheral nervous systems. A third bombesin receptor has been cloned from guinea pig and human. ICI 216,140 [124001-41-8], $C_{45}H_{65}N_{13}O_8$ **(70)** is a nonselective bombesin antagonist, whereas [D-Phe^6]bombesin$_{6--13}$ ethyl ester and AcGRP$_{20--26}$ ethyl ester are the most potent and selective BB_2 antagonists yet identified. CP 75998 [149142-70-1], $C_{16}H_9BrCl_2N_4O_3$ **(71)** is a nonpeptide bombesin antagonist. Potential therapeutic targets for bombesin agonists include satiety and analgesia.

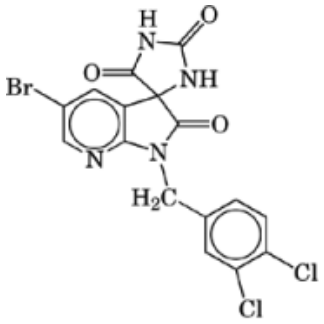
H–Ala–Pro–Val–Ser–Val–Gly–Gly–Gly–Thr–Val–Leu–Ala–Lys–

Met–Tyr–Pro–Arg–Gly–Asn–His–Trp–Ala–Val–Gly–His–Leu–Met–NH_2

(69)



(70)



(71)

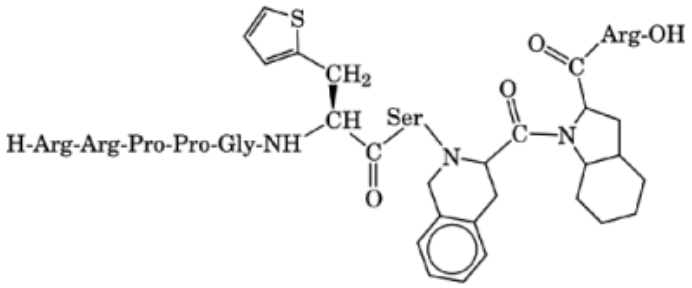
2.8. Bradykinin

Bradykinin [58-82-2] (BK), $C_{50}H_{73}N_{15}O_{11}$, H-Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg-OH, is a nonapeptide (25) released from plasma and exocrine glands by the action of kinin-generating enzymes, the kallikreins, on the α_2-globulins termed kininogens. Activation of plasma kallikrein leads to the formation of BK from high molecular weight but not from low molecular weight kininogen. Tissue kallikreins in contrast can liberate kinins from both forms of kininogen. LysylBK, also known as kallidin [342-10-9], $C_{56}H_{85}N_{17}O_{12}$, is an analogue of BK found in human tissues. T-kinin [86030-63-9] (Ile-Ser-BK), $C_{59}H_{89}N_{17}O_{14}$, is a BK analogue found only in rats. BK, kallidin, and T-kinin have similar pharmacological properties.

BK actions are mediated through at least two types of GPCR: B_1 and B_2. At the B_1 receptor, des-Arg^{9}BK is more potent than BK. The converse is true at the B_2 receptor. The effects of BK are primarily mediated by activation of the B_2 receptor because the B_1 receptor has limited tissue distribution and is induced by noxious stimuli such as apamin or an inflammatory mediator-type response. The existence of a B_3 receptor was suggested on the basis of limited efficacy of known antagonists in some systems. A B_4 receptor may also exist. The human B_2 receptor has been cloned.

Hoe 140 [130308-48-4], $C_{59}H_{89}N_{19}O_{13}S$ **(72)** and NPC 567 [109333-26-8], $C_{60}H_{87}N_{19}O_{13}$, H-D-Arg-Arg-Pro-(*trans*-4-hydroxy)Pro-Gly-Phe-Ser-D-Phe-Phe-Arg-OH, are modified peptides which are selective antagonists for the B_2 receptor. WIN 64338, $C_{44}H_{68}N_4OP$ **(73)** is the first competitive, nonpeptide B_2 antagonist. [Leu^8] des-Arg^{9}BK and [des-Arg^{10}] Hoe 140 are peptide analogues of BK that act as selective B_1 receptor antagonists.

BK and its congeners are involved in allergic reactions, asthma, viral rhinitis, hypertension, and septic shock. BK also is involved with the pathophysiological processes that accompany tissue damage, inflammation, and the production of pain. BK and kallidin are 100-fold more potent than histamine in increasing vascular permeability and thus are powerful mediators of edema by the release of release of platelet activating factor (PAF) and prostaglandins (qv). B_2 receptor antagonists thus may have analgesic and antiinflammatory actions in acute inflammatory pain.



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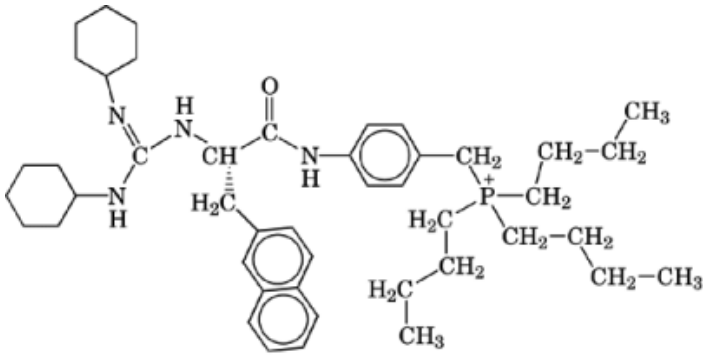


(73)

2.9. Calcitonin Gene-Related Peptide

Calcitonin gene-related peptide (CGRP) [83652-28-2] 4 is a 37-amino acid peptide (Fig. 4) (32).

CGRP is widely distributed throughout the peripheral and central nervous systems and is found in sensory neurons and in the autonomic and enteric nervous systems. In many instances CGRP is co-localized with other neuroregulators, eg, ACh in motor neurons, substance P, somatostatin, vasoactive intestinal polypeptide (VIP), and galanin in sensory neurons. It is also present in the CNS, with ACh in the parabigeminal nucleus and with cholecystokinin (CCK) in the dorsal parabrachial area. CGRP functions as a neuromodulator or co-transmitter.

Amylin [106602-62-4] 4 (Fig. 4) is a 37-amino acid peptide having approximately 46% sequence similarity to CGRP (33). Amylin is present in pancreatic β-cells along with insulin. It may function as a hormone in glucoregulation and has been proposed as an etiologic factor in certain forms of diabetes. Amylin is also present in dorsal root ganglia (see Insulin and other antidiabetic drugs).

CNS effects of CGRP include increased sympathetic outflow, increased temperature, reduced feeding and gastric secretion, reduced growth hormone release, reduced motor activity, and effects on nociception. In individual cells CGRP may be excitatory, potentiating transmitter release and/or increasing specific calcium channel activity, or inhibitory, increasing specific potassium channel activity.

CGRP produces its effects (32) by two GPCR receptor subtypes, $CGRP_1$ and $CGRP_2$. These have been classified according to the selectivities of the fragment $CGRP_{8--37}$ which is a $CGRP_1$ antagonist and of [acetoamidomethylcysteine^{2,7}] CGRP 4 which is a $CGRP_2$ agonist. In the nucleus accumbens there may be a third receptor sensitive to amylin and CGRP. This receptor is also sensitive to salmon calcitonin [47931-85-1],

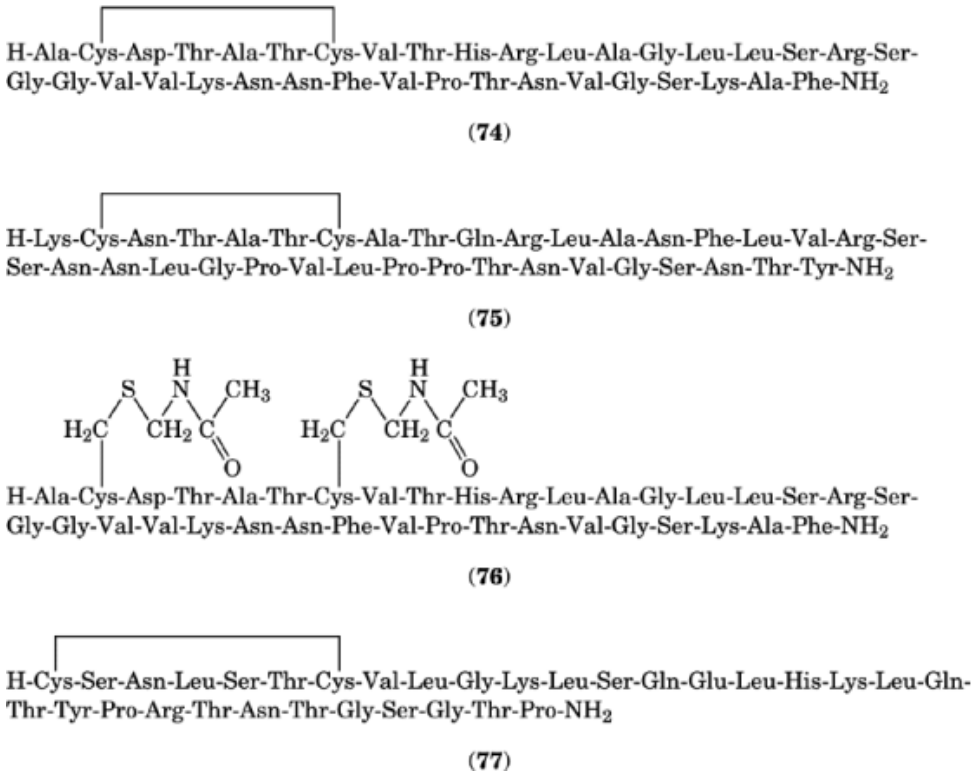


Fig. 4. Structures of human CGRP and related peptides.

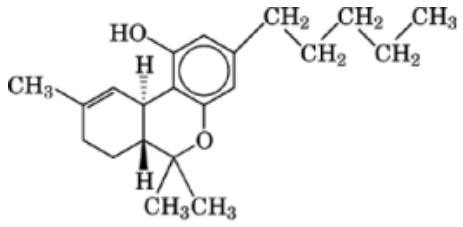
$C_{145}H_{240}N_{44}O_{48}S_2$ 4. Adenylate cyclase and Ca^{2+} and K^+ channel activation are involved in the transduction mechanism for $CGRP_1$. CGRP is vasodilatory and, in conjunction with other mediators, pro-inflammatory. In the heart, CGRP increases atrial contractile force and rate. In striated muscle, CGRP increases nicotinic receptor expression and the rate of desensitization, and augments ACh release from motor neurons (see Fig. 4).

2.10. Cannabinoids

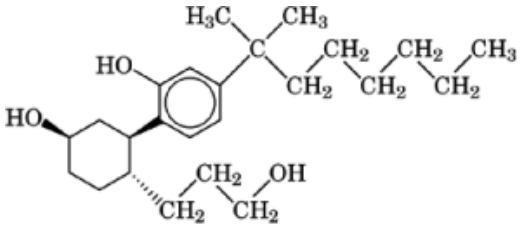
Like the BZ receptor, the cannabinoid receptor was initially identified using psychotropic alkaloids such as Δ^9-tetrahydrocannabinol (Δ-THC) **(78)** that were known to affect mammalian CNS function (see Psychopharmacological agents). The CNS receptor, CB_1, was identified by radioligand binding techniques and subsequently cloned. A second receptor subclass, CB_2, has been identified in human spleen and also has been cloned (34). Table 5 lists cannabinoid receptor ligands.

Table 5. Cannabinoid Receptor Ligands

Compound	CAS Registry Number	Molecular formula	Structure number
Δ^9-tetrahydrocannabinol	[1972-08-3]	$C_{21}H_{30}O_2$	**(78)**
CP 55940	[83002-04-4]	$C_{24}H_{40}O_3$	**(79)**
nabilone	[51022-71-0]	$C_{24}H_{36}O_3$	**(80)**
anandamide	[94421-68-8]	$C_{22}H_{37}NO_2$	**(81)**
HU 243	[140835-14-9]	$C_{25}H_{40}O_3$	**(82)**
WIN 55212-2	[131543-22-1]	$C_{27}H_{26}N_2O_3$	**(83)**
3-(1,1-dimethylheptyl), Δ^6-tetrahydrocannabinol-1-carboxylic acid		$C_{23}H_{32}O_4$	**(84)**

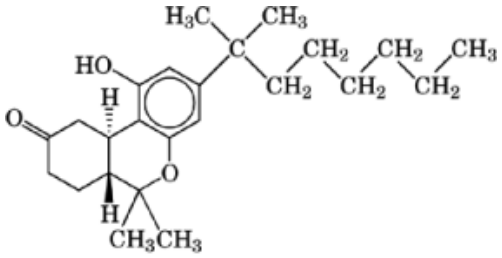


(78)



(79)

CP 55940 **(79)** and nabilone **(80)** are synthetic ligands for the cannabinoid receptor. However, the identification of the eicosanoid, anandamide **(81)**, as an endogenous cannabimimetic has provided an important tool to study cannabinoid receptor function.



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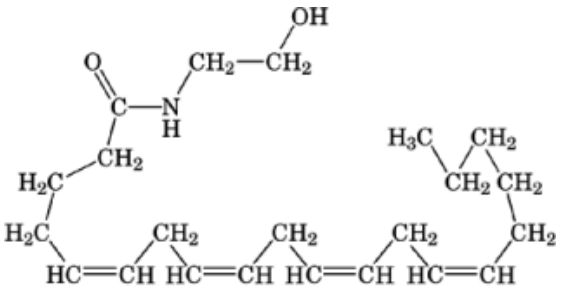
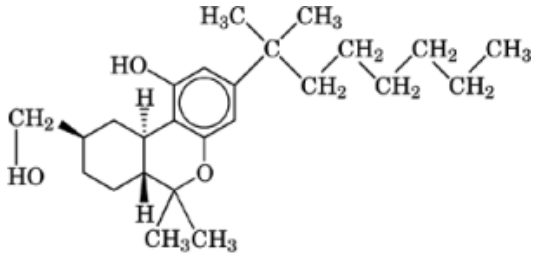


(81)

HU 243 **(82)** and WIN 55212-2 **(83)**, newer cannabimimetics, may be involved in the regulation of neurotransmitter release. Like anandamide, these are potent blockers of *N*-type calcium channels. Cannabimimetics are psychotropics, effecting on time perception, euphoria, sedation, and causing hallucinations and a decrease in aggressive behavior. Short-term memory is impaired as is the ability to carry out tasks requiring mental processing. Δ-THC and nabilone are also antinociceptive agents and are used as antiemetics in cancer patients and as antiglaucoma agents. Nonpsychotropic cannabinoids, eg, 3-(1,1-dimethylheptyl),Δ*6*-tetrahydrocannabinol-1-carboxylic acid **(84)** have antiinflammatory and leukocyte antiadhesion properties (34). Antagonists for cannabinoid receptors have yet to be identified.



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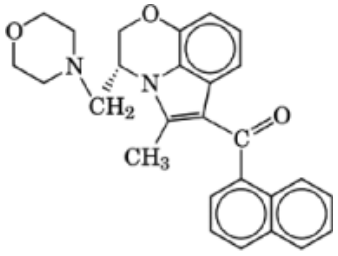

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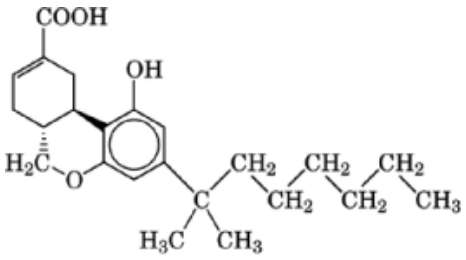
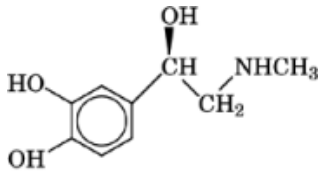


(84)

2.11. Catecholamines

The catecholamines, epinephrine (EPI; adrenaline) **(85)**, norepinephrine (NE; noradrenaline) **(86)** (see Epinephrine and norepinephrine), and dopamine (DA) **(2)**, are produced from tyrosine by the sequential formation of L-dopa, DA, NE, and finally EPI. EPI and NE produce their physiological effects via α- and β-adrenoceptors. α-Adrenoceptors can be further divided into α_1- and α_2-subtypes which in turn are divided into α_{1A}, α_{1B}, and α_{1D} (clones α_{1a}, α_{1b}, and α_{1d}) and α_{2A}, α_{2B}, and α_{2C}. There is no $\alpha_{1C/c}$ receptor. β-Adrenoceptors are divided into β_1-, β_2-, and β_3-subtypes (35–37).



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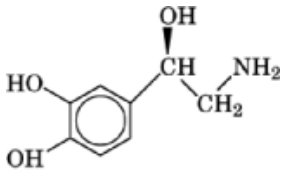

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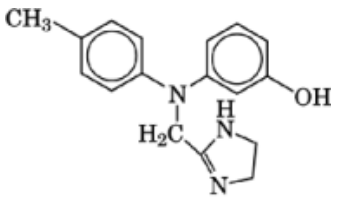
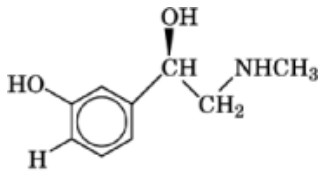


(87)

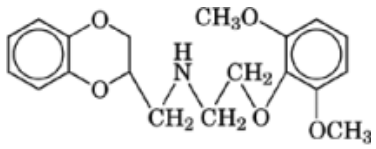
Table 6. Catecholamines and Adrenoceptor Agonists and Antagonists

Agonist/antagonist	CAS Registry Number	Molecular formula	Structure number
epinephrine	[51-43-4]	$C_9H_{13}NO_3$	**(85)**
norepinephrine	[51-41-2]	$C_8H_{11}NO_3$	**(86)**
phentolamine	[50-60-2]	$C_{17}H_{19}N_3O$	**(87)**
WB 4101	[613-67-2]	$C_{19}H_{23}NO_5$	**(88)**
chloroethylclonidine	[77472-95-8]	$C_{13}H_{17}Cl_3N_4$	**(89)**
phenylephrine	[59-42-7]	$C_9H_{13}NO_2$	**(90)**
(+)-niguldipine	[120054-86-6]	$C_{36}H_{39}N_3O_6$	**(91)**
prazosin	[19216-56-9]	$C_{19}H_{21}N_5O_4$	**(92)**
5-methylurapidil	[34661-85-3]	$C_{21}H_{31}N_5O_3$	**(93)**
UK 14,304	[59803-98-4]	$C_{11}H_{10}BrN_5$	**(94)**
clonidine	[4205-90-7]	$C_9H_9Cl_2N_3$	**(95)**
yohimbine	[146-48-5]	$C_{21}H_{26}N_2O_3$	**(96)**
rauwolscine	[131-03-3]	$C_{21}H_{26}N_2O_3$	**(97)**
sprioxatrine	[1054-88-2]	$C_{22}H_{25}N_3O_3$	**(98)**
imiloxan	[81167-16-0]	$C_{14}H_{16}N_2O_2$	**(99)**
BRL 44408	[118343-19-4]	$C_{13}H_{17}N_3$	**(100)**
idazoxan	[79944-58-4]	$C_{11}H_{12}N_2O_2$	**(101)**
L-agmatine	[306-60-5]	$C_5H_{14}N_4$	**(102)**
xamoterol	[81801-12-9]	$C_{16}H_{25}N_3O_5$	**(103)**
procaterol	[72332-33-3]	$C_{16}H_{22}N_2O_3$	**(104)**
BRL 37344	[90730-96-4]	$C_{19}H_{22}ClNO_4$	**(105)**
CL 316243	[138908-40-4]	$C_{20}H_{18}ClNO_7Na_2$	**(106)**
CGP 20712A	[81015-67-0, 105737-62-0]	$C_{23}H_{25}F_3N_4O_5$	**(107)**
betaxolol	[63659-18-7]	$C_{18}H_{29}NO_3$	**(108)**
atenolol	[29122-68-7]	$C_{14}H_{22}N_2O_3$	**(109)**
ICI 118551	[72795-19-8]	$C_{17}H_{27}NO_2$	**(110)**
butaxamine	[1937-89-9]	$C_{15}H_{25}NO_3$	**(111)**
(−)-pindolol	[26328-11-0]	$C_{14}H_{20}N_2O_2$	**(112)**



(90)

Phentolamine **(87)**, WB 4101 **(88)**, and the site directed alkylating agent, chloroethylclonidine (CEC) **(89)** have been traditionally used to define α_1-receptors. Table 6 lists the various catecholamines and adrenoreceptor agonists and antagonists.



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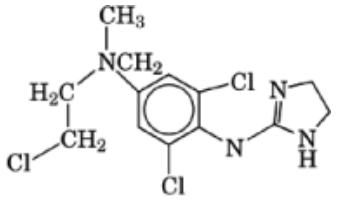
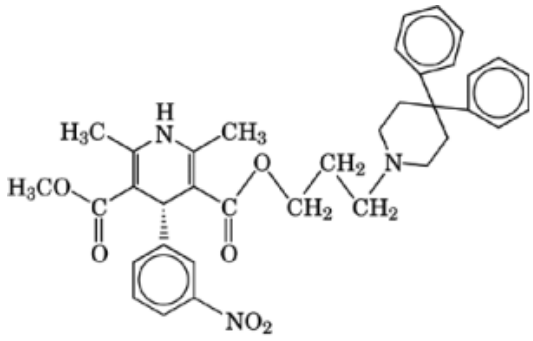
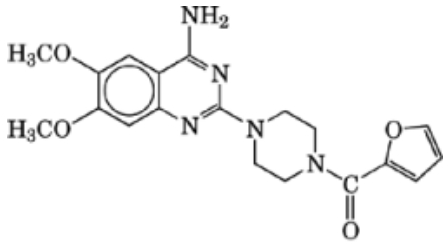


(89)

Phenylephrine **(90)** is a selective α_{1A} receptor agonist; (+)-niguldipine **(91)** is a selective antagonist for the α_{1A} receptor. Prazosin **(92)** and 5-methylurapidil **(93)** are nonselective α_1-receptor antagonists. CEC can differentiate α_{1b} receptors from the other α_1 receptors. Prazosin has low and high affinity for α_{2A} and α_{2B} receptors, respectively.



(91)



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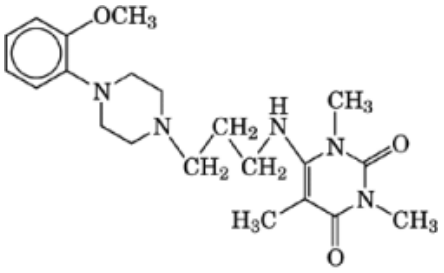
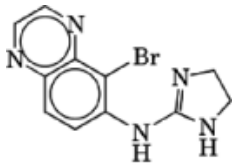


(93)

UK 14,304 **(94)**, clonidine **(95)**, yohimbine **(96)**, and rauwolscine **(97)** interact with all three α_2 receptors. However, the α_{2C} receptor, unlike the α_{2A} and α_{2B} receptors, has high affinity for **(97)**. Spiroxatrine **(98)** and imiloxan **(99)** bind to α_{2B} and α_{2C} receptors. BRL 44408 **(100)** is a selective α_{2A} antagonist.



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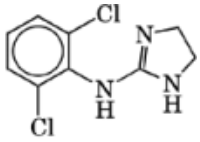

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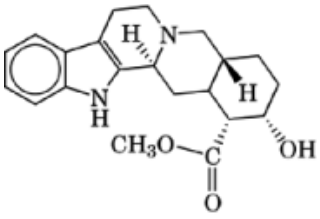

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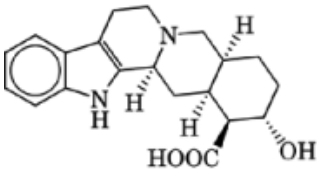

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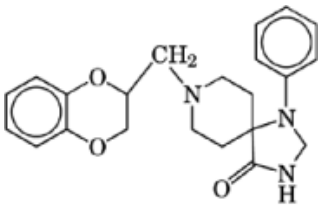

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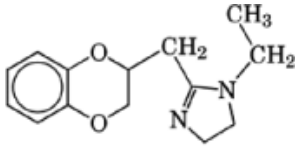

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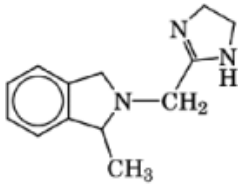
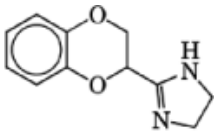


(100)

Imidazolines and imidazolidines, eg, clonidine, UK 14304, and idazoxan **(101)**, represent a class of compounds that interact with α_2-adrenoceptors but the pharmacology is not fully explained by interactions with this receptor. There might be yet another adrenoceptor-like imidazoline receptor or clonidine-like receptor through which these agents mediate their antihypertensive actions. L-Agmatine **(102)** has been identified as a potential endogenous clonidine-displacing substance (CDS) (38). Two nonadrenergic imidazoline binding sites or receptors identified as I_1 and I_2 have been identified.



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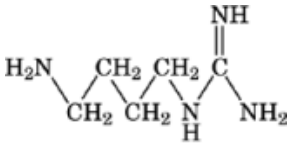
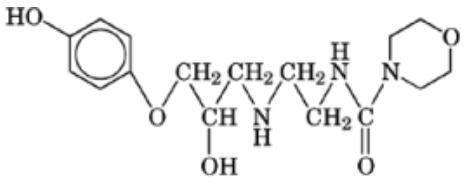


(102)

EPI and NE are also agonists at the β_1-adrenoceptor as is xamoterol **(103)**. Procaterol **(104)** is a β_2-adrenoceptor agonist. BRL 37344 **(105)** and CL 316243 **(106)** are β_3-adrenoceptor agonists. CGP 20712A **(107)**,

betaxolol **(108)**, and atenolol **(109)** are β_1-adrenoceptor antagonists. β_2-Adrenoceptor antagonists include ICI 118551 **(110)** and butaxamine **(111)**. (-)-Pindolol **(112)** is a β_3-adrenoceptor partial agonist (Table 6).



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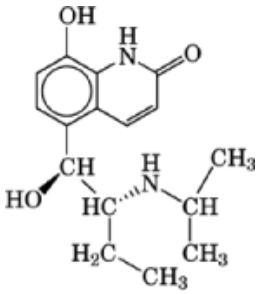

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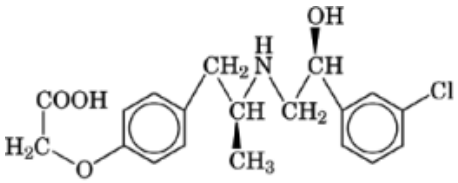

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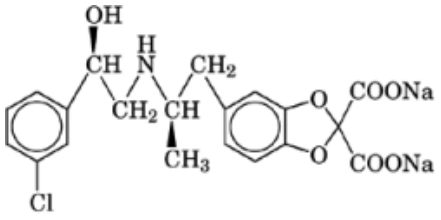

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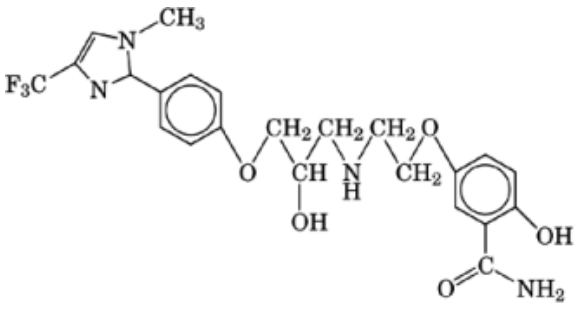
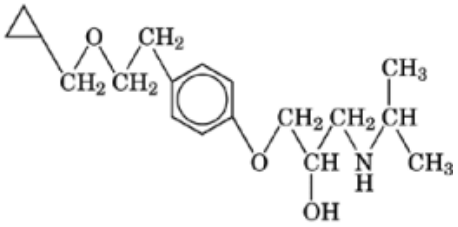
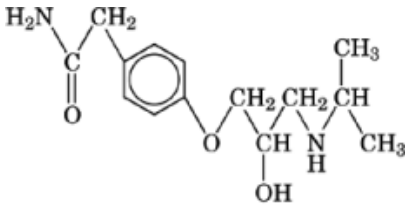


(**107**)



(**108**)



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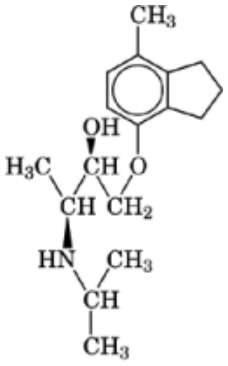
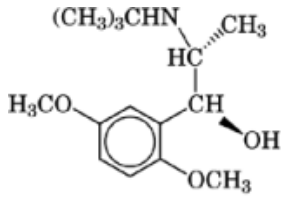


(**110**)



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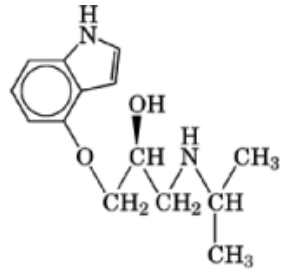


(112)

Adrenoceptors are involved in the regulation of blood pressure, myocardial contractile function, airway reactivity, smooth muscle tone, and a variety of metabolic functions. Presynaptic adrenoceptor antagonists can potentiate the effects of reuptake inhibitors by blocking feedback inhibition. Idazoxan has neuroprotective properties.β-Adrenoceptor antagonists are well known as antihypertensive agents. Agonists are used as antiasthmatics and may have potential as antiobesity agents or in the treatment of diabetes via β_3-adrenoceptor activation (see Antiasthmatic agents; Antiobesity drugs).

2.12. Cholecystokinin

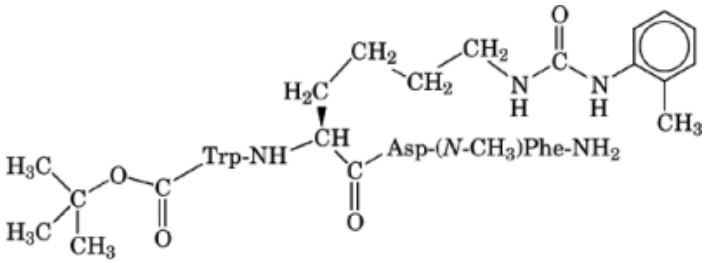
Cholecystokinin (CCK) is a peptide of gut/brain origin that is involved in digestive and homostatic functions (30). CCK originates from a 115-amino acid precursor, prepro-CCK, that is cleaved at a single arginine residue to yield active CCK moieties. The primary naturally occurring forms of CCK are CCK-8 [25126-32-3], $C_{49}H_{62}N_{10}O_{16}S_3$, H-Asp-Tyr($SO_3H$)-Met-Gly-Trp-Met-Asp-Phe-NH_2; CCK-33 [96827-04-2], $C_{167}H_{263}N_{51}O_{52}S_4$ (113), and CCK-4, also known as tetragastrin [1947-37-1], $C_{29}H_{36}N_6O_6S$, H-Trp-Met-Asp-Phe-NH_2. CCK-8 predominates.

H−Lys−Ala−Pro−Ser−Gly−Arg−Met−Ser−Ile−Val−Lys−Asn−Leu−Gln−Asn−Leu−Asp−Pro−Ser−

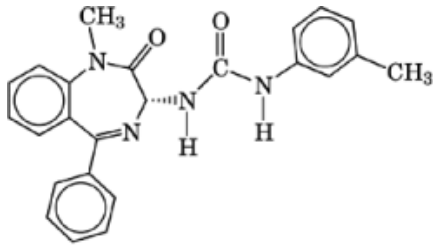
His−Arg−Ile−Ser−Asp−Arg−Asp−Tyr(SO_3H)−Met−Gly−Trp−Met−Asp−Phe−NH_2

(113)

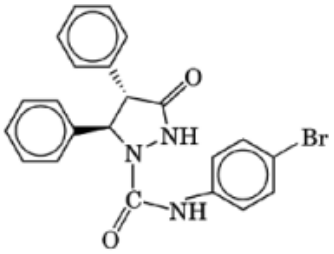
Two CCK receptor subtypes, CCK_A and CCK_B are known. A related receptor, the gastrin receptor, has also been described. CCK_A receptors predominate in the gastrointestinal tract and pancreas and are also localized in discrete brain regions. CCK_B receptors predominate in the brain. A 71623 [130408-77-4], $C_{44}H_{56}N_8O_9$ **(114)** is a selective CCK_A agonist. Devazepide **(65)** is a selective antagonist (40). Desulfated CCK_8 [25679-24-7], $C_{49}H_{62}N_{10}O_{13}S_2$, H-Asp-Tyr-Met-Gly-Trp-Met-Asp-Phe-NH_2, and pentagastrin [5534-95-2], $C_{37}H_{49}N_7O_9S$, $(CH_3)_3COCO$-β-Ala-Trp-Met-Asp-Phe-NH_2, are selective CCK_B receptor agonists. L 365260 [118101-09-0], $C_{24}H_{22}N_4O_2$ **(115)** and LY 262691, $C_{22}H_{18}BrN_3O_2$ **(116)** are species selective CCK_B antagonists.



(**114**)



(**115**)



(**116**)

CCK is found in the digestive tract and the central and peripheral nervous systems. In the brain, CCK coexists with DA. In the peripheral nervous system, the two principal physiological actions of CCK are stimulation of gall bladder contraction and pancreatic enzyme secretion. CCK also stimulates glucose and amino acid transport, protein and DNA synthesis, and pancreatic hormone secretion. In the CNS, CCK induces hypothermia, analgesia, hyperglycemia, stimulation of pituitary hormone release, and a decrease in exploratory behavior. The CCK family of neuropeptides has been implicated in anxiety and panic disorders, psychoses, satiety, and gastric acid and pancreatic enzyme secretions.

2.13. Cytokines and Immunophilins

A large number of inflammatory mediators and related proteins including the cytokines, colony stimulating factors (CSFs), interferons (IFNs), tumor necrosis factors (TNFs), growth factors (see Growth regulators), neurotrophic factors, and immunophilins are found in the mammalian CNS and appear to play a significant role in CNS function both in development and in aspects of brain homeostasis (40–43).

The cytokines are involved in the regulation of the growth, differentiation, and activation of the hematopoietic cells involved in the host immune response. Within the CNS, cytokines have been implicated in a number of hormonal, trophic, toxic, and immune functions and are classified into the CXC family where the first two conserved cysteine residues are separated by an amino acid, or into the CC family where the cysteines are adjacent (40). Members of the CXC family include interleukin (IL)-8, melanoma growth-stimulating activity (MGSA), and neutrophil-activating peptide-2 (NAP-2). Macrophage inflammatory proteins 1α and 1β (MIP-1α and -1β), monocyte chemotactic protein-1 (MCP-1), and regulated on activation normal T-cell and secreted (RANTES) are included in the CC family. The immunophilins interact with intracellular recognition sites for the immunosupressants, FK 506 [104987-11-3], $C_{44}H_{69}NO_{12}$, and cyclosporin-A [59865-13-3], $C_{62}H_{111}N_{11}O_{12}$, and are involved in cell signaling processes in a variety of tissues including the CNS (44) (see also Immunotherapeutic agents).

In the absence of selective antagonists, cytokines have been classified either on the basis of common functional properties or on the structural characteristics of their receptors.

The class 1 cytokine receptor family includes receptors for interleukins IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, and IL-9, granulocyte macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), erythropoietin [11096-26-7] (EPO), leukemia inhibitory factor (LIF), and ciliary neurotrophic factor (CNTF). As of this writing, data suggest that CNS cytokine receptors are distinct from those seen in the periphery. CNTF is highly localized to the myelin forming Schwann cells of the peripheral nervous system as well as activated astrocytes of the central nervous system, but levels in brain are moderate to low. CNTF is thought to act as an injury factor, released by Schwann cells under pathological conditions.

Interleukin-1 (IL-1) exists in two forms, α and β, that are products of different genes. Both polypeptides are synthesized as 33,000 mol wt precursors that are proteolytically cleaved by the action of interleukin converting enzyme (ICE) to generate the mature biologically active 17,000 mol wt proteins. ICE has been implicated in cellular apoptosis (45). The primary peripheral source of IL-1 is the activated mononuclear phagocyte. Within the CNS, IL-1 is synthesized by astrocytes and microglia, and IL-1β has been localized in neurons. IL-1 induces fever and slow-wave sleep, reduces feeding, stimulates immune or glial reactivity in the CNS as well as in the periphery, and modulates the release of adrenocorticotrophic hormone (ACTH), luteinizing hormone (LH), and gonadotropin-releasing hormone (GRH). IL-1 may also function as a trophic factor and as a mediator of ischemic neurotoxicity and may stimulate the production of β-amyloid protein which is a principal component in Alzheimer's disease plaques. The biological effects of IL-1 are mediated via two subtypes of IL-1 receptor (types I and II). Activation of these receptors causes rapid translocation of a pre-existing complex, NF–κB, from the cell cytoplasm to the nucleus where it binds to specific regulatory DNA sequences in the promoters of several cytokine-inducible genes. High levels of IL-1 receptor have been found in choroid plexus, hippocampus, dentate gyrus, and anterior pituitary. IL-1ra [143090-92-0] is a naturally occurring IL-1 antagonist (46).

Interleukin-2 [85898-30-2] (IL-2) ($\sim 15,000$ mol wt) and its receptor occur in high levels in the hippocampus and striatum. Hippocampal IL-2 binding is increased following an excitotoxic lesion. IL-2 can inhibit ACh release and the formation of long-term potentiation in the hippocampus. IL-6 ($\sim 26,000$) is present in astrocytes, microglia, and anterior pituitary cells and high levels have been found in the hypothalamus. IL-1, tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) stimulate the synthesis and secretion of IL-6 which acts as a trophic factor in cultured neurons, to induce nerve growth factor (NGF) secretion in astrocytes, to stimulate the release of hormones from anterior pituitary cells, and to reduce feeding.

The class II cytokine receptor family includes receptors for interferon α/β (IFN α/β) and γ (IFNγ) and IL-10. IFN-γ immunoreactivity has been found in neurons in the hypothalamus, cerebral cortex, mammilary nuclei, and dorsal tegmentum. Astrocytes and microglia *in vitro* can be stimulated to express class II histocompatibility complex (MHC-II) antigens by IFN-γ, which may be involved in the presentation of antigen to T-cells by astrocytes. Thus IFN-γ may be critical in CNS-immune function and dysfunction especially in regard to neuronal and glial apoptotic processes.

Table 7. Dopamine Receptor Agonists and Antagonists

Agonist/antagonist	CAS Registry Number	Molecular formula	Structure number
SKF 82958	[80751-65-1]	$C_{19}H_{20}ClNO_2$	**(117)**
dihydrexidine	[123039-93-0]	$C_{17}H_{17}NO_2$	**(118)**
ABT 431		$C_{22}H_{25}NO_4S$	**(119)**
MK 458	[99705-65-4]	$C_{15}H_{21}NO_2$	**(120)**
pergolide	[66104-22-1]	$C_{19}H_{26}N_2S$	**(121)**
quinpirole	[80373-22-4]	$C_{13}H_{21}N_3$	**(122)**
(*R*)-(+)-7-OH-DPAT		$C_{16}H_{25}NO$	**(123)**
thioridazine	[50-52-2]	$C_{21}H_{26}N_2S_2$	**(124)**
haloperidol	[52-86-8]	$C_{21}H_{23}ClFNO_2$	**(125)**
chlorpromazine	[50-53-3]	$C_{17}H_{19}ClN_2S$	**(126)**
SCH 23390	[87075-17-0]	$C_{17}H_{18}ClNO$	**(127)**
NNC 687	[128022-68-4]	$C_{19}H_{20}N_2O_4$	**(128)**
risperidone	[106266-06-2]	$C_{23}H_{27}FN_4O_2$	**(129)**
sertindole	[106516-24-9]	$C_{24}H_{26}ClFN_4O$	**(130)**
olanzapine	[132539-06-1]	$C_{17}H_{20}N_4S$	**(131)**
clozapine	[5786-21-0]	$C_{18}H_{19}ClN_4$	**(132)**

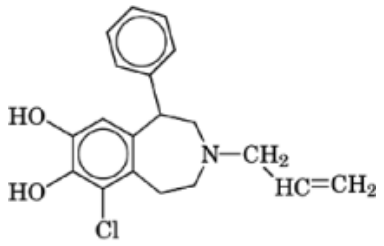
The class III cytokine receptor family includes two TNF receptors, the low affinity NGF receptor and 7-cell surface recognition sites that appear to play a role in proliferation, apoptosis, and immunodeficiency. TNF-α ($\sim$17, 000 protein) is produced by astrocytes and microglia and can induce fever, induce slow-wave sleep, reduce feeding, stimulate prostaglandin synthesis, stimulate corticotrophin-releasing factor and prolactin secretion, and reduce thyroid hormone secretion. TNF-α stimulates IL-1 release, is cytotoxic to oligodendrocytes, and reduces myelination; this has been implicated in multiple sclerosis and encephalomyelitis. Astrocyte TNF-α receptors mediate effects on IL-6 expression and augment astrocytic expression of MHC in response to other stimulants such as IFN-γ.

Activation of immunophilin receptors in the CNS is thought to be involved in certain aspects of AIDS dementia and the CNS side effects seen with the immunosupressants, FK 506 and cyclophilin. FK 506 and related compounds also have antiischemic effects.

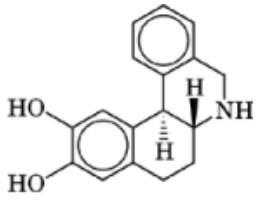
2.14. Dopamine

Dopamine (DA) **(2)** is an intermediate in the synthesis of NE and Epi from tyrosine. DA is localized to the basal ganglia of the brain and is involved in the regulation of motor activity and pituitary hormone release. The actions of DA are terminated by conversion to dihydroxyphenylacetic acid (DOPAC) by monoamine oxidase-A and -B (MAO-A and -B) in the neuron following reuptake, or conversion to homovanillic acid (HVA) through the sequential actions of catechol-*O*-methyl transferase (COMT) and MAO-A and -B in the synaptic cleft.

DA produces its effects through two GPCR families (47). The D_1 family which includes D_1 and D_5 receptors and the D_2 family which includes D_2, D_3, and D_4 receptors. All five receptors have been cloned. D_1 receptor agonists include SKF 82958 **(117)**, dihydrexidine **(118)**, and ABT-431 **(119)**. D_2 receptor agonists include MK 458 **(120)** and pergolide **(121)**. Quinpirole **(122)** and (*R*)-(+)-7-OH-DPAT **(123)** are D_3 agonists (Table 7).



(117)



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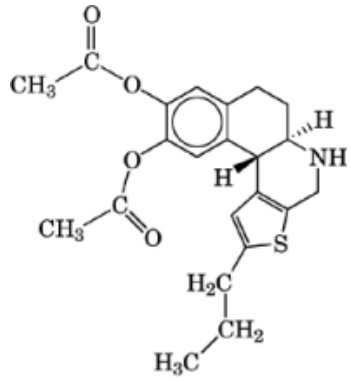

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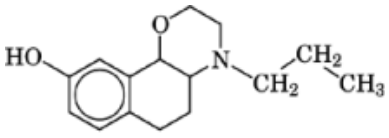

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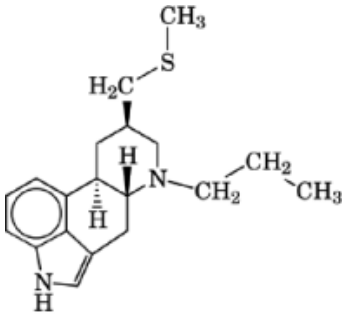

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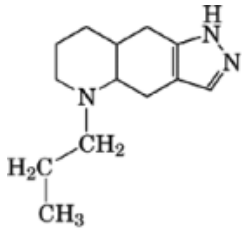

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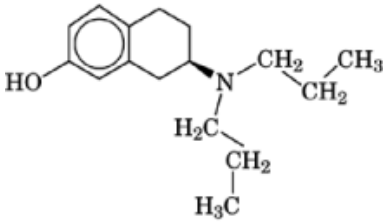
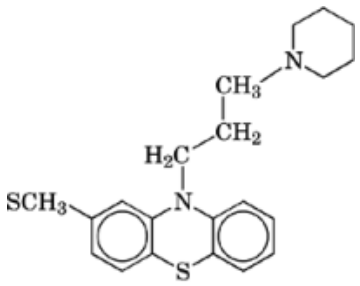


(**123**)

A loss of dopaminergic neurons in the basal ganglia underlies the etiology of Parkinson's disease (PD), a progressive neurodegenerative disorder, which is associated with motor deficits including tremors, muscular rigidity, a loss of postural reflexes, and freezing, ie, difficulty in initiating motor movement. Hyperactivity of brain dopaminergic systems is thought to be involved in the pathology of schizophrenia and many clinically useful antipsychotics produce their effects by blockade of post-synaptic dopamine receptor-mediated responses. DA is also produced in peripheral tissues and can modulate cardiovascular and renal function. Central dopaminergic systems also regulate pituitary hormone release.

DA replacement therapy is the primary palliative treatment regimen for PD (48) though it has limiting side effects including dyskinesias, hallucinations, sleep disturbances, and response fluctuations. Approaches to direct replacement to date have been limited to D_2 selective agents which are used as adjunct therapy with L-dopa **(3)**. Dihydrexidine and ABT 431 are D_1 agonists for potential monotherapy in PD. DA antagonists include a broad range of neuroleptic agents used in the clinical treatment of schizophrenia. These include thioridazine **(124)**, haloperidol **(125)**, and chlorpromazine **(126)** which are D_2 selective antagonists. SCH 23390 **(127)** and NNC 687 **(128)** are D_1 selective antagonists. Because of their effects on DA-mediated motor function, the classical antipsychotics can produce extrapyramidal side effects (EPS), symptoms similar to those seen in PD. For this reason, there is a concerted effort to develop neuroleptics that have reduced side-effect liability. Agents

selective for the D_1 receptor may represent compounds of this type although none have advanced very far in the clinic. Alternative approaches include compounds with combined D_2/5-HT_2 (serotonin) receptor blocking activity, that include risperidone **(129)**, sertindole **(130)**, and olanzapine **(131)**. Clozapine **(132)** is an atypical antipsychotic that has a reduced EPS liability and has been reported to show preferential interactions with D_3 and D_4 receptors, although this is controversial (49). Clinically, clozapine elicits blood dyscrasias that can be fatal. There is an ongoing search for clozapine-like agents that lack this side effect. NGD 94-1 is a selective D_4 antagonist of undisclosed structure.



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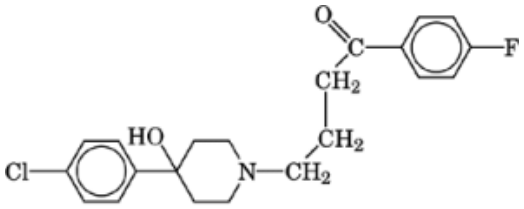

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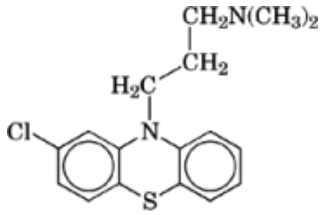

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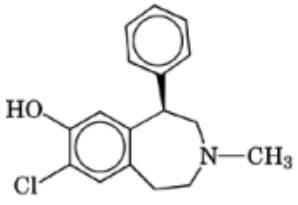

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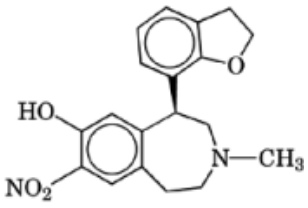

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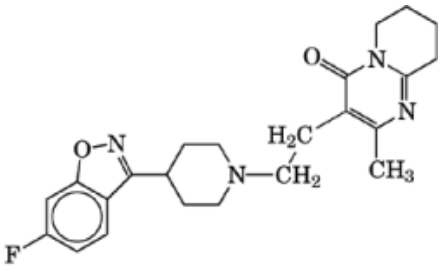

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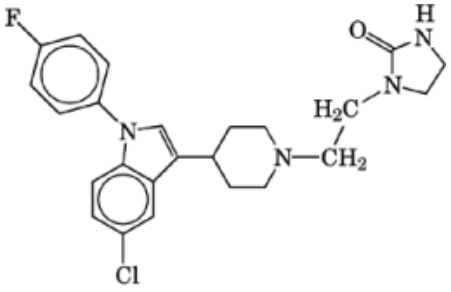

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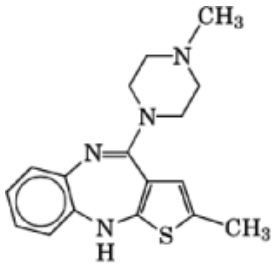

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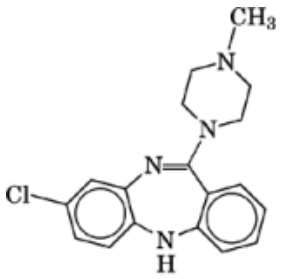


(132)

2.15. Endothelin

The endothelin (ET) peptide family (50) comprises three peptides: ET-1 **(133)**, ET-2 **(134)**, and ET-3 **(135)**. ET-1, the most abundant, is a 21-amino acid peptide. A 203-amino acid peptide precursor, preproET, is cleaved after translation by endopeptidases to form a 38-amino acid proET which is converted to active ET by a putative endothelin-converting enzyme (ECE). ET-3 differs from ET-1 and ET-2 by six amino acids.

Asp-Lys-Glu-Cys-Val-Tyr-Phe-Cys-His-Leu-Asp-Ile-Ile-Trp-OH
Met-Leu-Ser-Ser-Cys-Ser-Cys-H

(133)

Asp-Lys-Glu-Cys-Val-Tyr-Phe-Cys-His-Leu-Asp-Ile-Ile-Trp-OH
Leu-Trp-Ser-Ser-Cys-Ser-Cys-H

(134)

Asp-Lys-Glu-Cys-Val-Tyr-Tyr-Cys-His-Leu-Asp-Ile-Ile-Trp-OH
Lys-Tyr-Thr-Phe-Cys-Thr-Cys-H

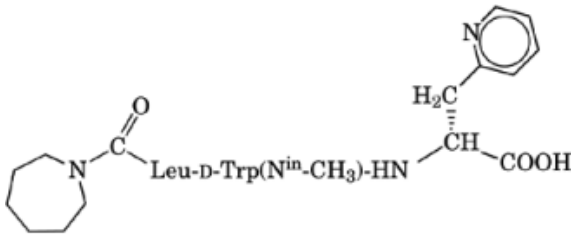
(135)

Two ET GPCR subtypes, ET_A and ET_B, have been cloned from human tissues. Both receptors utilize IP_3/DAG for transduction. ET-1 and ET-2 have similar affinities for the ET_A subtype, whereas the affinity of ET-3 is much lower. All three peptides have similar affinities for the ET_B subtype. Both receptor subtypes are widely distributed, but ET_A receptors are more abundant in human heart, whereas ET_B receptors constitute 70% of the ET receptors found in kidney. BQ 123 [136553-81-6], $C_{31}H_{42}N_6O_7$, cyclo-[D-Asp-Pro-D-Val-Leu-D-Trp], and FR 139317 **(136)** are selective ET_A antagonists. [$Ala^{1,3,11,15}$]ET-1 and BQ 3020 **(137)** are selective ET_B agonists. [Cys^{11--15}]endothelin 1_{11--21}, IRL 1038 **(138)**, and BQ 788 **(139)** are selective ET_B antagonists. Ro 46-2005 **(140)** and SB 209670 **(141)** are the first synthetic orally active endothelin receptor antagonists. The ET_C receptor is a third ET receptor. Peptides and receptors are listed in Table 8.

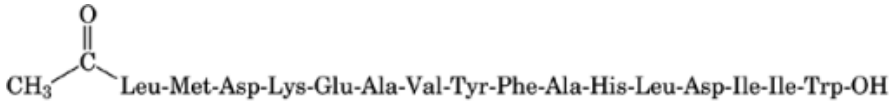
Table 8. Endothelin Peptides and Receptors

Agonist/antagonist	CAS Registry Number	Molecular formula	Structure number
endothelin-1	[117399-94-7]	$C_{109}H_{159}N_{25}O_{32}S_5$	**(133)**
endothelin-2	[122879-69-0]		**(134)**
endothelin-3	[125692-40-2]		**(135)**
FR 139317	[142375-60-8]	$C_{33}H_{44}N_6O_5$	**(136)***a*
BQ 3020	[143113-45-5]	$C_{96}H_{140}N_{20}O_{25}S$	**(137)**
IRL 1038	[144602-02-8]	$C_{68}H_{92}N_{14}O_{15}S_2$	**(138)**
BQ 788			**(139)***a*
Ro 46-2005	[150725-87-4]	$C_{23}H_{27}N_3O_6S$	**(140)**
SB 209670	[157659-79-5]	$C_{29}H_{28}O_9$	**(141)**

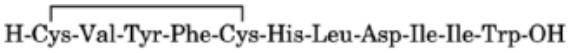
[a] $Trp(N^{in}-CH^3)$ = *N*−methyltryptophan where the methyl group is on the indole nitroge.



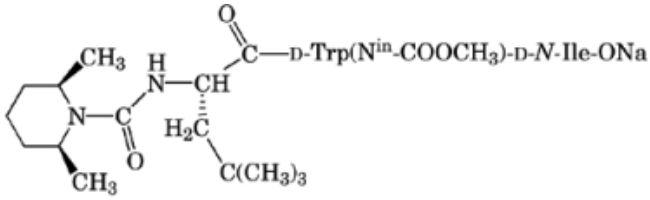
(**136**)



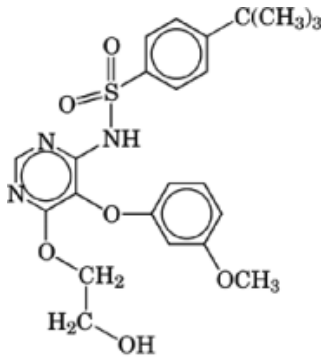
(**137**)



(**138**)



(**139**)



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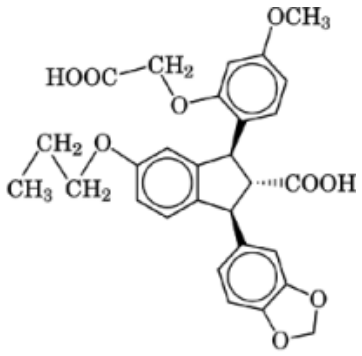


(141)

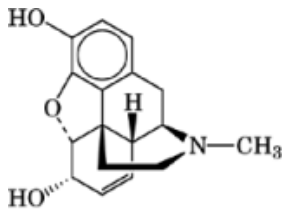
Long-lasting vasoconstriction is produced by the ETs in almost all arteries and veins and several studies have shown that ET-1 causes a reduction in renal blood flow and urinary sodium excretion. ET-1 has been reported to be a potent mitogen in fibroblasts and aortic smooth muscle cells and to cause contraction of rat stomach strips, rat colon and guinea pig ileum. In the central nervous system, ETs have been shown to modulate neurotransmitter release.

2.16. Enkephalins and Endorphins

Morphine **(142)**, an alkaloid found in opium, was first isolated in the early nineteenth century and widely used in patent medicines of that era. It is pharmacologically potent and includes analgesic and mood altering effects. Endogenous opiates, the enkephalins, endorphins, and dynorphins were identified in the mid-1970s (3, 51) (see Opioids, endogenous). Enkephalins and endorphins are listed in Table 9.

Table 9. Enkephalins and Endorphins

Agonist/antagonist	CAS Registry Number	Molecular formula	Structure number
morphine	[57-27-2]	$C_{17}H_{19}NO_3$	**(142)**
β-endorphin	[60118-07-2]		(143)
naloxone	[465-65-6]	$C_{19}H_{21}NO_4$	**(144)**
naltrexone	[16590-41-3]	$C_{20}H_{23}NO_4$	**(145)**
DAMGO	[78123-71-4]	$C_{26}H_{35}N_5O_6$	**(146)**
sufentanil	[56030-54-7]	$C_{22}H_{30}N_2O_2S$	**(147)**
DPDPE		$C_{30}H_{41}N_5O_7S_2$	**(148)**
U 69593	[96744-75-1]	$C_{22}H_{32}N_2O_2$	**(149)**
CI 977	[124439-07-2]	$C_{24}H_{32}N_2O_3$	**(150)**
β-FNA	[72782-05-9]	$C_{25}H_{30}N_2O_6$	**(151)**
ICI 174864	[89352-67-0]	$C_{34}H_{46}N_4O_6$	**(152)**
naltrindole	[111555-53-4]	$C_{26}H_{26}N_2O_3$	**(153)**
naltriben	[111555-58-9]	$C_{26}H_{25}NO_4$	**(154)**
norbinaltorphimine	[105618-26-6]	$C_{40}H_{43}N_3O_6$	**(155)**



(142)

β-Endorphin (143) is produced from pro-opiomelanocortin, a precursor for α-, β-, and γ-melanocyte stimulating hormones (MSH), adrenocorticotropin (ACTH), which includes the α-MSH sequence, and β-lipotropin (β-LPH), which includes β-MSH and β-endorphin sequences. (Met)-enkephalin [58569-55-4], $C_{27}H_{35}N_5O_7S$, H-Tyr-Gly-Gly-Phe-Met-OH, and (Leu)-enkephalin [61090-95-7], $C_{28}H_{37}N_5O_7$, H-Tyr-Gly-Gly-Phe-Leu-OH, are derived from proenkephalin, each molecule of which contains six (Met)-enkephalin sequences and one (Leu)-enkephalin sequence. Dynorphin-A, dynorphin-B, neoendorphin, and β-neoendorphin are all derived from prodynorphin and contain the Leu-enkephalin sequence at their *N*-terminal region. The opioid precursors and the opioids themselves may be processed to other peptidergic neuroregulators, depending on peptidases that may be regulated in a tissue- or activity-dependent manner. Enkephalin and dynorphin systems are widespread in the brain and spinal cord and are found in adrenal medulla and the enteric nervous system. Enkephalins are associated with areas thought to be involved in pain sensation, affective behavior, autonomic regulation, and endocrine regulation. The activity of the enkephalins, endorphins, and dynorphins is terminated by proteases, most notably the neutral endopeptidase 23.11, also known as enkephalinase .

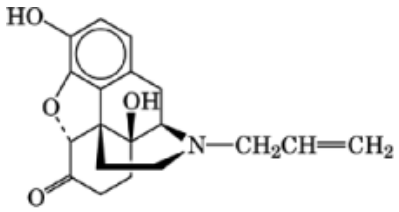
H–Tyr–Gly–Gly–Phe–Met–Thr–Ser–Glu–Lys–Ser–Gln–Thr–Pro–Leu–Val–Thr–

Leu–Phe–Lys–Asn–Ala–Ile–Ile–Lys–Asn–Ala–Tyr–Lys–Lys–Gly–Glu–OH

(143)

Opiates interact with three principal classes of opioid GPCRs:μ-selective for the endorphins,δ-selective for enkephalins, and κ-selective for dynorphins (51). All three receptors have been cloned. Each inhibits adenylate cyclase, can activate potassium channels, and inhibit *N*-type calcium channels. The classical opiates,

morphine and its antagonists naloxone **(144)** and naltrexone **(145)**, have moderate selectivity for the μ-receptor. Pharmacological evidence suggests that there are two subtypes of the μ-receptor and three subtypes each of the δ- and κ-receptor. An ϵ-opiate receptor may also exist.



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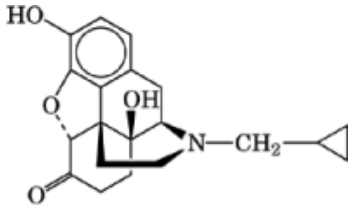
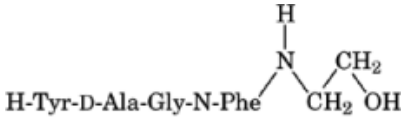


(145)

The search for nonpeptidic enkephalin-like analogues to replace morphine has been unsuccessful as of this writing. The majority of known enkephalin mimics are modified peptides or morphine congeners and include the selective μ-receptor agonists, DAMGO **(146)**, sufentanil **(147)**, and PL017 [83397-56-2], $C_{29}H_{37}N_5O_5$, H-Tyr-Pro-(N-Me)Phe-D-Pro-NH_2; the δ_1 agonists DPDPE **(148)**, DSBULET, H-Tyr-D-Ser(Ot-Bu)-Gly-Phe-Leu-Thr-OH, and [D-Ala^2]-deltorphin [122752-15-2], H-Tyr-D-Ala-Phe-Asp-Val-Val-Gly-NH_2; the δ_2 receptor agonist, DSLET, H-Tyr-D-Ser-Gly-Phe-Leu-Thr-OH; and the κ-receptor agonists, U 69593 **(149)** and CI 977 **(150)**. β-FNA **(151)** is a μ-receptor antagonist, ICI 174864 **(152)** and naltrindole **(153)** are δ_1 receptor antagonists, and naltriben **(154)** and norbinaltorphimine **(155)** are δ_2 and κ-antagonists, respectively.



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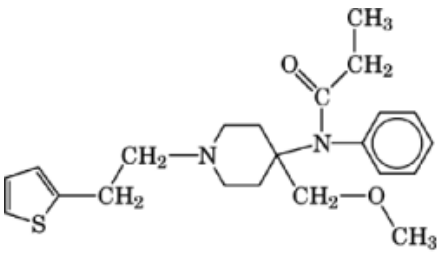

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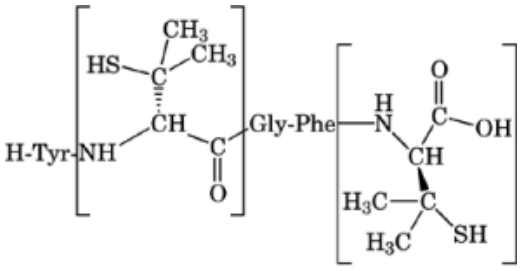

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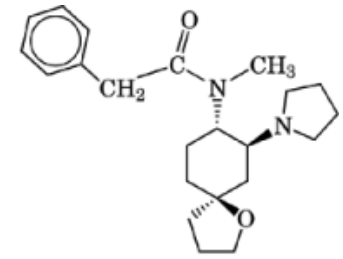

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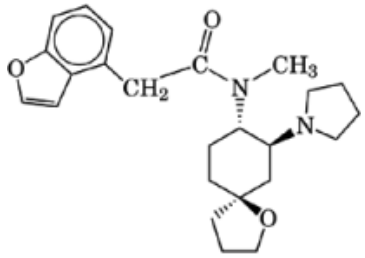

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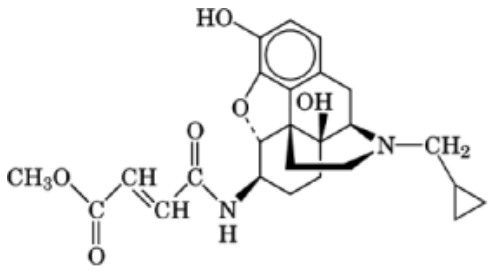
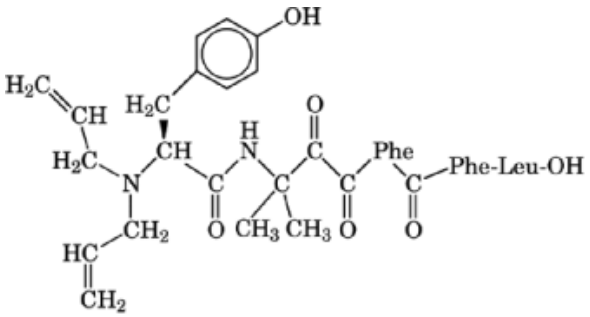


(151)



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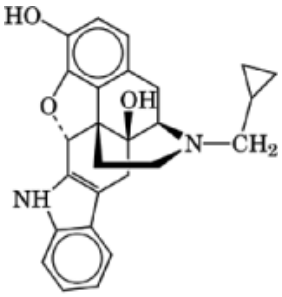

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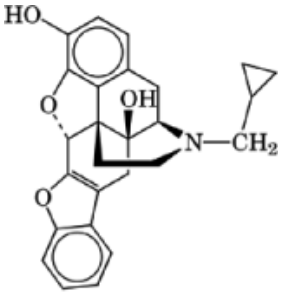

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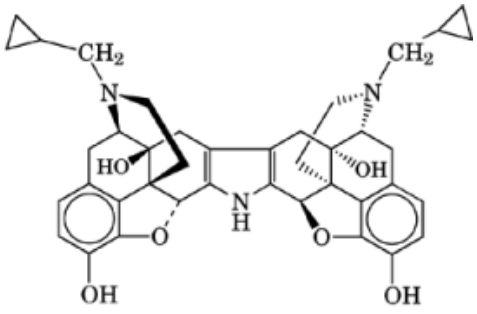


(155)

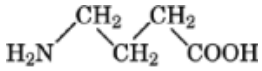
Table 10. GABA and GABA Receptor Agonists and Antagonists

Agonist/antagonist	CAS Registry Number	Molecular formula	Structure number
γ-aminobutyric acid	[56-12-2]	$C_4H_9NO_2$	**(156)**
muscimol	[2763-96-4]	$C_4H_6N_2O_2$	**(157)**
isoguvacine	[64603-90-3]	$C_6H_9NO_2$	**(158)**
THIP	[64603-91-4]	$C_6H_8N_2O_2$	**(159)**
(*R*)-(+)-baclofen	[69308-37-8]	$C_{10}H_{12}ClNO_2$	**(160)**
3-APPA	[103680-47-3]	$C_3H_{10}NO_2$	**(161)**
bicuculline	[485-49-4]	$C_{20}H_{17}NO_6$	**(162)**
SR 95531	[104104-50-9]	$C_{15}H_{17}N_3O_3$	**(163)**
Ro 5-3663	[70656-87-0]	$C_{10}H_{10}N_2O$	**(164)**
phaclofen	[114012-12-3]	$C_9H_{13}ClNO_3P$	**(165)**
CGP 36742	[123690-78-8]	$C_7H_{18}NO_2P$	**(166)**
CGP 35348	[123690-79-9]	$C_8H_{20}NO_4P$	**(167)**
CACA	[55199-25-2]	$C_4H_7NO_2$	**(168)**

Opiates are useful analgesics because they reduce pain sensation without blocking feeling or other sensations. However, they also affect mood, induce euphoria, reduce mental acuity, and induce physical dependence. They can be immunosuppressive and disrupt other homeostatic processes through inhibition of autonomic and enteric nervous systems. The molecular basis of opiate drug dependence and these side-effect liabilities remain unclear except for specific roles for the various receptor subtypes. An analgesic opioid without significant liabilities has yet to be identified.

2.17. GABA

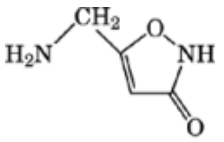
γ-Aminobutyric acid (GABA) **(156)** is the primary inhibitory neurotransmitter in the mammalian brain (52). It is formed by the α-decarboxylation of L-glutamate catalyzed by the enzyme glutamic acid decarboxylase (GAD). GABA also plays a role in the oxidative metabolism of carbohydrates in the Krebs cycle via GABA transminase (GABA-T). The actions of GABA are terminated by reuptake and metabolism.



(156)

GABA interacts with three subclasses of receptor: $GABA_A$ with an associated central BZ receptor; $GABA_B$, a GPCR that may exist in as many as four subclasses; and a newly described $GABA_C$ receptor also referred to as a non-$GABA_A$, non-$GABA_B$ receptor. The transduction mechanism for the $GABA_A$ receptor involves a Cl^- channel, and the transduction mechanism for the $GABA_{B1\alpha}$ receptor involves adenylate cyclase and K^+ and Ca^{2+} channels.

Muscimol **(157)**, isoguvacine **(158)**, and THIP **(159)** are selective $GABA_A$ agonists. (*R*)-(+)-Baclofen **(160)** and 3-APPA **(161)** are $GABA_B$ agonists. 3-APPA has selectivity for the $GABA_{B2}$ receptor. Baclofen is also active at the $GABA_C$ receptor, which is characterized as being GABA agonist-sensitive, but insensitive to isoguvacine and bicuculline. Bicuculline **(162)**, SR 95531 **(163)**, and Ro 5-3663 **(164)** are $GABA_A$ receptor antagonists. Phaclofen **(165)** and CGP 36742 **(166)** are $GABA_B$ receptor antagonists. CGP 35348 **(167)** is a GABA $_{B1\beta}$ antagonist. CACA **(168)** is an antagonist for the $GABA_C$ receptor (Table 10).



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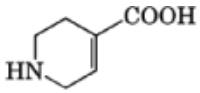

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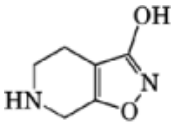

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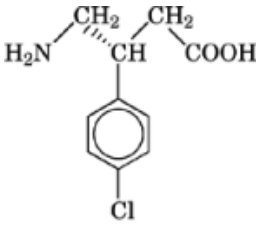

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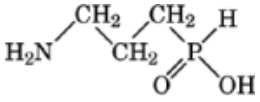

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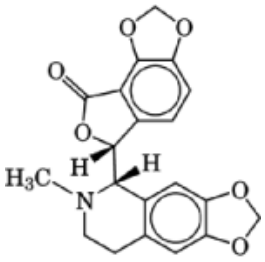

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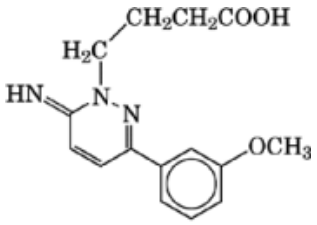
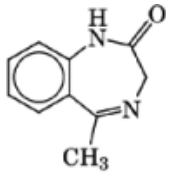


(**163**)



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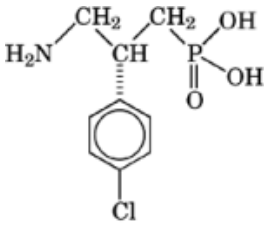

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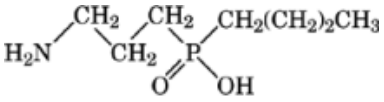

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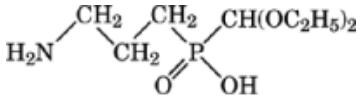
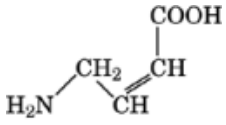


(**167**)



(**168**)

Agents that modulate GABA-ergic neurotransmission have been implicated in processes related to anxiety, hearing, pain sensation, and epilepsy. $GABA_A$ antagonists may also have cognition enhancing activity. $GABA_B$

receptor antagonists, eg, CGP 36742, may have cognition enhancing activity and utility in the treatment of absence seizures and depression.

2.18. Galanin

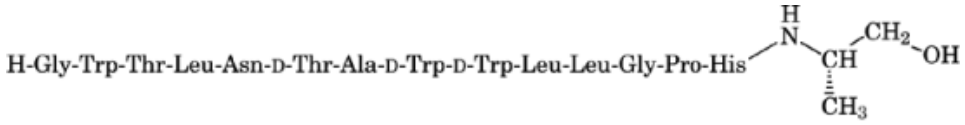
Galanin [*119418-04-1]* (169) is a 29-amino acid neuropeptide derived from the precursor protein prepro-galanin (53). It is widely distributed throughout the peripheral and central nervous systems often co-existing with other neurotransmitters such as ACh, NE, and 5-HT. Prepro-galanin also contains a 59-amino acid C-terminal flanking peptide, a galanin message associated peptide (GMAP), whose function is as yet unknown.

Although numerous biological effects have been attributed to galanin, precise knowledge regarding galanin receptor function has yet to appear. No definitive evidence exists to demonstrate the existence of multiple galanin receptor subtypes. The galanin receptor is a member of the GPCR family; cAMP and Ca*2+* and K+ channels are involved in transduction. Potent nonpeptide agonists or antagonists of the galanin receptor have not yet been reported. The peptides [D-Thr^6, D-Trp^{8,9}]galanin(1–15)-ol **(170)** and [D-Trp^{8,9}]galanin(1–15)-ol **(171)** are potent galanin antagonists *in vitro* (54). The antagonistic properties of another galanin-receptor antagonist, galantide [138579-66-5], $C_{104}H_{151}N_{25}O_{26}S$ (172), are controversial.

H–Gly–Trp–Thr–Leu–Asn–Ser–Ala–Gly–Tyr–Leu–Leu–Gly–Pro–His–Ala–Ile–Asp–Asn–His–Arg–Ser–Phe–

His–Asp–Lys–Tyr–Gly–Leu–Ala–NH_2

(169)



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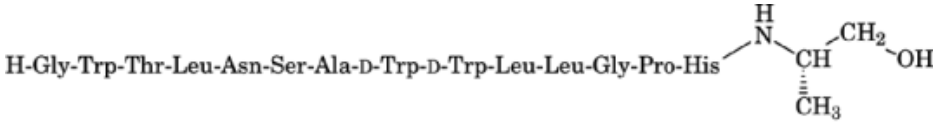


(171)

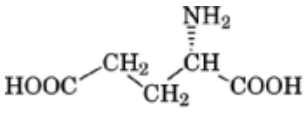
H–Gly–Trp–Thr–Leu–Asn–Ser–Ala–Gly–Tyr–Leu–Leu–Gly–Pro–Gln–Gln–Phe–Phe–Gly–Leu–Met–NH_2

(172)

Galanin receptor activation reduces intracellular free calcium in most cell types. Galanin is a potent inhibitor of glucose-induced insulin release and has been proposed to be the sympathetic transmitter inhibiting insulin release during stress. In the CNS, galanin is a potent inhibitor of locus coeruleus noradrenergic neuron firing. It also acts tonically as a presynaptic inhibitor of ACh release in the hippocampus which may lead to a decline in cognitive performance. There is abnormally high galanin innervation of the basal forebrain in Alzheimer's disease (AD). Galanin antagonists have therefore been considered for the treatment of AD. Galanin acts synergistically with opiates to suppress the nociceptive flexor reflex suggesting that related agents may prove useful in chronic pain.

2.19. Glutamate

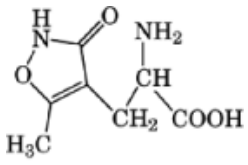
Glutamate [56-86-0], $C_5H_9NO_4$ **(173)**, the primary excitatory neurotransmitter in the CNS (3), is a direct precursor of GABA via the enzyme glutamic acid decarboxylase (GAD), and is also coupled to cellular energy processes by the tricarboxylic acid cycle (55, 56). Glutamate is taken up by glia and neurons. Astrocytic uptake of glutamate appears to predominate over neuronal uptake and may play a predominant role in maintaining extracellular glutamate levels in the brain. Glutamate and glutamine can be interconverted by the enzymes glutamine synthase, which is found predominantly in astrocytes, and phosphate-activated glutaminase. Glial glutamine may serve as a storage form and precursor for neuronal glutamate.



(173)

Glutamate interacts with two principal classes of neuronal receptor, an ionotropic LGIC class and the metabotropic GPCR class, each of which exists in multiple subtypes (57). Three distinct types of glutamate LGIC exist, designated AMPA, kainate, and NMDA receptors, each with additional subtypes based on pharmacological, electrophysiological, and structural criteria. Fourteen glutamate LGIC subunits and seven glutamate GPCRs have been cloned. The subunits comprising the LGIC superfamily, unlike those for nicotinic acetylcholine, GABA, and glycine receptors, do not appear to be derived from a common ancestral gene.

AMPA receptors have a high affinity for the agonist, D,L-α-amino-3-hydroxy-5-methyl-4-isoxazole-4-propionic acid (AMPA) **(174)** and relatively fast activation kinetics. There are four known AMPA receptor subunits. GluR-1, -3, and -4 subunits can form homomeric LGIC receptors in *in vitro* expression systems, but inclusion of GluR-2 with any one of the other three subunits is required for receptor and channel properties similar to most native ionotropic receptors. AMPA receptors lacking GluR-2 subunits are present in cerebellar glia. Numerous additional AMPA receptors can be formed through physiological editing of the RNA to alter an amino acid in transmembrane segment II, ie, the Q/R site that influences divalent ion permeability of the channel, through formation of a C-terminal splice variant of GluR-4, and through alternative splicing of an exon between transmembrane segments III and IV in all four AMPA receptor subunits. AMPA, quisqualate **(175)**, and 5-fluorowillardiine **(176)** are AMPA agonists. AMPA antagonists include GYKI 52446 **(177)**, LY 215490 **(178)**, and NBQX **(179)** (Table 11).



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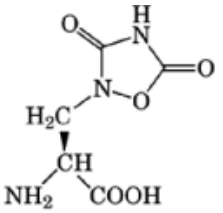

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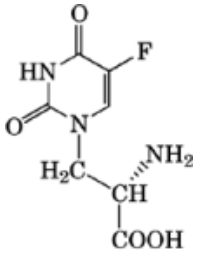

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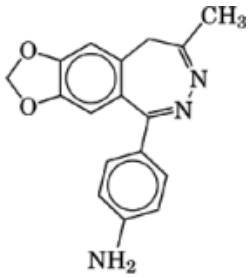

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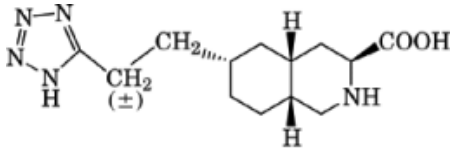

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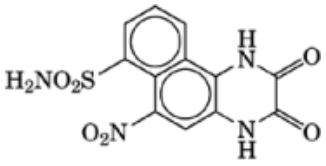


(179)

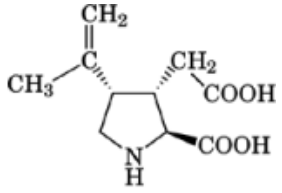
Kainate receptors are LGICs selectively activated by kainic acid **(180)** and domoate **(181)**. Kainate receptors are formed by combination of the subunits GluR-5, -6, or -7 plus KA-1 or -2. GluR-5 and GluR-6, but

Table 11. Glutamate Receptor Agonists and Antagonists

Agonist/antagonist	CAS Registry Number	Molecular formula	Structure number
	Ionotropic glutamate receptors		
D,L-α-amino-3-hydroxy-5-methyl-4-isoxazole-4-propionic acid	[77521-29-0]	$C_7H_{10}N_2O_4$	**(174)**
quisqualate	[52809-07-1]	$C_5H_7N_3O_5$	**(175)**
5-fluorowillardiine	[140187-23-1]	$C_7H_8FN_3O_4$	**(176)**
GYKI 52446	[102771-26-6]	$C_{17}H_{15}N_3O_2$	**(177)**
LY 215490	[150010-68-7]	$C_{13}H_{21}N_5O_2$	**(178)**
NBQX	[118876-58-7]	$C_{12}H_8N_4O_6S$	**(179)**
	Kainate receptors		
kainic acid	[487-79-6]	$C_{10}H_{15}NO_4$	**(180)**
domoate	[14277-97-5]	$C_{15}H_{21}NO_6$	**(181)**
	NMDA receptors		
N-methyl-D-aspartate	[6384-92-5]	$C_5H_9NO_4$	**(182)**
CGS 19755	[110347-85-8]	$C_7H_{14}NO_5P$	**(183)**
LY 233053	[125546-04-5]	$C_9H_{18}NO_5P$	**(184)**
phencylidine	[77-10-1]	$C_{17}H_{25}N$	**(185)**
MK 801	[77086-21-6]	$C_{16}H_{15}N$	**(186)**
glycine	[56-40-6]	$C_2H_5NO_2$	
serine	[56-45-1]	$C_3H_7NO_3$	
HA 966	[1003-51-6]	$C_4H_8N_2O_2$	**(187)**
ACBC	[22264-50-2]	$C_5H_9NO_2$	**(188)**
quinolinic acid	[89-00-9]	$C_7H_5NO_4$	**(189)**
kynurenic acid	[492-27-3]	$C_{10}H_7NO_3$	**(190)**
5,7-dichlorokynurenate	[131123-76-7]	$C_{10}H_5Cl_2NO_3$	**(191)**
ACEA 1021	[153506-21-5]	$C_8H_3Cl_2N_3O_4$	**(192)**
L 705,022		$C_9H_{12}ClNO_3S$	**(193)**
MNQX	[136529-54-9]	$C_8H_4N_4O_6$	**(194)**[a]
spermine	[71-44-3]	$C_{10}H_{26}N_4$	**(195)**
spermidine	[124-20-9]	$C_7H_{19}N_3$	**(196)**
eliprodil	[119431-25-3]	$C_{20}H_{23}ClFNO$	**(197)**
	Metabotropic glutamate receptors		
1*S*,3(*R*)-ACPD	[111900-32-4]	$C_7H_{11}NO_4$	**(198)**
MCPG	[146665-29-6]	$C_{10}H_{11}NO_4$	**(199)**

[a]MNQX is also a metabotropic glutamate receptor ligand.

not the other subunits, can be expressed as a homomeric LGIC. Coexpression of either KA subunit with GluR-5 or -6 affects the functional and pharmacologic properties of the complex. Seven different forms of GluR-6 derived from one DNA sequence arise from editing. Five splice variants of GluR-5 have also been identified. Selective antagonists have not yet been identified.



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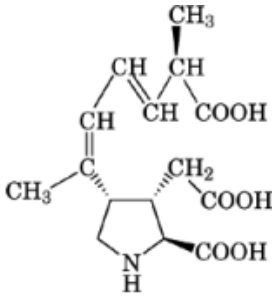

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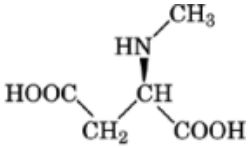
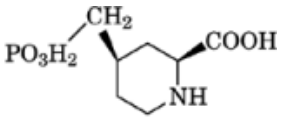


(182)

NMDA receptors are selectively activated by *N*-methyl-D-aspartate (NMDA) **(182)**. NMDA receptor activation also requires glycine or other co-agonist occupation of an allosteric site. NMDAR-1, -2A, -2B, -2C, and -2D are the five NMDA receptor subunits known. Two forms of NMDAR-1 are generated by alternative splicing. NMDAR-1 proteins form homomeric ionotropic receptors in expression systems and may do so *in situ* in the CNS. Functional responses, however, are markedly augmented by co-expression of a NMDAR-2 and NMDAR-1 subunits. The kinetic and pharmacological properties of the NMDA receptor are influenced by the particular subunit composition.

The phosphonic acid derivatives, CGS 19755 **(183)** and LY 233053 **(184)** are NMDA antagonists, binding at the glutamate site. The channel associated with the NMDA receptor has a binding site for the psychotomimetic, phencylidine (PCP) **(185)**, and the noncompetitive antagonist, MK 801 **(186)**. Because directly acting and channel blocking NMDA antagonists induce psychosis, there has been considerable interest in agents that modulate the NMDA receptor via NMDA receptor-associated allosteric modulatory sites, namely the glycine and polyamine sites. Glycine, serine, HA 966 **(187)**, and the cyclobutane ACBC **(188)** are glycine-site agonists. Quinolinic acid **(189)** and kynurenic acid **(190)**, endogenous tryptophan metabolites, are glycine-site antagonists suggesting that these or related ligands may function physiologically as antagonist neuromodulators of NMDA transmission. 5,7-Dichlorokynurenate **(191)**, ACEA 1021 **(192)**, L 705,022 **(193)**, and MNQX **(194)** are also glycine-site antagonists. At the polyamine site, spermine **(195)**, spermidine **(196)**, and eliprodil **(197)** modulate NMDA receptor function.



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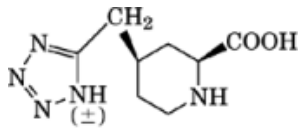

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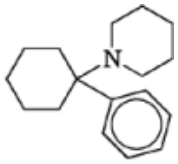

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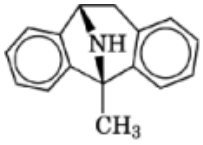

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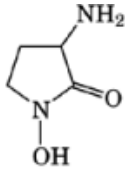

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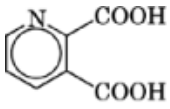

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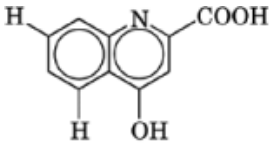

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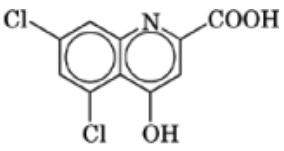

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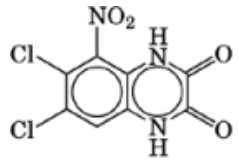

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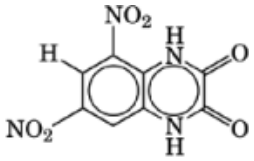

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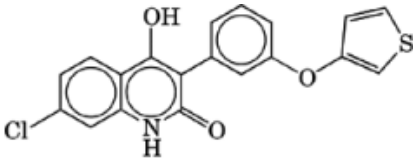

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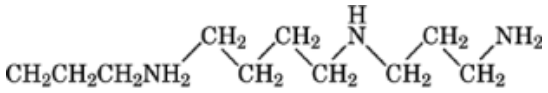

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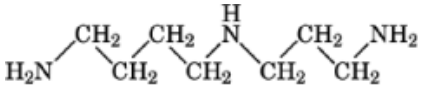

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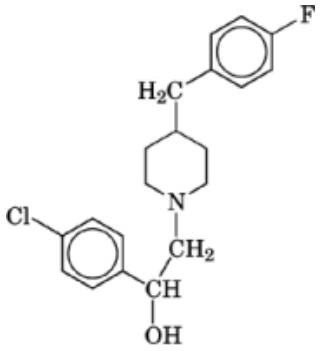
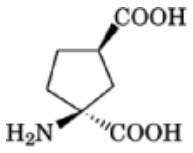


(197)

NMDA LGICs exhibit slow activation kinetics but are highly permeable to calcium relative to other glutamate receptors. They are known for their involvement in calcium-dependent phenomena such as the formation of long-term potentiation (LTP) and long-term depression (LTD), that are thought to underlie learning and memory. However, excess activation of NMDA receptors may contribute to pathologic processes such as excess excitability and calcium-dependent cell death following the hypoxia or ischemia associated with stroke. While MK 801 encountered problems in clinical trials for this indication, CGS 19755 may represent the first NMDA receptor ligand for the treatment of stroke. NMDA receptor modulators may also have potential as anxiolytics, antipsychotics, cognition enhancers, and in the treatment of certain types of pain.

Metabotropic glutamate receptors are GPCRs, although there is little sequence homology between these and other GPCRs (57, 58). There are seven mammalian metabotropic glutamate receptor genes, mGluR-1 to -7, with three variants of mGluR-1 formed by alternative splicing. mGluR-1 may stimulate adenylate cyclase whereas the other metabotropic glutamate receptors inhibit cyclic AMP synthesis. mGluR-4 and mGluR-7 are candidate L-AP4 (L-amino-4-phosphonobutanoic acid) receptors, thought to be presynaptic inhibitory feedback autoreceptors.

Enantiomers of 1-aminocyclopentane dicarboxylic acid (ACPD), such as *trans*- or 1(*S*),3(*R*)-ACPD **(198)**, activate metabotropic glutamate receptors selectively, but in some cases the activation may be weak and/or less potent than other glutamate agonists such as quisqualate. MNQX **(194)**, an agonist at metabotropic glutamate receptors, is also an NMDA glycine-site antagonist. MCPG **(199)** is a metabotropic receptor antagonist.



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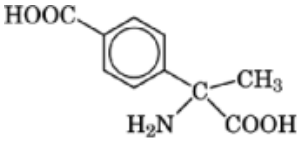


(199)

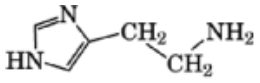
Table 12. Histamine Receptor Agonists and Antagonists

Agonist/antagonist	CAS Registry Number	Molecular formula	Structure number
	H_1 receptors		
2-methylhistamine	[34392-54-6]	$C_6H_{11}N_3$	**(201)**
pyrilamine	[91-84-9]	$C_{17}H_{23}N_3O$	**(202)**
astemizole	[68844-77-9]	$C_{28}H_{31}FN_4O$	**(203)**
terfenadine	[50679-08-8]	$C_{32}H_{41}NO_2$	**(204)**
	H_2 receptors		
dimaprit	[65119-89-3]	$C_6H_{15}N_3S$	**(205)**
impromidine	[55273-05-7]	$C_{14}H_{23}N_7S$	**(206)**
cimetidine	[51481-61-9]	$C_{10}H_{16}N_6S$	**(207)**
ranitidine	[66357-35-5]	$C_{13}H_{22}N_4O_3S$	**(208)**
	H_3 receptors		
(*R*)-α-methylhistamine	[75614-87-8]	$C_6H_{11}N_3$	**(209)**
imetit	[102203-18-9]	$C_6H_{10}N_4S$	**(210)**
thioperamide	[106243-16-7]	$C_{15}H_{24}N_4S$	**(211)**
clobenpropit	[145231-45-4]	$C_{14}H_{17}ClN_4S$	**(212)**

Metabotropic receptors may mediate increased excitability through inhibition of certain potassium channels, or decreased excitability, through activation of calcium-dependent potassium channels or inhibition of evoked glutamate release. Metabotropic receptors also may regulate the function of ionotropic glutamate receptors, eg, NMDA receptors, or other receptors. The roles of metabotropic glutamate receptors in the formation of long-term potentiation and the regulation of other synaptic processes are under active study (Table 11).

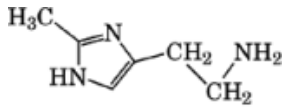
2.20. Histamine

Histamine [51-45-6], $C_5H_9N_3$ **(200)** is an inflammatory autacoid involved in allergic and anaphylactic reactions (3, 39, 59) (see Histamine and histamine antagonists). It is formed from histidine by the enzyme L-histidine decarboxylase. In the periphery, histamine is stored in mast cells, basophils, cells of the gastric mucosa, and epidermal cells. In the CNS, histamine is released from nerve cells and acts as a neurotransmitter. The actions of histamine are terminated by methylation and subsequent oxidation via the enzymes histamine-*N*-methyltransferase and monoamine oxidase.



(200)

Histamine interacts with three distinct receptor subtypes, H_1, H_2, which have been cloned, and H_3. 2-Methylhistamine **(201)** and 2-(*n*-fluorophenyl) histamine are selective H_1 agonists (Table 12). Activation of the H_1 receptor results in smooth muscle contraction, bronchoconstriction, and gut contraction. Classical antihistamines like pyrilamine **(202)** are histamine H_1 receptor antagonists that block smooth muscle contraction and allergen release, limiting the scope of the reaction. Such first-generation antagonists generally produce sedation and other CNS effects in addition to their beneficial effects. Second-generation peripherally selective H_1 antagonists, such as astemizole **(203)** and terfenadine **(204)**, that do not cross the blood brain barrier have reduced sedative properties.



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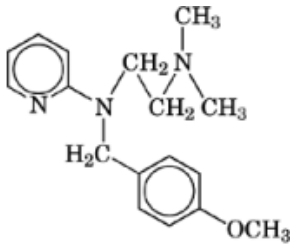

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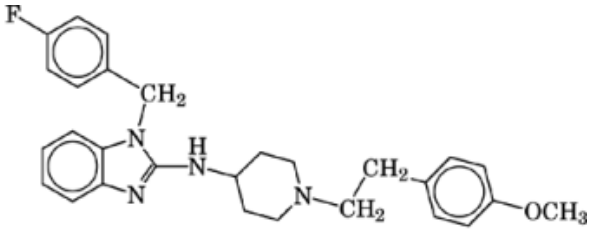

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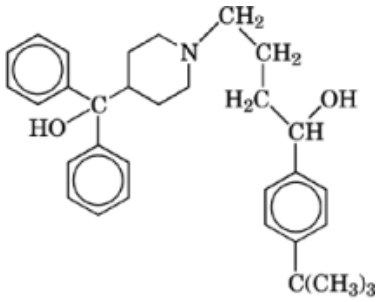
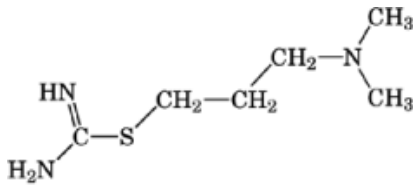
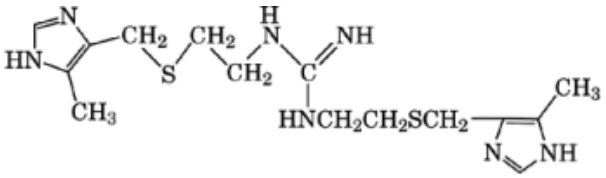


(204)

Activation of histamine H_2 receptors with histamine and selective agonists such as dimaprit **(205)** and impromidine **(206)** results in gastric acid secretion and ulcer formation. The selective H_2 blockers, cimetidine **(207)** and ranitidine **(208)** have revolutionized gastric ulcer treatment replacing expensive, debilitating surgery with cost-effective drug therapy (see Gastrointestinal agents).



(205)



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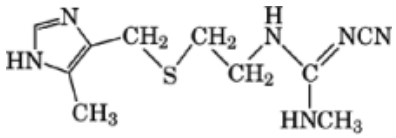

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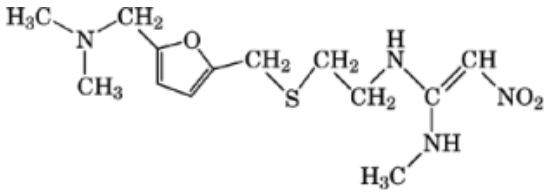
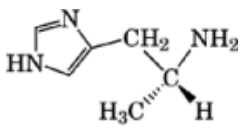


(208)

H_1 and H_2 receptors also evoke depressor and vasodilator responses. In the heart, ionotropic effects are H_2-mediated; the negative dromotropic effects of histamine appear to be H_1-mediated. All three types of histamine receptor are present in the CNS, and H_1 receptors in cortex, hippocampus, amygdala, caudate, and putamen are involved in sedative responses. CNS H_3 receptors are localized to cortex, striatum, hippocampus, and olfactory nuclei and appear to be involved in attention and cognition. Activation of presynaptic H_3 receptors by histamine leads to inhibition of both histamine release as well as inhibition of histamine synthesis. (*R*)-α-Methylhistamine **(209)** and imetit **(210)** are H_3 agonists. Thioperamide **(211)** and clobenpropit **(212)** are H_3 antagonists. All four ligands contain an imidazole moiety and consequently do not penetrate the blood brain barrier well.



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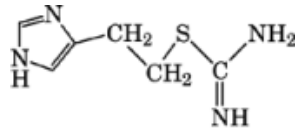

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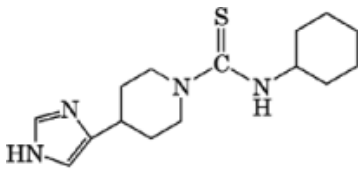

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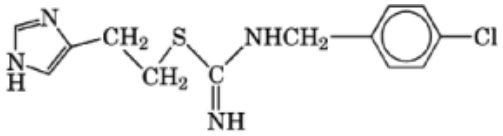


(**212**)

2.21. Insulin and Amylin

Insulin is a member of a family of related peptides, the insulin-like growth factors (IGFs), including IGF-I and IGF-II (60) and amylin (75), a 37-amino acid peptide that mimics the secretory pattern of insulin. Amylin is deficient in type 1 diabetes mellitus but is elevated in hyperinsulinemic states such as insulin resistance, mild glucose intolerance, and hypertension (33). Insulin is synthesized in pancreatic β cells from proinsulin, giving rise to the two peptide chains, *A* and *B*, of the insulin molecule. IGF-I and IGF-II have structures that are homologous to that of proinsulin (see Insulin and other antidiabetic drugs).

Insulin elicits a remarkable array of biological responses in a number of tissues including liver, gut, and brain (61). Insulin and IGF-1 receptors (IGF1R) are ligand-activated tyrosine protein kinases. The insulin receptor does not directly bind effector molecules but rather phosphorylates its primary substrate, insulin receptor substrate-1 (IRS1), and IRS1 in turn binds effector molecules. Insulin and IGF-1 receptors are widely distributed throughout the brain and undergo discrete alterations in expression levels during development and post-natal differentiation. Both IGF-1 and -2 are present in the brain and participate in the growth and differentiation of neurons and astrocytes in developing organisms, in synapse formation, in repair processes, in the modulation of satiety, and in feedback regulation of growth hormone secretion. High affinity (K_d = 28 pM) binding sites for amylin have been identified in rat brain, particularly in nucleus accumbens. Amylin may be involved in aspects of amyloid formation in both the pancreas and brain (33).

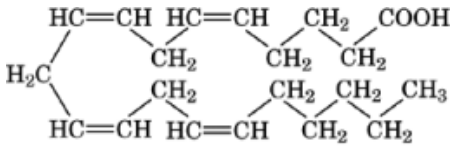
2.22. Leukotrienes and Prostanoids

Arachidonic acid (AA) **(213)** and its metabolites are involved in cellular regulatory processes in all three principal chemical signaling systems: endocrine , immune, and neuronal (62). Following receptor activation or increased intracellular calcium, AA is liberated from membrane phospholipids through the action of phospholipase A_2, or the sequential actions of phospholipase C and diacylglycerol lipase. AA may act within the cell or diffuse extracellularly. It is metabolized to a number of other secondary messenger substances through three main pathways. Cyclooxygenase (COX) is the key enzyme in the formation of the prostanoids, the

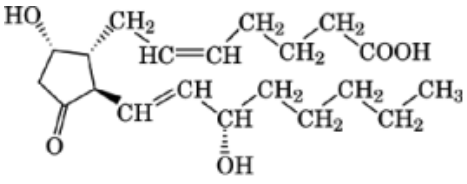
Table 13. Metabolites of Arachidonic Acid

Metabolite	CAS Registry Number	Molecular formula	Structure number
PGD_2	[41598-07-6]	$C_{20}H_{32}O_5$	**(214)**
PGE_2	[353-24-6]	$C_{20}H_{32}O_5$	**(215)**
$PGF_{2\alpha}$	[551-11-1]	$C_{20}H_{34}O_5$	**(216)**
PGH_2	[42935-17-1]	$C_{20}H_{32}O_5$	**(217)**
PGI_2	[35121-78-9]	$C_{20}H_{32}O_4$	**(218)**
thromboxane A_2	[57576-52-0]	$C_{20}H_{32}O_5$	**(219)**
14,15-EET	[155073-43-1]	$C_{20}H_{30}O_3$	**(220)**
5-HETE	[70608-72-9]	$C_{20}H_{32}O_3$	**(221)**
leukotriene A_4	[74807-57-1]	$C_{20}H_{30}O_3$	**(222)**
LTB_4	[71160-24-2]	$C_{20}H_{32}O_4$	**(223)**
LTC_4	[72025-60-6]	$C_{30}H_{37}N_3O_9S$	**(224)**
LTD_4	[73836-78-9]	$C_{25}H_{40}N_2O_6S$	**(225)**
LTE_4	[75715-89-8]	$C_{23}H_{37}NO_5S$	**(226)**

prostaglandins, and thromboxanes. Two forms of COX are known: COX-1, a constitutive enzyme, and COX-2, an inducible form. The prostaglandins, PGD_2 **(214)**, PGE_2 **(215)**, $PGF_{2\alpha}$ **(216)**, PGH_2 **(217)**, and PGI_2 **(218)**, and the prostanoid, thromboxane A_2 **(219)**, are products of the COX pathway. Cytochrome P_{450} is the key enzyme in the generation of epoxyeicosatrienoic acids (EETs), eg, 14,15-EET **(220)** and hydroxyeicosatetraenoic acids, eg, 5-HETE **(221)**. Various lipoxygenases (LOs) generate 5-, 12-, and 15-hydroperoxyeicosatetraenoic acids (5-, 12-, and 15-HPETE). 5-HPETE is metabolized to leukotriene A_4 (LTA_4) **(222)** which is a precursor to other leukotrienes. LTB_4 **(223)** is generated by LTA_4 hydrolase. The peptidoleukotrienes are generated sequentially: LTA_4 is converted to LTC_4 **(224)** by glutathione-*S*-transferase; LTC_4 to LTD_4 **(225)** by glutamyl transferase; and LTD_4 to LTE_4 **(226)** by a dipeptidase (Table 13).



(213)



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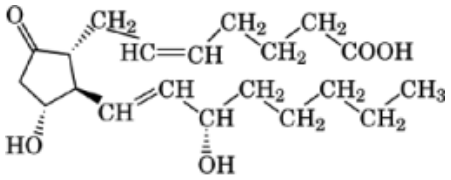

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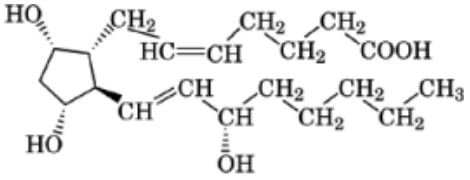

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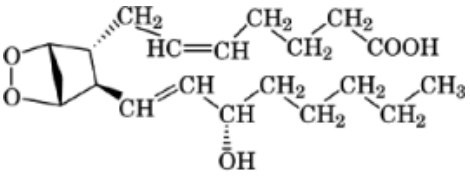

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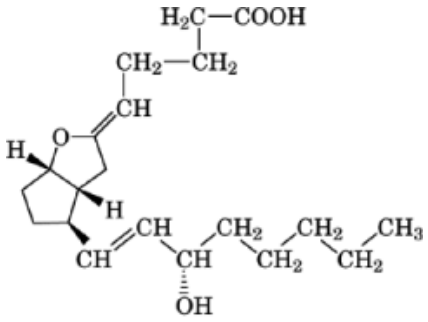

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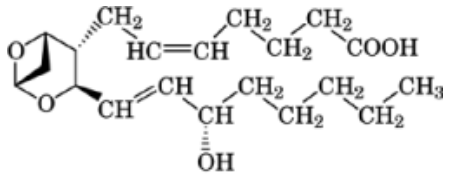

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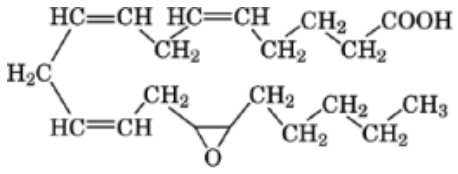

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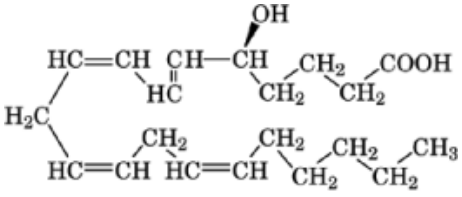

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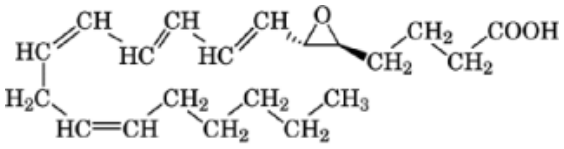

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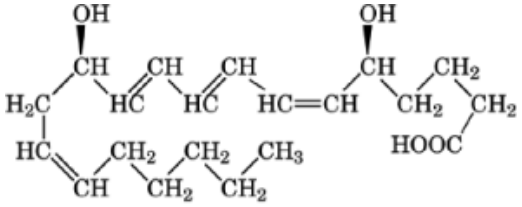

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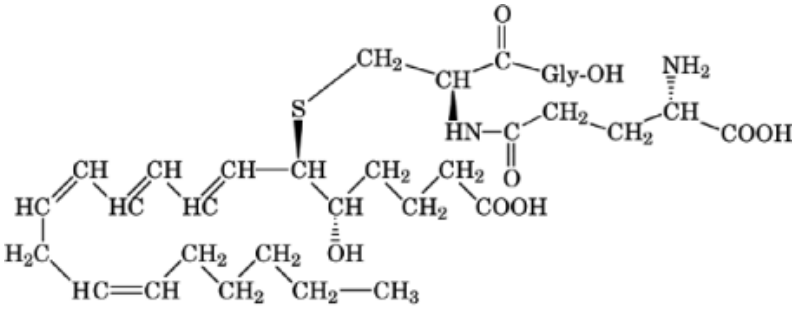

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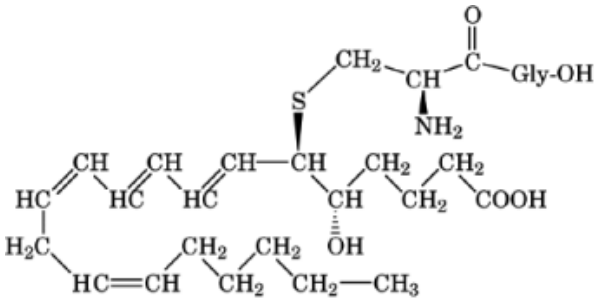

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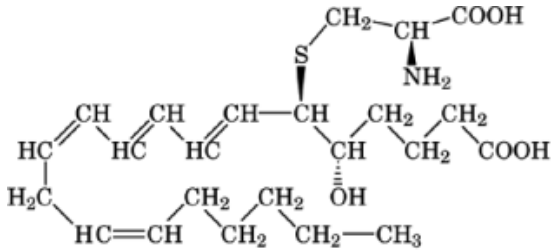
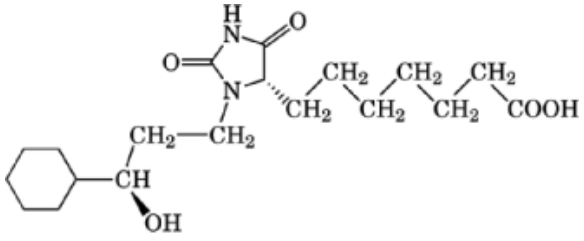
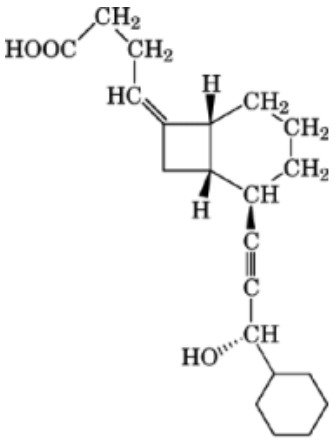


(226)

The prostanoids produce effects via five main subclasses of GPCR: DP, EP, FP, IP, and TP (63). The EP receptor exists in four subtypes, EP_1–EP_4. BW 245C **(227)**, RS 93520 **(228)**, and ZK 110841 **(229)** are DP receptor agonists. Iloprost and enprostil are EP receptor agonists. Fluprostenol **(230)** and cicaprost **(231)** are FP ($PGF_{2\alpha}$) and IP (PGI_2) agonists, respectively. U 46619 **(232)** and STA_2 **(233)** are TP (TXA_2) receptor agonists. GR 32191 **(234)**, SQ 29548 **(235)**, and ONO 3708 **(236)** are TP (TXA_2) antagonists. AY23626 [37786-01-9] is an EP_2 selective agonist; SC19220 [19395-87-0] is an EP_1 selective antagonist. No selective FP or IP antagonists are known.



(227)



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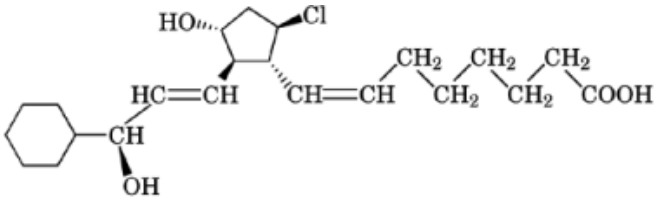

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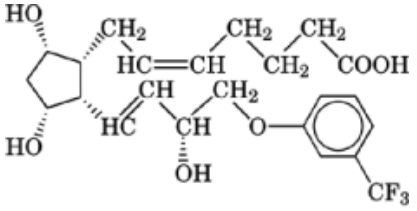

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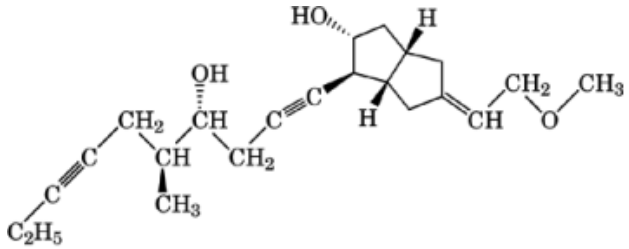

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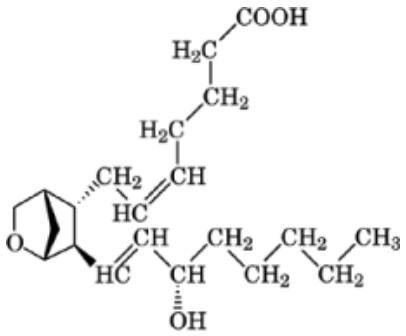
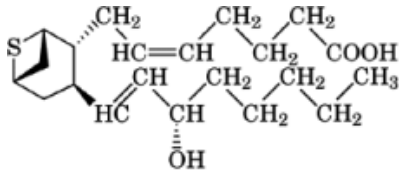


(232)



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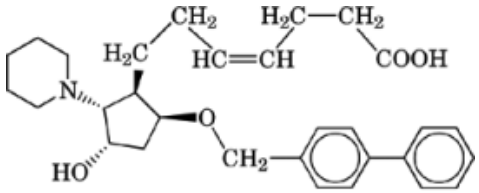
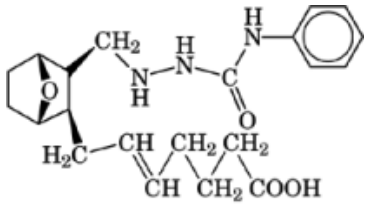
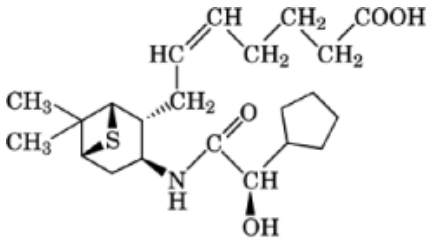


(234)

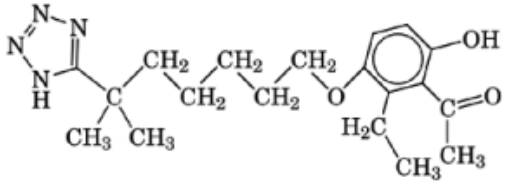


(235)

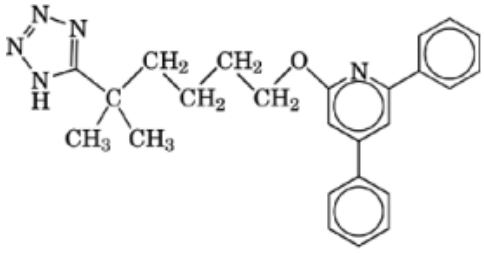


(236)

The leukotrienes also produce effects on tissue function via discrete GPCR subtypes. The leukotriene receptors (LTRs) comprise two main groups: OH LTRs that bind noncysteinyl, dihydroxy LTs such as LTB_4; and Cys-LTRs that bind the cysteinyl LTs, LTC_4, LTD_4, and LTE_4, and exist in two subtypes, Cys-LTR_1 and Cys-LTR_2. The transduction mechanisms for OH-LTR and Cys-LTR_2 involve IP_3/DAG. Leukotrienes are the only known agonists for LTRs. LY 255283 **(237)** and RP 69698 **(238)** are selective OH-LTR antagonists. ICI 198615 **(239)**, ONO 1078 **(240)**, MK 571 **(241)**, and SKF 104353 **(242)** are selective Cys-LTR_1 antagonists. Bay u9773 **(243)** is the antagonist used to define the Cys-LTR_2 receptor (Table 14).



(237)



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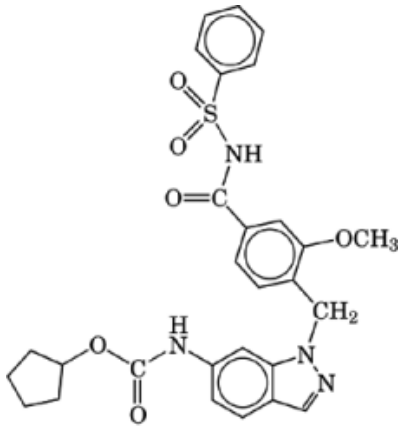

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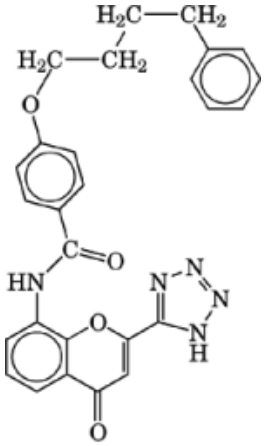

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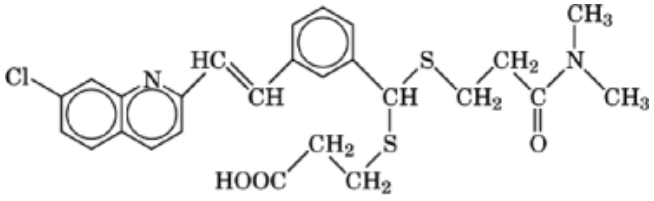
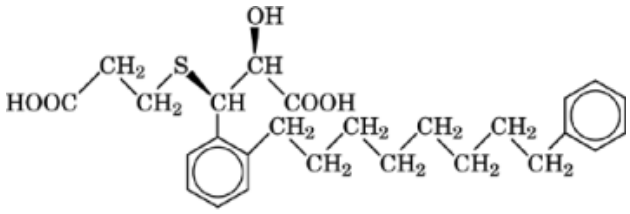


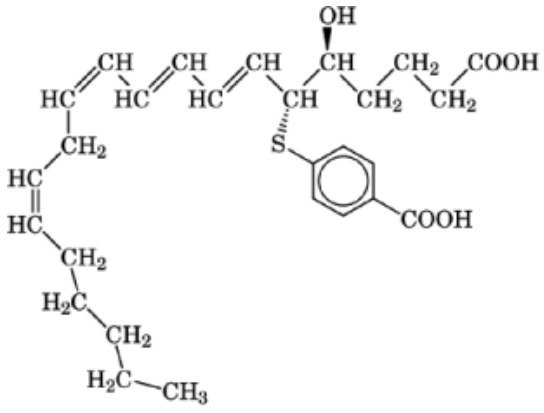
(241)

Table 14. Prostanoid and Leukotriene Receptor Agonists and Antagonists

Agonist/antagonist	CAS Registry Number	Molecular formula	Structure number
	Prostanoid receptors		
BW 245C	[72814-32-5]	$C_{19}H_{32}N_2O_5$	**(227)**
RS 93520	[105880-66-8]	$C_{21}H_{30}O_3$	**(228)**
ZK 110841	[105595-17-3]	$C_{22}H_{35}ClO_4$	**(229)**
fluprostenol	[40666-16-8]	$C_{23}H_{29}F_3O_6$	**(230)**
cicaprost	[94079-80-8]	$C_{22}H_{32}O_3$	**(231)**
U 46619	[56985-40-1]	$C_{21}H_{34}O_4$	**(232)**
STA_2	[89617-02-7]	$C_{21}H_{34}O_3S$	**(233)**
GR 32191	[85505-64-2]	$C_{30}H_{37}NO_4$	**(234)**
SQ 29548	[98672-91-4]	$C_{21}H_{29}N_3O_4$	**(235)**
ONO 3708	[102191-05-9]	$C_{22}H_{37}NO_4S$	**(236)**
	Leukotriene receptor antagonists		
LY 255283	[117690-79-6]	$C_{19}H_{28}N_4O_3$	**(237)**
RP 69698	[141748-00-7]	$C_{25}H_{27}N_5O$	**(238)**
ICI 198615	[104448-53-5]	$C_{28}H_{28}N_4O_6S$	**(239)**
ONO 1078	[103177-37-3]	$C_{27}H_{23}N_5O_4$	**(240)**
MK 571	[115104-28-4]	$C_{26}H_{27}ClN_2O_3S_2$	**(241)**
SKF 104353	[107023-41-6]	$C_{26}H_{34}O_5S$	**(242)**
Bay u9773		$C_{27}H_{36}O_5S$	**(243)**



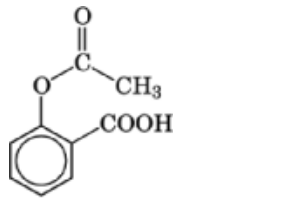
(242)



(243)

Leukotrienes are potent endogenous regulators of bronchial and vascular smooth muscle, vascular permeability, and allergic and inflammatory responses including leukocyte activation (64). As such, leukotrienes are of considerable interest physiologically and pharmaceutically in asthma, rheumatoid arthritis, psoriasis, allergic rhinitis, and ulcerative colitis. Most work has centered on peripheral airway, vascular, and isolated cell systems. Cerebral vasculature, mast cells, and other immune competent cells in the brain also may be relevant targets as AA is a second messenger in the CNS and may be intimately involved in neurodegenerative processes.

Direct receptor antagonists for the various products of either the COX or 5-LO pathways have not proven especially efficacious in the clinic. Thus therapeutic efforts related to modulation of the AA pathway have focused on enzyme inhibitors (see Enzyme inhibitors). COX and its inducible form, COX-2 are inhibited by nonsteroidal antiinflammatory agents like aspirin [50-78-2], $C_9H_8O_4$ **(244)** and ibuprofen [15687-27-1], $C_{13}H_{18}O_2$ **(245)**. L-745,337, $C_{16}H_{13}F_2NO_3S$ **(246)** is a selective COX-2 inhibitor. 5-LO inhibitors include zileuton [111406-87-2], $C_{11}H_{12}N_2O_2S$ **(247)** and D 2138 [140841-32-3], $C_{22}H_{24}FNO_4$ **(248)**. MK 886 [118414-82-7], $C_{26}H_{32}ClNO_2S$ **(249)** inhibits 5-LO by inhibiting its association with 5-LO activating protein (FLAP).



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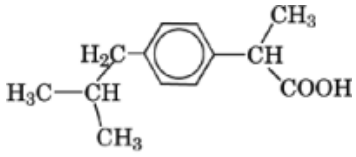

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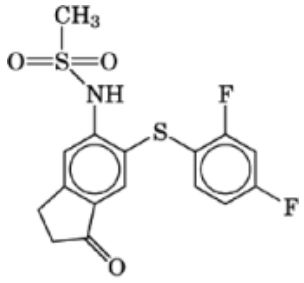

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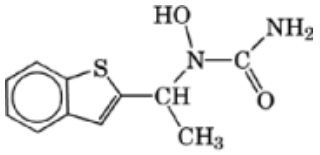

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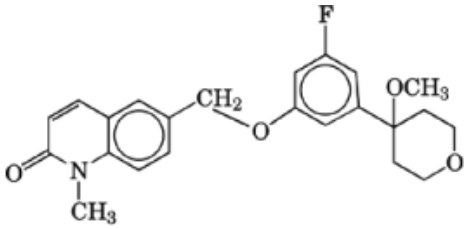

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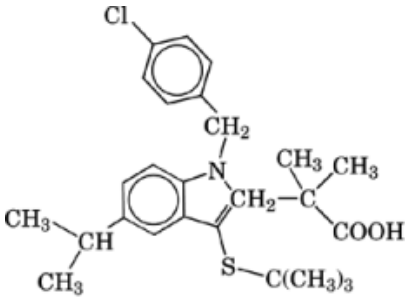


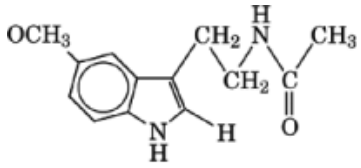
(**249**)

2.23. Melatonin

Melatonin (*N*-acetyl-5-methoxytryptamine) [73-31-4], $C_{13}H_{16}N_2O_2$**(250)** is secreted from the pineal gland and retina during dark periods of the vertebrate circadian rhythm (65). Melatonin regulates biological rhythms and neuroendocrine function and is formed from serotonin (5-HT).

Melatonin produces its effects via the GPCR, ML-1. A second lower affinity form, ML-2, has been described on the basis of binding data. Activation of melatonin receptors can inhibit DA release in the retina.

Melatonin, 2-iodomelatonin [93515-00-5], $C_{13}H_{15}IN_2O_2$ **(251)** and S 20098 [138112-76-2], $C_{15}H_{17}NO_2$**(252)** are ML-1 agonists. Luzindole [117946-91-5], $C_{19}H_{20}N_2O$ **(253)** is a melatonin antagonist. GR 135,531, $C_{14}H_{17}N_2O_3$ **(254)** is a selective ligand for the ML-2 receptor. In addition to a role in controlling circadian rhythms that may provide an approach to the treatment of the jet lag associated with air travel, melatonin may also be involved in the processes underlying migraine and cluster headaches.



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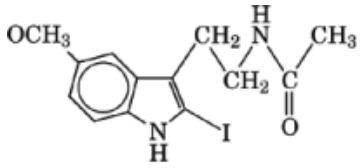

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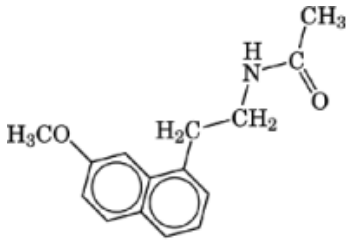

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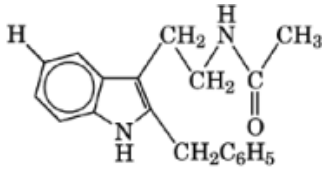

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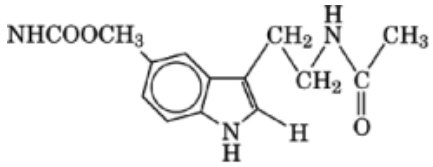


(254)

2.24. Neuropeptide Y

Neuropeptide Y [82785-45-3] (NPY) (255) is a 36-amino acid peptide that is a member of a peptide family including peptide YY (PYY) [81858-94-8, 106338-42-5] (256) and pancreatic polypeptide (PPY) [59763-91-6] (257). In the periphery, NPY is present in most sympathetic nerve fibers, particularly around blood vessels and also in noradrenergic perivascular and selected parasympathetic nerves (66). Neurons containing NPY-like immunoreactivity are abundant in the central nervous system, particularly in limbic structures. Coexistence

with somatostatin and NADPH-diaphorase, an enzyme associated with NO synthesis, is common in the cortex and striatum.

H–Tyr–Pro–Ser–Lys–Pro–Asp–Asn–Pro–Gly–Glu–Asp–Ala–Pro–Ala–Glu–Asp–Met–Ala–

Arg–Tyr–Tyr–Ser–Ala–Leu–Arg–His–Tyr–Ile–Asn–Leu–Ile–Thr–Arg–Gln–Arg–Tyr–NH_2

(255)

H–Tyr–Pro–Ile–Lys–Pro–Glu–Ala–Pro–Gly–Glu–Asp–Ala–Ser–Pro–Glu–Glu–Leu–Asn–

Arg–Tyr–Tyr–Ala–Ser–Leu–Arg–His–Tyr–Leu–Asn–LeuVal–Thr–Arg–Gln–Arg–Tyr–NH_2

(256)

H–Ala–Pro–Leu–Lys–Pro–Asp–Asn–Pro–Gly–Glu–Asp–Ala–Glu–Asp–Met–Ala–Arg–

Tyr–Tyr–Ser–Ala–Leu–Arg–His–Tyr–Ile–Asn–Leu–Ile–Thr–Arg–Gln–Arg–Tyr–NH_2

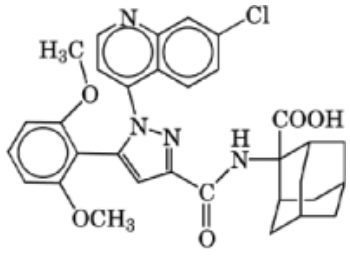
(257)

NPY exerts its physiological effects by three receptor subtypes, Y_1, Y_2, and Y_3. The Y_3 receptor recognizes NPY in preference to PPY and shows a rank order potency for agonists that is different from both Y_1 and Y_2 receptors. All three NPY receptor subtypes are GPCRs. The substituted analogues [Pro^{34}]NPY and [Leu^{31}]NPY are selective Y_1 agonists. NPY_{18--36} and NPY_{13--36} are Y_2 selective. No selective or potent NPY antagonists have been identified to date. In many cell types NPY raises intracellular calcium concentrations. Y_1 receptors are abundant on vasular smooth muscle cells where they mediate the vasoconstrictor effects of NPY. In rodent brain Y_1 receptors are localized primarily to discrete layers of the cerebral cortex, olfactory nucleus, and thalamic and hypothalamic nuclei where they are linked to NPY-induced stimulation of feeding behavior. Y_1 receptors appear to mediate the anxiolytic and sedative actions of NPY, although NPY is elevated in stress.

2.25. Neurotensin

Neurotensin [39379-15-2] (NT), *p*-Glu-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Try-Ile-Leu-OH, is a tridecapeptide that is cleaved from the ribosomally synthesized precursor, proneurotensin. NT is distributed through the peripheral and central nervous systems as well as in certain other cell types (3, 67). NT is colocalized with catecholamines in some neurons.

Although high and low affinity NT binding sites have been described, only one high affinity NT receptor has been clearly demonstrated. It has been cloned from rat and human brain and is a member of the GPCR family. There are few pharmacologic tools for NT systems, but the nonpeptide NT antagonist, SR 48692 [14632-70-1], $C_{32}H_{31}ClN_4O_5$**(258)** may help to delineate the physiological functions of NT.



(258)

NT has been implicated in neuroendocrine function, thermal and circadian regulation, cardiovascular and digestive system function, nociception, and in psychoses as a DA modulator.

2.26. Nerve Growth Factor and Neurotrophins

Nerve growth factor [9061-61-4] (NGF) is a member of a family of neurotrophic peptides that interact with cell surface recognition sites on neurons to affect growth and maintain viability (68). This class of receptor agonist can supress apoptosis and can act either acutely, being liberated as the result of tissue trauma, or chronically in terms of differentiation and development. Other neurotrophins include brain-derived neurotrophic factor (BDNF), and neurotrophin-3 (NT-3), NT-4, NT-5, and NT-6. Cilliary neurotrophic factor (CNTF) is a member of the cytokine family.

NGF interacts with two distinct receptors. A high affinity receptor (HNGFR) (K_d = 25 pM) also known as trkA or p140^{c-trk}, is the proto-oncogene product of the *trk* gene and contains a tyrosine kinase in its internal domain. p75 is a low affinity NGF receptor (LNGFR) (K_d = 1 nM) that is linked to G-protein activation. p140^{c-trk} is the main receptor for NGF (69). Other members of the NGF neurotrophin family also use *trk*A or *trk* homologues as their receptors indicating that tyrosine phosphorylation is the common transduction factor for neurotrophin receptor activation. The LNGFR is related to the TNF receptor, the lymphokine receptor, CD 40, and APO-1 (Fas antigen), a lymphocyte antigen involved in apoptosis.

The relationship between the two receptors for NGF is complex and not yet completely understood. It has been suggested that the functional form of the NGF receptor is a heterodimer of p75 and p140^{c-trk} proteins. BDNF and NT-3 bind to p75, but the functional receptors for these neurotrophins are the proto-oncogene products of *trk*B and *trk*C.

In addition to cell surface recognition sites, NGF can also interact with nuclear chromatin receptors. Receptors for CNTF include CNTF-α, leukemia inhibitor factor receptorβ (LIFRβ), and gp130. Little is known regarding pharmacological aspects of neurotrophin receptor activation or blockade. Levels of NGF can be increased by gene activation by a large number of conventional neurotransmitters including ACh. The involvement of neurotrophins in cell viability and apoptosis suggests that either the trophic factors themselves or agents that elicit production or mimic effects may be used in treating neurodegenerative diseases like Parkinson's or Alzheimer's disease, or be of use in reversing the effects of nerve trauma. Because NGF, BDNF, CNTF, and NT-3, NT-4, and NT-5 are peptidic in nature, usefulness as therapeutic agents is somewhat limited.

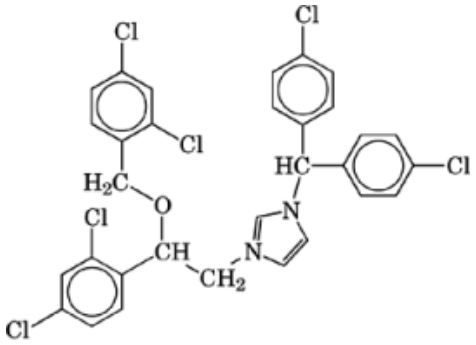
2.27. Nitric Oxide

Nitric oxide [10102-43-9], NO, is a ubiquitous intracellular and intercellular messenger serving a variety of functions including vasodilation, cytotoxicity, neurotransmission, and neuromodulation (9). NO is a paramagnetic diatomic molecule that readily diffuses through aqueous and lipid compartments. Its locus of action is dictated by its chemical reactivity and the local environment. NO represents the first identified member of a series of gaseous second messengers that also includes CO.

The half life for NO in cellular systems ranges from 5–30 seconds. Superoxide, hemoglobin, and other radical trapping agents remove NO after it has been formed.

Nitric oxide synthases (NOS) (EC 1.14.13.39) are both constitutive and inducible and produce NO from L-arginine (K_m = 1.5 − 2.8 μM) (9). The endothelial isoform eNOS (type III NOS) and the brain or neuronal isoform nNOS (type I NOS) are constitutive. A third isoform is the inducible NOS (iNOS or type II) found in macrophages, astrocytes, and microglia. All isoforms require calcium and calmodulin for activity. NADPH, FAD, FMN, and tetrahydrobiopterin (BH_4) are required co-factors. Agents that increase intracellular calcium activate constitutive NOSs. Calmodulin antagonists such as calmidazolium **(259)** and diphenylene iodonium **(260)**, an inhibitor of NADPH-dependent oxidase, inhibit NOS. NOS also contains a heme in the form of

protoporphyrin. Both iNOS and nNOS are cytosolic and exist as dimers, whereas eNOS is monomeric and membrane bound by myristolylation.



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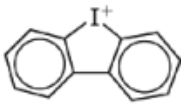


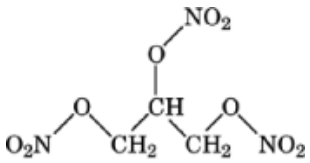
(260)

In the vascular system endothelial cells produce NO which diffuses into smooth muscle cells activating soluble guanylate cyclase (sGC) thus initiating vasodilation. Diffusion of NO into platelets inhibits aggregation. In neurons, NO has multiple transduction pathways including activation of sGC and stimulation of ADP ribosylation. NO is a retrograde messenger which has been implicated both in long-term depression (LTD) and long-term potentiation (LTP).

iNOS is induced in several cell types by cytokines and lipopolysaccharides. Macrophages utilize iNOS-produced NO as a cytotoxic agent. Reaction with iron-containing metabolic enzymes and oxygen and superoxide produces peroxynitrite (ONO_2^-), a potentially more cytotoxic agent. In the CNS microglia and astrocytes produce iNOS. This NO source has been implicated in a number of CNS pathologies. Only a limited number of CNS neurons contain nNOS.

NO synthons, including the vasodilators sodium nitroprusside (SNP) **(261)** and nitroglycerin **(262)**, have been in clinical use since the 1970s. Newer synthons include molsidomine **(263)** and the NONOates, prodrug dimers of NO.

(261)



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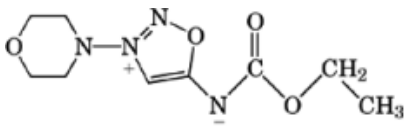
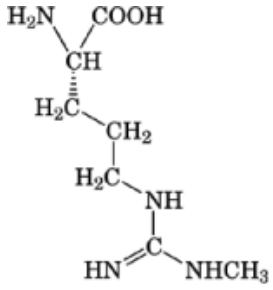


(**263**)

Most NOS inhibitors are structurally related to L-arginine and do not differentiate between the isoforms (Table 15). L-N^{γ}-Methylarginine (L-NMA) **(264)** is a competitive inhibitor and also irreversibly inhibits NOS. L-N^{γ}-Nitroarginine (L-NNA) **(265)**, L-N^{γ}-nitroarginine methyl ester (L-NAME) **(266)**, L-N^{γ}-cyclopropylarginine **(267)**, and L-N^{δ}-aminoarginine **(268)** are also arginine-like inhibitors. L-N^{δ}-Iminoethylornithine (L-NIO) **(269)** has been reported to be an irreversible inhibitor (Table 15).



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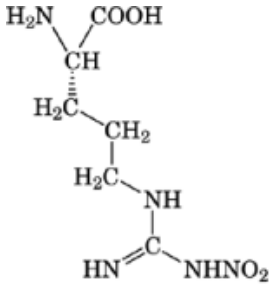

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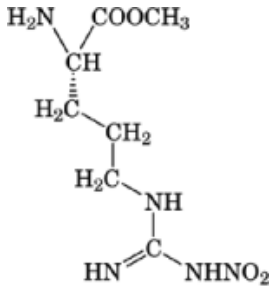

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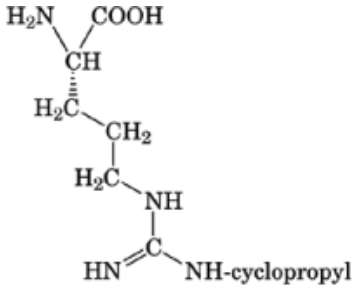

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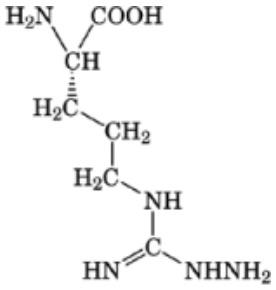

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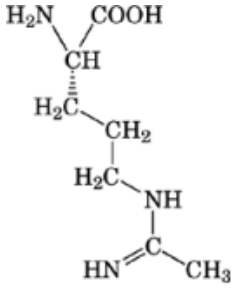


(**269**)

Therapeutic opportunities for NO synthons include angina, for which nitroglycerin is effectively used, as well as penile erectile dysfunction. NOS inhibitors have demonstrated some protection in cerebral ischemia

Table 15. Nitric Oxide Synthons and Inhibitors

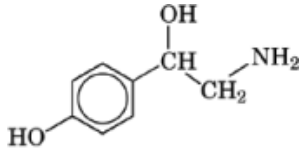
Material	CAS Registry Number	Molecular formula	Structure number
	Calmodulin antagonists		
calmidazolium	[95013-41-5]	$C_{31}H_{24}C_{16}N_{2O}$	**(259)**
diphenylene iodonium	[244-54-2]	$C_{12}H_8I$	**(260)**
	NO Synthons		
sodium nitroprusside	[14402-89-2]	$C_5FeN_6Na_2O$	**(261)**
nitroglycerin	[55-63-0]	$C_3H_5N_3O_9$	**(262)**
molsidomine	[25717-80-0]	$C_9H_{14}N_4O_4$	**(263)**
	NOS inhibitors		
L-N^{γ}-methylarginine	[17035-90-4]	$C_7H_{16}N_4O_2$	**(264)**
L-N^{γ}-nitroarginine	[2149-70-4]	$C_7H_{13}N_5O_4$	**(265)**
L-N^{γ}-nitroarginine methyl ester	[50903-99-6]	$C_8H_{15}N_5O_4$	**(266)**
L-N^{γ}-cyclopropylarginine		$C_9H_{18}N_4O_2$	**(267)**
L-N^{γ}-aminoarginine	[57444-72-1]	$C_6H_{15}N_5O_2$	**(268)**
L-N^{γ}-iminoethylornithine	[36889-13-1]	$C_7H_{15}N_3O_2$	**(269)**

models and may be potentially beneficial in alleviating cell death associated with cerebral ischemia. L-NMA is under clinical study for treatment of sepsis.

2.28. Octopamine

Octopamine [104-14-3] (OA), $C_8H_{11}NO_2$ **(270)** is a monoamine found in the insect CNS (70). It is involved in feeding behavior and in stimulating light production from the firefly light organ. The presence of octopamine in mammalian nervous tissue has yet to be determined.

Three classes of OA receptor, OA-1–OA-3, have been described on the basis of antagonist sensitivities and location (71). The OA-1 receptor is antagonized by the adrenoceptor antagonist, phentolamine **(87)** and the OA-2 receptor is blocked by mianserin [24219-97-4], $C_{18}H_{20}N_2$ **(271)**. The OA-3 receptor is similar to the OA-2 receptor but is found in nerve cord and insect brain. TMP, $C_{12}H_{16}N_2$ **(272)** and NC5Z, $C_{13}H_{17}N_5$ **(273)** are more potent than OA at the OA-1 receptor. Tyramine [51-67-2], $C_8H_{11}NO$ **(274)** is an agonist at all three receptor subtypes. The OA-2 receptor is linked to activation of adenylate cyclase.



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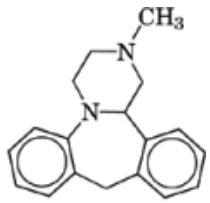

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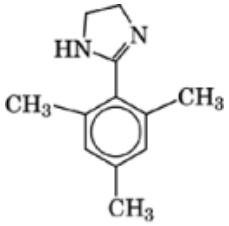

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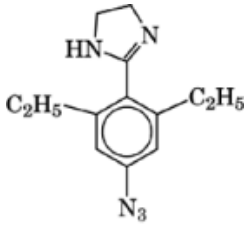

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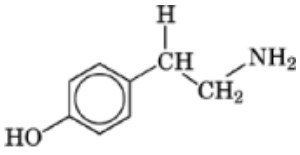
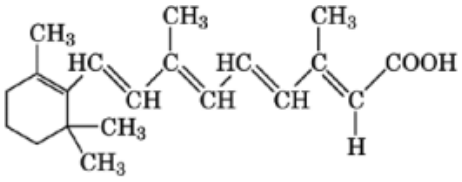


(274)

2.29. Retinoic Acid and Thyroid Hormone

The steroid hormones, vitamin D_3, the retinoic acids (RAs), *trans*-RA **(275)**, 13-*cis*-RA **(276)**, and 9-*cis*-RA **(277)**, and thyroid hormone (TH) alter cell function by acting as ligand-controlled transactivating factors or signal transducers and activators of transcription (STATs). They selectively interact with intracellular transcription factors to alter gene expression by interaction with hormone-responsive elements (HREs) on promotor regions of DNA (49, 72). RA plays a pivotal role in development and embryogenesis; however, excessive doses are teratogenic. RA induces differentiation in neuronal cells *in vitro* and is likely to play a role in neuronal differentiation *in vivo*.



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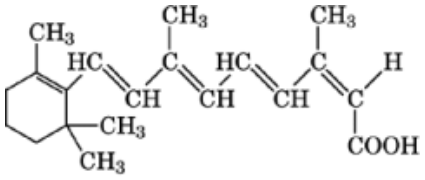

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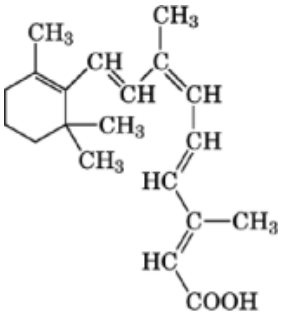


(277)

The steroid hormone receptor family includes Type I receptors that include estrogen, progesterone, and glucocorticoid receptor families. These bind to DNA at pallidromically arranged half-sites separated by three nucleotides and require ligand for initiation of DNA binding. The Type II (RAR) receptor group includes the RA, TH, vitamin D_3, and peroxisome proliferator activated receptor (PPAR) families (Table 16). RA receptors are subdivided into retinoic acid receptors (RARs) and retinoid X receptors (RXRs) based on differing affinities for 9-*cis* RA **(277)**. Type II receptors activate transcription through DNA binding of closely related sequences arranged as direct repeats. They bind to such sites in the absence of ligand and require heterodimer formation with RXR for high affinity binding.

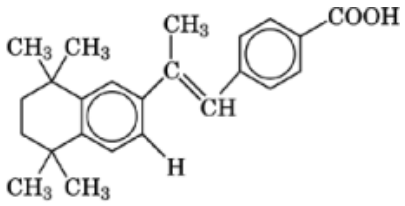
The RAR receptor family includes a variety of separate receptors, each having specific distribution and ligand binding specificities. Many of these receptors have been cloned. α, β, and γ forms of each subtype exist that may have several different isoforms differing in the 5′-untranslated region of the mRNA and/or the sequence encoding the A domain of the protein. Receptors have discrete domains for ligand binding, DNA binding, and transactivation. The presence of eight highly conserved Cys residues in the RAR receptor sequence has been correlated with the so-called zinc fingers necessary for DNA binding at HREs.

The primary endogenous ligand for RARs is *trans*-RA **(275)**. 9-*cis* RA is the endogenous ligand for RXRs. Ro13-7410 **(278)** and Ro 41-5253 **(279)** are selective for RAR subtypes over RXR. Ro 41-5253 is characterized as RAR_α selective. LGD 1069 **(280)** is RXR receptor selective. TTAB **(281)** is RAR_γ selective. The characterization of RA ligands as agonist or antagonist is not always clear because ligands can interact with RAR or RXR subtypes to form inactive heterodimers that compete with transcription activation pathways. RAR_α is ubiquitous,

Table 16. Retinoic Acids, Vitamin D_3, and Type II Receptor Agonists and Antagonists

Agonist/antagonist	CAS Registry Number	Molecular formula	Structure number
trans-retinoic acid	[302-79-4]	$C_{20}H_{28}O_2$	**(275)**
13-*cis*-retinoic acid	[4759-48-2]	$C_{20}H_{28}O_2$	**(276)**
9-*cis*-retinoic acid	[5300-03-8]	$C_{20}H_{28}O_2$	**(277)**
Ro 13-7410	[71441-28-6]	$C_{24}H_{28}O_2$	**(278)**
Ro 41-5253	[144092-31-9]	$C_{28}H_{36}O_5S$	**(279)**
LGD 1069			**(280)**
TTAB	[107430-51-3]	$C_{25}H_{26}O_2$	**(281)**
Ro 10-9359	[54350-48-0]		**(282)**
1,25-dihydroxyvitamin D_3	[35211-63-0, 32222-06-3]	$C_{28}H_{46}O$	**(283)**
thyroxine	[51-48-9]	$C_{15}H_{11}I_4NO_4$	**(284)**
triiodothyronine	[6893-02-3]	$C_{15}H_{12}I_3NO_4$	**(285)**
TRIAC	[51-24-1]	$C_{14}H_9I_3O_4$	**(286)**

RAR_γ is predominant in the skin and lungs, and RAR_β is expressed in the heart, lungs, and spleen (73). The antimalignant effects of retinoids are well documented. In addition, retinoids such as *trans*-RA, 13-*cis*-RA, and Ro 10-9359 **(282)** are used in the treatment of acne and psoriasis.



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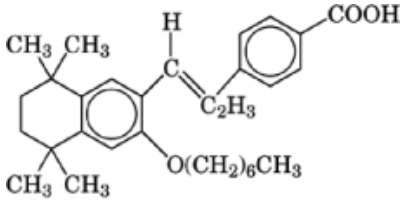

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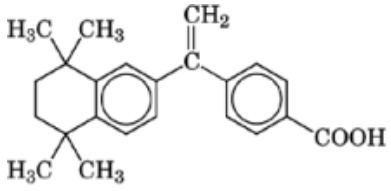

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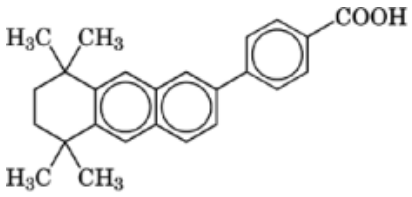

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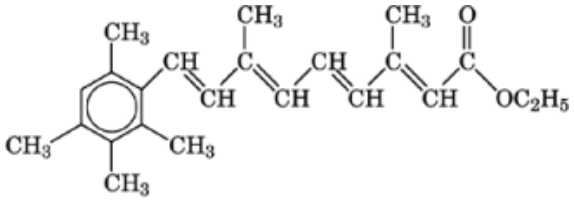
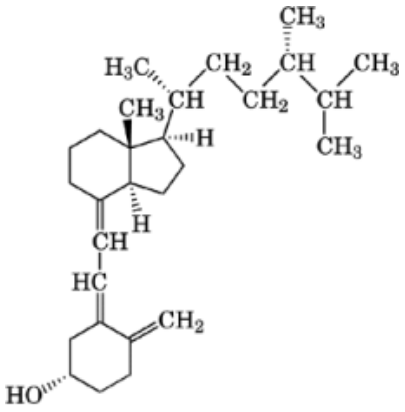


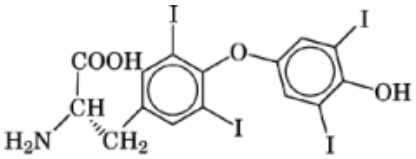
(**282**)

1,25-Dihydroxyvitamin D_3 **(283)** is the endogenous ligand for the vitamin D_3 receptor (VDR). It modulates genomic function in a tissue and developmentally specific manner and affects cell proliferation, differentiation, and mineral homeostasis (74). Vitamin D_3 mobilizes calcium from the bone to maintain plasma Ca^{2+} levels. Vitamin D_3 and VDR are present in the CNS where they may play a role in regulating Ca^{2+} homeostasis. Vitamin D_3 has potent immunomodulatory activity *in vivo*.



(**283**)

Thyroid hormone receptors (THRs) are subdivided intoα and β types, each having two isoforms. In rat brain, THR_α mRNA is present in hippocampus, hypothalmus, cortex, cerebellum, and amygdala. Thyroxine (L-T_4) **(284)** and triiodothyronine (L-T_3) **(285)** are endogenous ligands for the THRs. TRIAC **(286)** is a THR antagonist. Selective ligands for PPARs have yet to be identified (Table 16).



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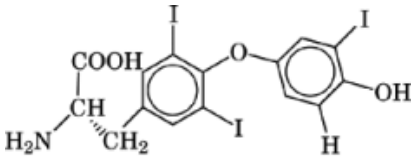

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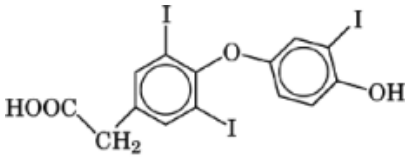
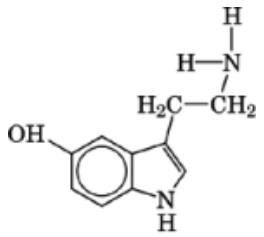


(286)

2.30. Serotonin

Serotonin [50-67-9] (5-HT), $C_{10}H_{12}N_2O$ **(287)** is a hydroxyethylaminoindole with widespread distribution. 5-HT is synthesized from L-tryptophan by hydroxylation to 5-hydroxy-L-tryptophan by the enzyme, tryptophan-5-hydroxylase. 5-Hydroxy-L-tryptophan is then rapidly decarboxylated by aromatic-L-amino acid deacarboxylase to 5-HT. The actions of 5-HT as a neurotransmitter are terminated by neuronal reuptake and metabolism.



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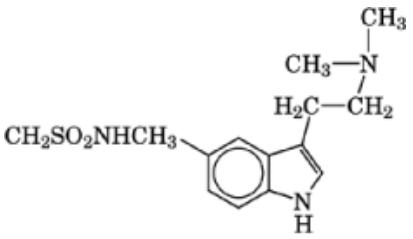

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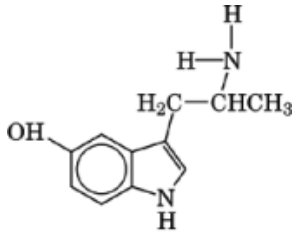
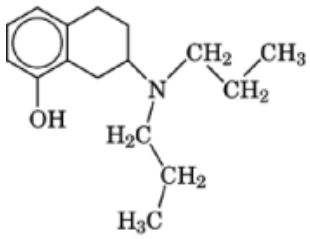


(**295**)

5-HT produces its effects by a diversity of receptor subtypes (75) that are divided into seven pharmacologically distinct classes designated 5-HT_1–5-HT_7. The 5-HT_1, 5-HT_2, and 5-HT_5 subclasses can be further subdivided into five, three, and two subtypes, respectively, based on pharmacological and cloning criteria. With the exception of the 5-HT_3 receptor, which is an LGIC, all members of the 5-HT receptor superfamily are GPCRs. The 5-HT_{1A} receptor was identified using the selective agonist 8-OH-DPAT **(288)**. WAY 100135 **(289)** is a 5-HT_{1A} receptor antagonist, CP 93129 **(290)** is a selective 5-HT_{1B} agonist, CGS 12066B **(291)** is a selective 5-HT_{1B} receptor antagonist, sumatriptan **(292)** is a 5-HT_{1D} agonist, and GR 127935 **(293)** is a selective 5-HT_{1D} antagonist (Table 17).



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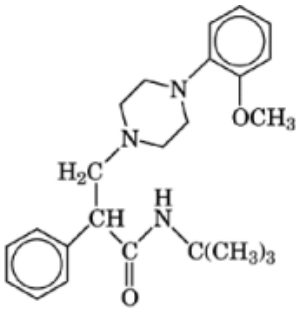
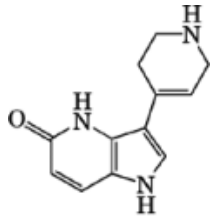


(**289**)

Table 17. Serotonin and Serotonin Receptor Agonists and Antagonists

Agonist/antagonist	CAS Registry Number	Molecular formula	Structure number
8-OH-DPAT	[78950-78-4]	$C_{16}H_{25}NO$	**(288)**
WAY 100135	[133025-23-7]	$C_{24}H_{33}N_3O_2$	**(289)**
CP 93129	[127792-75-0]	$C_{12}H_{13}N_3O$	**(290)**
CGS 12066B	[109028-10-0]	$C_{17}H_{17}F_3N_4$	**(291)**
sumatriptan	[103628-46-2]	$C_{14}H_{21}N_3O_2S$	**(292)**
GR 127935		$C_{29}H_{31}N_5O_3$	**(293)**
DOI	[82830-53-3]	$C_{11}H_{16}INO_2$	**(294)**
α-methyl-5-HT	[304-52-9]	$C_{11}H_{14}N_2O$	**(295)**
ketanserin	[74050-98-9]	$C_{22}H_{23}N_3O_3$	**(296)**
ritanserin	[87051-43-2]	$C_{27}H_{25}F_2N_3OS$	**(297)**
SB 200646	[143797-62-0]	$C_{15}H_{14}N_4O$	**(298)**
2-methyl-5-hydroxytryptamine	[78263-90-8]	$C_{11}H_{14}N_2O$	**(299)**
m-chlorophenylbiguanide	[48144-44-1]	$C_8H_{10}ClN_5$	**(300)**
ondansetron	[99614-02-5]	$C_{18}H_{19}N_3O$	**(301)**
BIMU 8	[134296-40-5]	$C_{19}H_{26}N_4O_2$	**(302)**
SB 204070A	[148688-01-1]	$C_{19}H_{27}ClN_2O_4$	**(303)**
GR 113808	[144625-51-4]	$C_{19}H_{27}N_3O_4S$	**(304)**
LSD	[50-37-3]	$C_{20}H_{25}N_3O$	**(305)**



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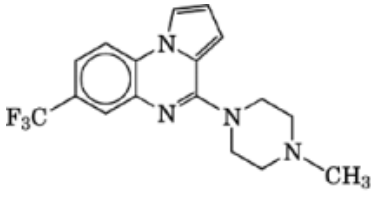

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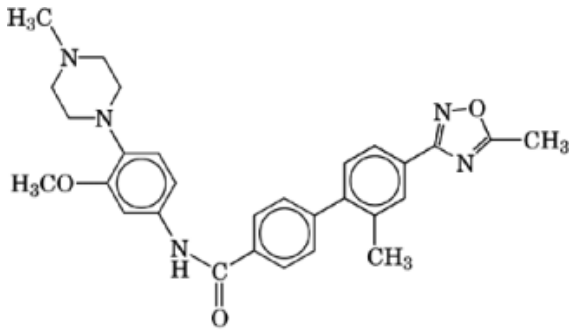
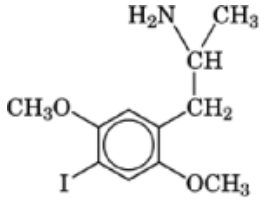


(293)

DOI **(294)** and α-methyl-5-HT **(295)** are selective 5-HT_2 receptor agonists. Ketanserin **(296)** and ritanserin **(297)** are potent and selective 5-HT_{2A} antagonists. SB 200646 **(298)** is an antagonist which has greater selectivity toward 5-HT_{2B} and 5-HT_{2C} receptors compared to the 5-HT_{2A} subtype. 2-Methyl-5- hydroxytryptamine **(299)** and *m*-chlorophenylbiguanide **(300)** are 5-HT_3 agonists. Ondansetron **(301)** is a selective 5-HT_3 antagonist. BIMU 8 **(302)** is a potent 5-HT_4 agonist, although the most selective antagonists at this subtype are SB 204070 **(303)** and GR 113808 **(304)**. Selective pharmacological probes for the 5-HT_5, 5-HT_6, and 5-HT_7 subtypes have yet to be identified. LSD **(305)** is active at the 5-HT_6 receptor.



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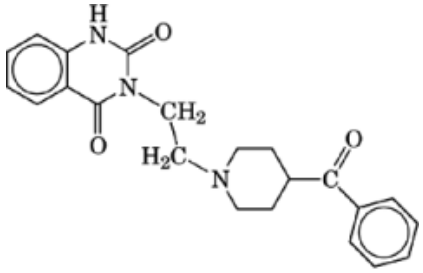

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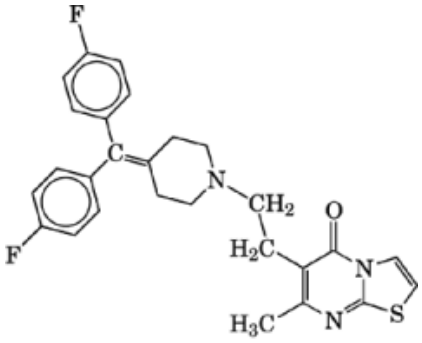

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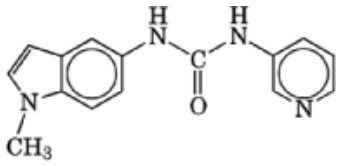

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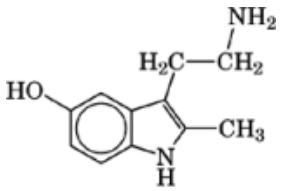

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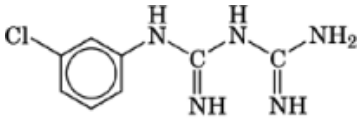

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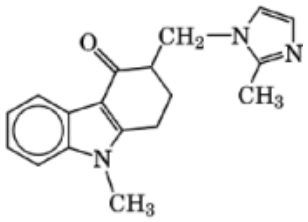

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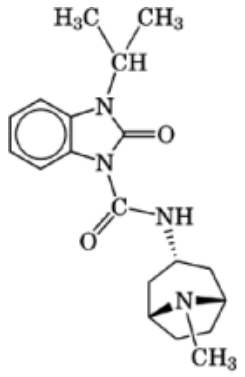

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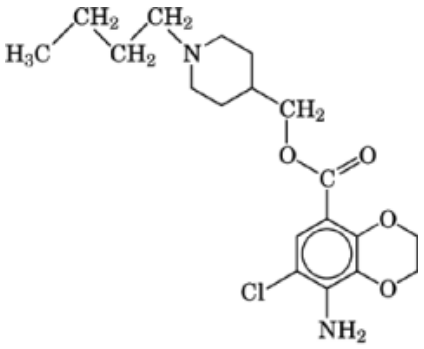

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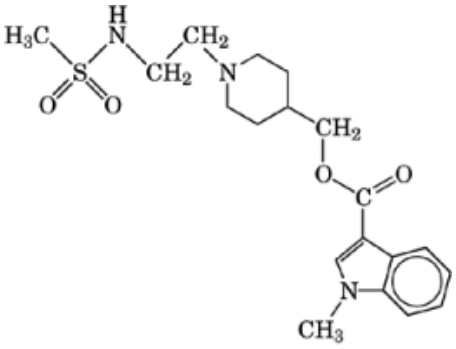

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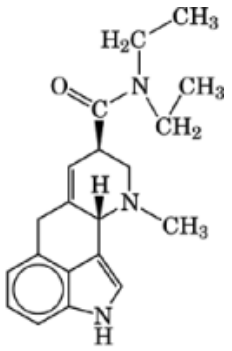
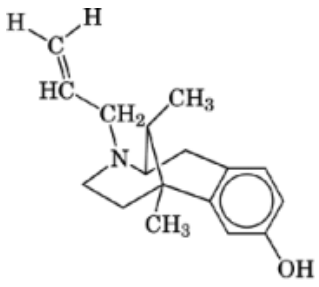


(305)

Serotonin is a key transmitter in CNS function. Altered serotonergic function has been implicated in many CNS disorders including depression, feeding behavior, sleep disorders, schizophrenia, and Alzheimer's disease.

2.31. Sigma Receptor Ligands

Sigma (σ-) receptors (76) were originally defined on the basis of the psychotomimetic effects of the benzomorphan opioid, SKF 10047 **(306)**. Although σ-receptors were initially designated as opiate receptors, the binding of SKF 10047 to phencyclidine (PCP) **(185)** receptors suggested that σ and PCP receptors might be the same. The neuroleptic, haloperidol **(126)** also binds to σ-receptors. (+)-Pentazocine **(307)** distinguishes between σ_1 and σ_2 sites. (+)-Pentazocine and BD 737 **(310)** have higher affinity for σ_1 sites (Table 18). The dopamine autoreceptor agonist, (+)-3-PPP (1-propyl-3-(3′-hydroxyphenyl)-piperidine) **(308)** labels two σ-sites with K_d values of 25 and 900 nM. A σ_3 receptor has also been described (77). The antitussive dextromethorphan **(309)**, a ligand for the NMDA receptor complex, labels two sites termed DM_1 and DM_2, with the higher affinity DM_1 site corresponding to a σ-site.



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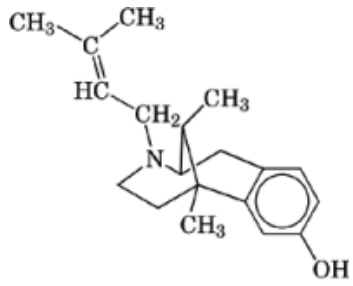

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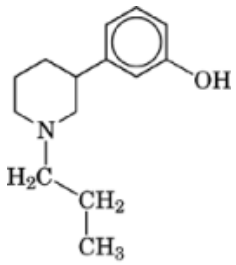

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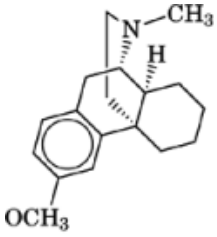

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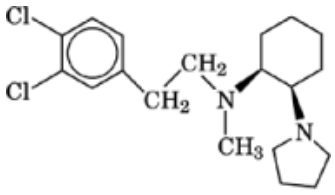
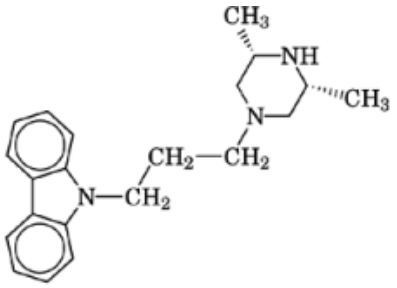


(**310**)

In addition to haloperidol, the putative neuroleptics, rimcazole **(311)**, remoxipride **(312)**, and gevotroline **(313)** bind to σ-receptors as does the dopamine uptake blocker, GBR 12909 **(314)** and two ligands active at the NMDA receptor, ifenprodil **(315)** and CNS 1102 **(316)**. NPC 16377, **(317)** is a selective σ-receptor ligand. MAO inhibitors and antidepressants also bind to σ-receptors. Some evidence indicates that σ-receptors in the brain are in fact a form of cytochrome P_{450} which may account for the diversity of ligands interacting with σ-sites.

Table 18. Sigma-Receptor Ligands

Ligand	CAS Registry Number	Molecular formula	Structure number
SKF 10047	[14198-28-8]	$C_{17}H_{23}NO$	**(306)**
(+)-pentazocine	[7361-76-4]	$C_{19}H_{27}NO$	**(307)**
(+)-1-propyl-3-(3′-hydroxy-phenyl) piperidine	[75240-91-4]	$C_{14}H_{21}NO$	**(308)**
dextromethorphan	[125-71-3]	$C_{18}H_{25}NO$	**(309)**
BD 737	[130609-93-7]	$C_{19}H_{28}C_{12}N_2$	**(310)**
rimcazole	[75859-04-0]	$C_{21}H_{27}N_3$	**(311)**
remoxipride	[80125-14-0]	$C_{16}H_{23}BrN_2O_3$	**(312)**
gevotroline	[107266-06-8]	$C_{19}H_{20}FN_3$	**(313)**
GBR 12909	[67469-78-7]	$C_{28}H_{32}F_2N_2O$	**(314)**
ifenprodil	[23210-56-2]	$C_{21}H_{27}NO$	**(315)**
CNS 1102	[137160-11-3]	$C_{20}H_{21}N_3$	**(316)**
NPC 16377		$C_{27}H_{33}NO_4$	**(317)**



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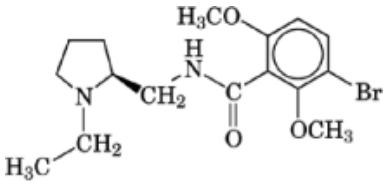

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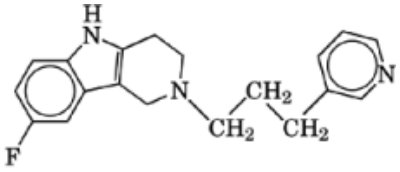

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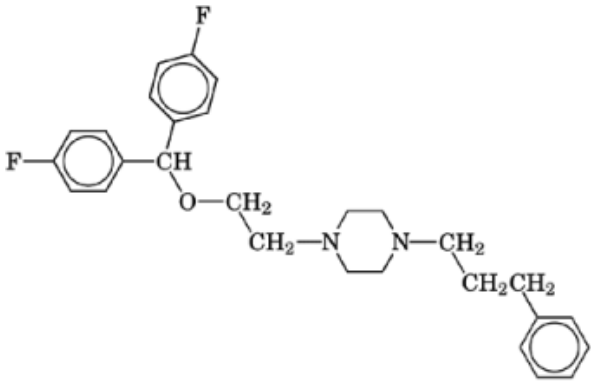

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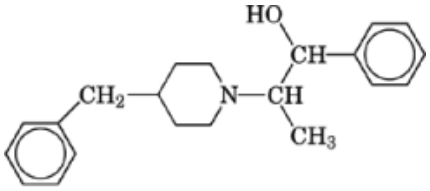

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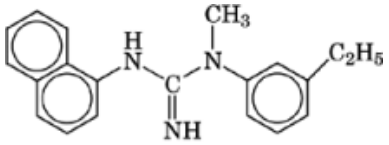

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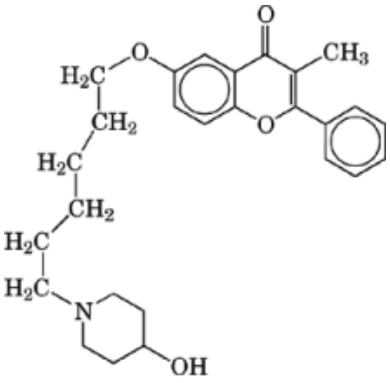


(317)

σ-Receptors are localized in the brain stem and limbic structure, regions associated with endocrine function (76). In the periphery, σ-receptors are found in the liver, heart, ileum, vas deferens, and on lymphocytes and thymocytes. Although there is insufficient evidence to clearly define the functional role of CNS σ-sites, based

on the effects of PCP and the interaction of haloperidol with σ-sites, σ-receptor ligands may be antipsychotics or used for the treatment of substance abuse. Several σ-receptor ligands have shown neuroprotective effects *in vivo*. Ifenprodil **(315)** and CNS 1102 **(316)** are being developed for treatment of stroke (Table 18).

2.32. Steroid Hormones and Neurosteroids

Steroids (qv) can affect neuroendocrine function, stress responses, and behavioral sexual dimorphism (78, 79) (see Steroids). Mineralocorticoid, glucocorticoid, androgen, estrogen, and progesterone receptors are localized in the brain and spinal cord. In addition to genomic actions, the neurosteroid can act more acutely to modulate the actions of other receptors or ion channels (80). Pregnenolone [145-13-1], $C_{21}H_{32}O_2$ 5 and dehydroepiandosterone [53-43-0], $C_{19}H_{26}O_2$ 5 are excitatory neurosteroids found in rat brain, independent of adrenal and gonadal sources, and show circadian fluctations in their CNS levels. Glia are a primary source of neurosteroids that inhibit the function of $GABA_A$ and glycine receptors at micromolar concentrations. CNS active steroids are also known to have anesthetic and sedative actions. Pregnenolone and dehydroepiandosterone have been reported to have memory-enhancing actions in male mice (see Memory-enhancing drugs).

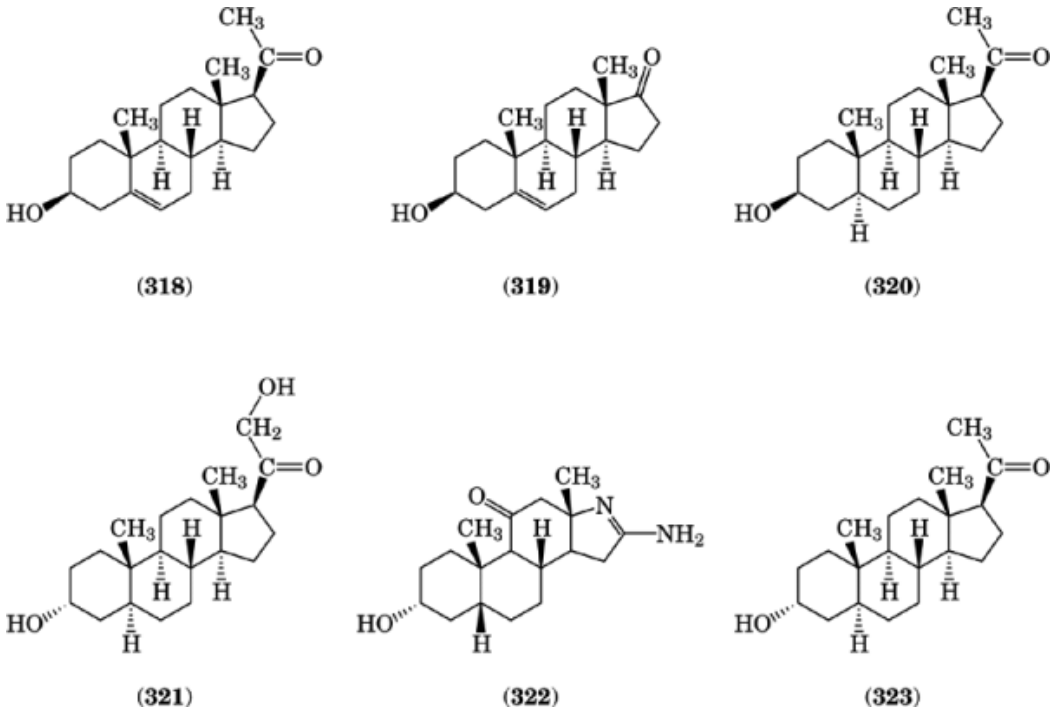
Allopregnanolone [516-55-2], $C_{21}H_{34}O_2$ 5 and allotetrahydro-DOC, $C_{21}H_{34}O_3$ 5, metabolites of the steroids progesterone and deoxycorticosterone, augment $GABA_A$ receptor activation at low (10–50 nM) nanomolar concentrations and have anxiolytic- and antiepileptic-like activities as well as producing barbiturate-like effects. RU 5135 [78774-26-2], $C_{18}H_{28}N_2O_2$ 5, which lacks steroid activity, is a potent inhibitor of GABA and glycine receptor function. The epalons, a novel series of neurosteroids based on epiallopregnanolone [516-54-1], $C_{21}H_{34}O_2$ 5, are being developed as novel anticonvulsants, anxiolytics, and hypnotics (see Hypnotics, sedatives, anticonvulsants, and anxiolytics) (Fig. 5).

2.33. Somatostatin

Somatostatin (SRIF or SS) is a cyclic peptide existing primarily in 14 and 28 amino acid forms $SRIF_{1--14}$ [38916-34-6], $C_{76}H_{104}N_{18}O_{19}S$ **(324)** and $SRIF_{1--28}$ [75037-27-3] **(325)**, respectively. SRIF was originally isolated from the hypothalmus and shown to regulate growth hormone (GH) secretion from the anterior pituitary (3). SRIF is present throughout the CNS where it modulates neuronal firing (81). It is also present in pancreas and gut where it regulates endocrine and exocrine secretions, particularly insulin and glucagon release.

SRIF produces its effects through two classes of GPCR, SRIF-1 and SRIF-2 that are structurally related to cloned opiate receptors. The agonists, seglitide [81377-02-8] (MK 678), cyclo((*N*-CH_3)Ala-Tyr-D-Trp-Lys-Val-Phe), and ocreotide [83150-76-9] (SMS 201-995), D-Phe-cyclo[Cys-Phe-D-Trp-Lys-Thr-Cys]-Thr-ol, are used to distinguish between the two SRIF receptor classes. These can be subdivided into three and two subtypes, respectively, based on pharmacology and cloning data. Originally termed $SRIF_{1A}$, $SRIF_{1B}$, $SRIF_{1C}$, $SRIF_{2A}$, and $SRIF_{2B}$, they have been renamed $SSTR_{1--5}$. Activation of SSTR receptors results in adenylate cyclase inhibition, modulation of K^+ and Ca^{2+} channel conductance, and regulation of tyrosine phosphatases and the Na^+–H^+ antiporter through pertussis toxin-insensitive mechanisms. High levels of mRNA for $SSTR_1$, $SSTR_3$, and $SSTR_5$ are found in the CNS; these levels tie $SSTR_1$ to the inhibition of GH secretion. $SSTR_1$, $SSTR_3$, and $SSTR_4$ are present in the pancreas and gut. The endogenous ligands for SSTR receptors are $SRIF_{1--14}$ (SS_{1--14}) and $SRIF_{1--28}$ (SS_{1--28}). SS_{1--28} generally has greater affinity than SS_{1--14} for SSTR receptors. There are no known nonpeptide ligands for SSTR receptors.

Seglitide readily distinguishes $SSTR_1$ with picomolar affinity. This compound has nanomolar affinity for $SSTR_2$ and is much weaker at the other subtypes. Ocreotide binds to $SSTR_1$, $SSTR_2$ and $SSTR_5$ receptor types. BIM 23052 [133073-82-2] D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH_2, and BIM 23056 [150155-61-6], **(326)** differentiate the $SSTR_1$ and $SSTR_2$ subtypes. NC4 28B [150155-58-1] **(327)** and CGP 23996 [86170-12-9] *c*(Lys-Asn-Phe-Phe-Trp-Lys-Thr-Tyr-Thr-Ser-Asn), $C_{73}H_{99}N_{15}O_{18}$, are $SSTR_1$ agonists. L 362855



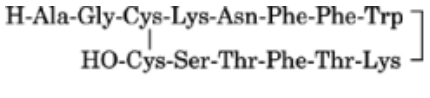
(318) (319) (320)

(321) (322) (323)

Fig. 5. Structures of neurosteroids.

[81710-71-6] *c*(Ala-Phe-Trp-D-Trp-Lys-Thr-Phe), is a selective agonist for the $SSTR_4$ receptor. There are no known antagonists for any of the SSTR receptor classes.

SRIF acts as an excitatory neuromodulator in the CNS inhibiting the release of TRH, corticotropin-releasing hormone (CRH), growth hormone releasing factor (GHRH), and NE. It produces general arousal and hypotension. It inhibits the release of a number of peptides and modulators in the GI tract.



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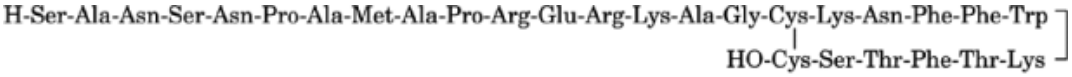

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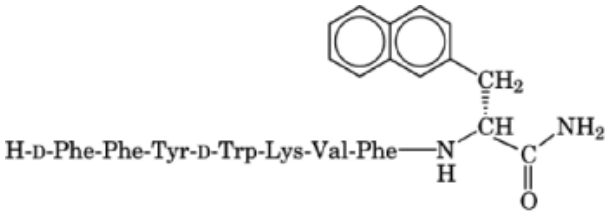

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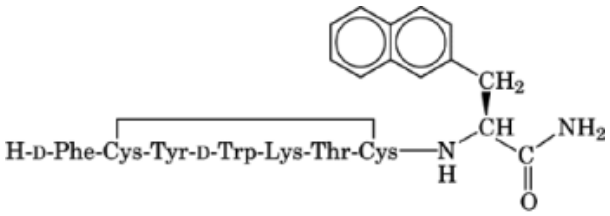


(327)

2.34. Tachykinins and Substance P

The tachykinins (82) include the undecapeptide, substance P, H-Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2, and the decapeptides, neurokinin A (NKA; also known as substance K, neuromedin L), H-His-Lys-Thr-Asp-Ser-Phe-Val-Gly-Leu-Met-NH_2, and neurokinin B (NKB, also known as neuromedin K), H-Asp-Met-His-Asp-Phe-Phe-Val-Gly-Leu-Met-NH_2. Physalaemin, eledoisin, kassinin, SCYI, and SCYII are nonmammalian tachykinins. Two larger peptides have been identified, neuropeptide K (328) and neuropeptide γ (329), both of which interact with tachykinin receptors (Table 19). The NKA sequence is contained within the carboxy-terminal sequences of both neuropeptide K and neuropeptide γ. Like other neuroactive peptides, tachykinin peptide precursors are synthesized ribosomally and transported to nerve terminals where further processing occurs.

Asp–Ala–Asp–Ser–Ser–Glu–Lys–Gln–Val–Ala–Leu–Leu–Lys–Ala–Leu–Tyr–Gly–His–

Gly–Gln–Ile–Ser–His–Lys–Arg–His–Lys–Thr–Asp–Ser–Phe–Val–Gly–Leu–Met–NH_2

(328)

Asp–Ala–Gly–His–Gly–Gln–Ile–Ser–His–Lys–Arg–His–Lys–Thr–Asp–Ser–Phe–Val–

Gly–Leu–Met–NH_2

(329)

As a neurotransmitter in the sensory nervous system, high levels of substance P are found in the dorsal horn of the spinal cord as well as in peripheral sensory nerve terminals. However, substance P also plays a significant role as a neuromodulator in the central, sympathetic, and enteric nervous system. NKA and NKB are also localized selectively in the CNS.

Neurokinin effects are terminated by proteolysis. *In vitro*, acetylcholinesterase (ACE) and enkephalinase can hydrolyze substance P. However, there appears to be no clear evidence that either acetylcholinesterase or ACE limit the actions of released substance P. Enkephalinase inhibitors, eg, thiorphan, can augment substance

Table 19. Tachykinins and Receptor Agonists and Antagonists

Agonist/antagonist	CAS Registry Number	Molecular formula	Structure number
	Tachykinins		
substance P	[33507-63-0]		
neurokinin A	[86933-74-6]		
neurokinin B	[102577-23-1]		
neuropeptide K	[106441-70-7]		(328)
neuropeptide γ	[123515-59-3]		(329)
	NK_1 receptor		
SP methyl ester	[76260-78-1]	$C_{64}H_{99}N_{17}O_{14}S$	
[Sar^9, Met$(O_2)^{11}$] SP[a]			
[Pro^9] SP			
L 668,169	[137012-28-3]	$C_{82}H_{108}N_{16}O_{14}S_2$	**(330)**
CP 99994	[136982-36-0]	$C_{19}H_{24}N_2O$	**(331)**
WIN 51708	[138091-24-4]	$C_{29}H_{33}N_3O$	**(332)**
SR 140333	[153050-21-6]	$C_{37}H_{45}Cl_2N_2O_2$	**(333)**
RP 67580	[135911-02-3]	$C_{29}H_{30}N_2O_2$	**(334)**
GR 82334	[129623-01-4]	$C_{69}H_{91}N_{15}O_{16}$	**(335)**
	NK_2 receptor		
[β-Ala^8] NKA$_{4--10}$			
GR 64349	[137593-52-3]	$C_{42}H_{68}N_{10}O_{11}S$	**(336)**
[Lys^5, (N-CH$_3$)Leu^9, Nle^{10}] NKA$_{4--10}$[b]			
SR 48968	[142001-63-6]	$C_{31}H_{35}Cl_2N_3O_2$	**(337)**
MEN 10376	[135306-85-3]	$C_{57}H_{68}N_{12}O_{10}$	
	NK_3 receptor		
senktide	[106128-89-6]	$C_{40}H_{55}N_7O_{11}S$	**(338)**
[CH$_3$Phe^7] NKB			
[Pro^7] NKB			

[a] Sar = sarcasine, Met(O_2) = $\begin{matrix}\mathrm{CHCH_2CH_2SO_2CH_3}\\ |\\ \mathrm{NH_2COOH}\end{matrix}$

[b] Nle = norleucine, $_{4--10}$

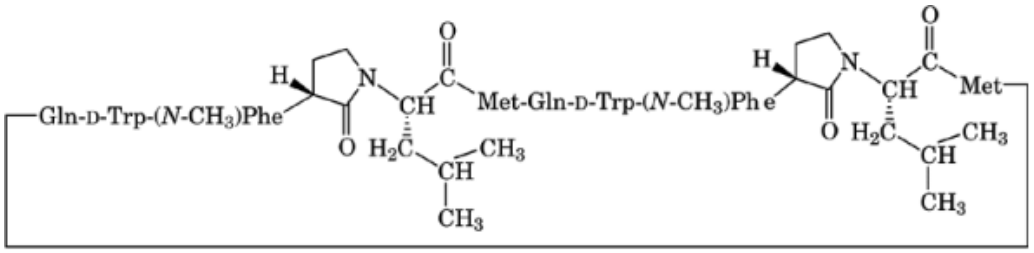
P release or action in some systems but the distribution of enkephalinase in the brain does not precisely mirror that of substance P. There appears to be a substance P-selective enzyme in brain and spinal cord.

Capsaicin, an active ingredient in red pepper, is well known for its ability to release and deplete substance P in sensory C fibers. However, this action is not specific for substance P, as neurokinin A, calcitonin gene-related peptide (CGRP), and somatostatin also are released.

Three tachykinin GPCRs, NK_1, NK_2, and NK_3, have been identified and cloned. All are coupled to phosphatidylinositol hydrolysis. The NK_1 receptor is selective for substance P (SP) and is relatively abundant in the brain, spinal cord, and peripheral tissues. The NK_2 receptor is selective for NKA and is present in the gastrointestinal tract, urinary bladder, and adrenal gland but is low or absent in the CNS. The NK_3 receptor is selective for NKB and is present in low amounts in the gastrointestinal tract and urinary bladder, but is abundant in some areas of the CNS, ie, the spinal dorsal horn, solitary nucleus, and laminae IV and V of the cortex with moderate amounts in the interpeduncular nucleus. Mismatches in the distribution of the tachykinins and tachykinin receptors suggest the possibility of additional tachykinin receptor subtypes.

At the NK_1 receptor, SP, SP methyl ester, Sar^9, Met$(O_2)^{11}$ SP, and [Pro^9]SP are agonists. L 668,169 **(330)** is a peptide NK_1 antagonist. CP 99994 **(331)**, WIN 51708 **(332)**, SR 140333 **(333)**, RP 67580 **(334)**, and GR 82334 **(335)** are nonpeptide antagonists. At the NK_2 receptor, NKA, [β-Ala^8] NKA$_{4--10}$, GR 64349 **(336)**, and [Lys^5, (NMe)Leu^9, Nle^{10}]NKA$_{4--10}$ are selective agonists. SR 48968 **(337)** and the peptide MEN 10376,

H-Asp-Tyr-D-Trp-Val-D-Trp-D-Trp-Lys-NH_2, are selective antagonists. NKB, senktide **(338)**, [MePhe^7]NKB and [Pro^7]NKB are agonists at the NK_3 receptor. There are no selective antagonists for this receptor subtype. The neurotransmitter actions of tachykinins are generally excitatory. The vasodilation caused by substance P results from the stimulation NO synthesis in the endothelium (Table 19).



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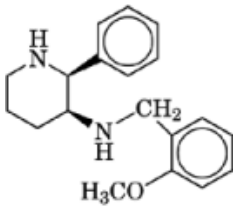

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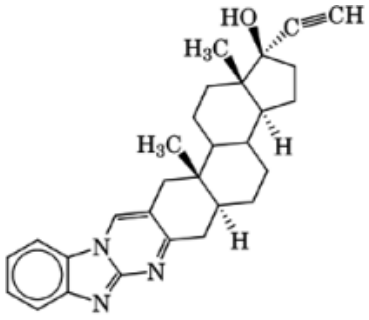

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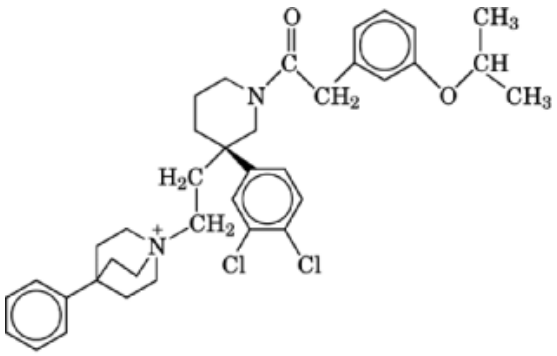

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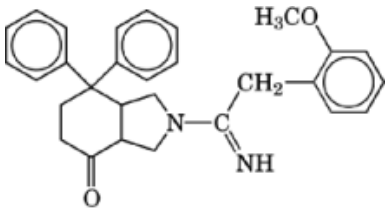

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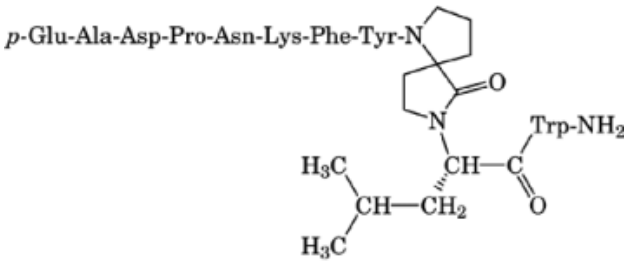

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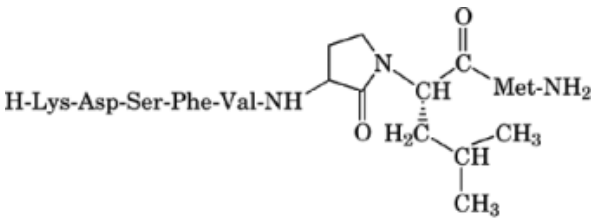

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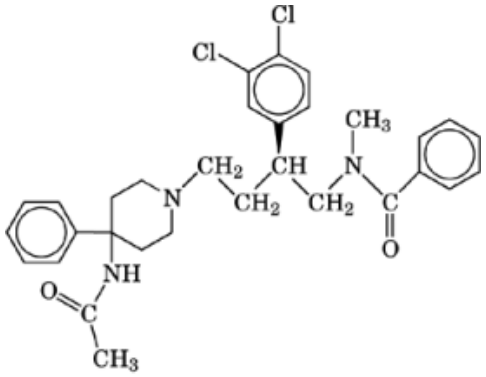

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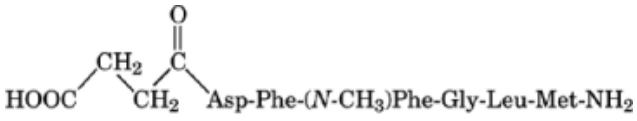


(338)

2.35. Vasoactive Intestinal Peptide and Pituitary Adenylate Cyclase Activating Peptide

Vasoactive intestinal peptide (VIP) [37221-79-7] (339), a 28-amino acid peptide, is a member of a family of structurally related peptides that includes secretin [1393-25-5], (340), growth hormone releasing factor (GRF), and pituitary adenylate cyclase-activating peptide (PACAP) [137061-48-4] (341) (83).

H–His–Ser–Asp–Ala–Val–Phe–Thr–Asp–Asn–Tyr–Thr–Arg–Leu–Arg–Lys–

Gln–Met–Ala–Val–Lys–Lys–Tyr–Leu–Asn–Ser–Ile–Leu–Asn–NH_2

(339)

H–His–Ser–Asp–Gly–Thr–Phe–Thr–Phe–Thr–Ser–Glu–Leu–Ser–Arg–Leu–

Arg–Asp–Ser–Ala–Arg–Leu–Gln–Arg–Leu–Leu–Gln–Gly–Leu–Val–NH_2

(340)

H–His–Ser–Asp–Gly–Ile–Phe–Thr–Asp–Ser–Tyr–Ser–Arg–Tyr–Arg–Lys–Gln–Met–Ala–Val–

Lys–Lys–Tyr–Leu–Ala–Ala–Val–Leu–Gly–Lys–Arg–Tyr–Lys–Gln–Arg–Val–Lys–Asn–Lys–NH_2

(341)

The effects of VIP and PACAP are mediated by three GPCR subtypes, VIP_1, VIP_2, and PACAP receptor, coupled to the activation of adenylate cyclase (54). The VIP_1 subtype is localized in the lung, liver, and intestine, and the cortex, hippocampus, and olfactory bulb in the CNS. The VIP_2 receptor is most abundant in the CNS, in particular in the thalamus, hippocampus, hypothalamus, and suprachiasmatic nucleus. PACAP receptors have a wide distribution in the CNS with highest levels in the olfactory bulb, the dentate gyrus, and the cerebellum (84). The receptor is also present in the pituitary. The VIP_1 and PACAP receptors have been cloned.

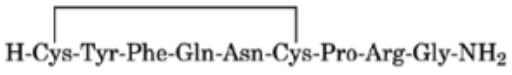
There are few pharmacological tools to distinguish between the three receptors. Secretin has significant biological activity at VIP_1 receptors but is inactive at VIP_2 receptors, whereas VIP and PACAP have equivalent

affinities for both the VIP_1 and VIP_2 receptors. PACAP displays marked selectivity for the PACAP receptor. $PACAP_{6--27}$ is the most potent and selective antagonist of the PACAP receptor identified as of this writing.

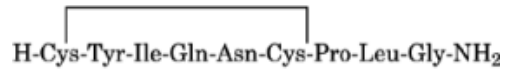
VIP and PACAP are found throughout the CNS and in the gastrointestinal, genitourinary, respiratory, and cardiovasular systems. VIP is a potent vasodilator and bronchodilator and plays a role in the control of prolactin secretion from the pituitary gland. PACAP may regulate the synthesis and secretion of catecholamines from adrenal medulla and can modulate pancreatic exocrine activity. The presence of PACAP receptors in the reproductive tract suggests that PACAP may be involved in the regulation of spermatogenesis.

2.36. Vasopressin and Oxytocin

Arginine[8]-vasopressin (AVP, vasopressin; also known as antidiuretic hormone, ADH) **(342)** is a nonapeptide amide that functions both as a neuroregulator and a hormone (84, 85). Oxytocin (OT) **(343)** is a nonapeptide amide related to AVP.



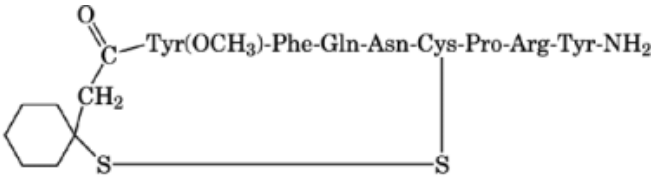
(342)



(343)

AVP and OT protein precursors are separate gene products. The AVP precursor is processed post-translationally to generate AVP, neurophysin II which binds AVP, and a glycopeptide. A sexual dimorphism has been observed with testosterone increasing AVP expression. AVP is co-localized with a number of peptides in the hypothalamus, with galanin in the bed nucleus of the stria terminalis and the medial amygdala, and with NE in the locus coeruleus. AVP and OT are produced by magnocellular neurons of the hypothalamic paraventricular nucleus, supraoptic nucleus, and accessory nuclei that project to the posterior pituitary and release the hormones into the circulation.

AVP produces its effects via V_{1A}, V_{1B}, and V_2 receptors. There is one receptor for OT. V_{1A} and V_{1B} receptors are linked to phosphatidylinositol, hydrolysis, while the V_2 receptor is linked to cAMP formation. The brain contains predominantly V_{1A} receptors with little evidence for the presence of V_{1B} or V_2 receptors. V_{1A} receptors are distinguished from V_{1B} receptors on the basis of antagonist potency with $d(CH_2)_5[Tyr(CH_3)^2$ AVP] **(344)** being three orders of magnitude more potent at V_{1A} than at V_{1B} receptors, whereas [D-Pen^1,$Tyr(CH_3)^2$]AVP **(345)** has similar low nanomolar potency at both receptors. SR 49059 **(346)** and OPC 21268, **(347)** are nonpeptide V_1 antagonists (Table 20).

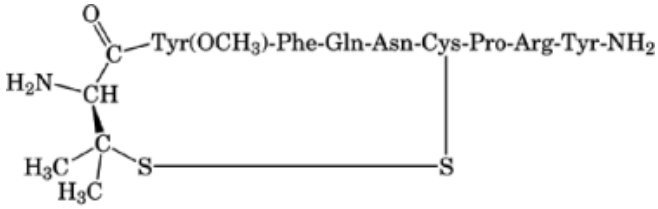


(344)

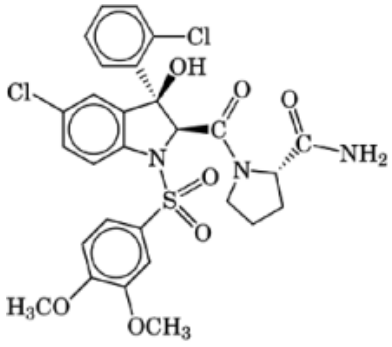
Table 20. Vasopressin and Oxytocin and Receptor Agonists and Antagonists

Agonist/antagonist	CAS Registry Number	Molecular formula	Structure number
arginine^8 vasopressin	[9034-50-8]		**(342)**
oxytocin	[50-56-6]		**(343)**
$d(CH_2)_5$[Tyr(Me)^{2}AVP			**(344)**
[D-Pen^1, Tyr(Me)^2]AVP			**(345)**
SR 49059	[150375-75-0]	$C_{28}H_{27}Cl_2N_3O_7S$	**(346)**
OPC 21268		$C_{26}H_{31}N_3O_4$	**(347)**
d(D-Arg^8]VP			
d[Val^4]VP			
$d(CH_2)_5$[D-Ile^2,Ile^4]AVP			
[Thr^4, Gly^7] oxytocin			
$d(CH_2)_5$[Tyr$(CH_3)^2$, Thr^4, Orn^8] oxytocin (1–8)[a]			
cyclo(D1-Nal, Ile, D-piperazyl, piperazyl, D-His, Pro)[b]			
L-368,899	[148927-60-0]	$C_{27}H_{42}N_4O_5S_2$	**(348)**

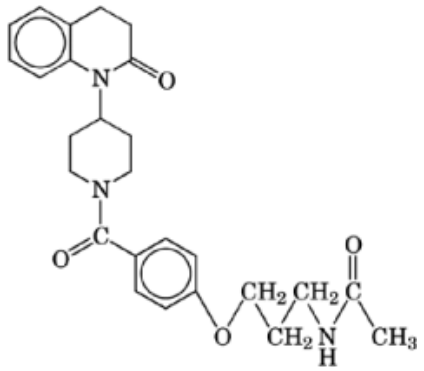
[a] Orn = ornithine.
[b] Nal = naphthylalanine.



(345)

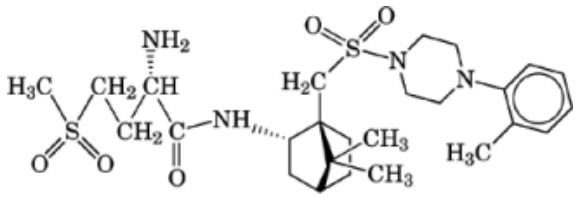


(346)



(347)

OT receptors are localized in the brain hypothalamus, limbic system, cortex, striatum, olfactory system, and brain stem. In the periphery, OT is best known for its stimulation of uterine smooth muscle and the milk ejection reflex. $d(CH_2)_5$[Tyr$(CH_3)^2$·Thr^4,Orn^8]oxytocin(1–8), cyclo(D-1–Nal-Ile-D-pipecolic acid D-His-Pro) and L-368,899 **(348)** are OT antagonists, the latter being nonpeptidic and under evaluation for use in preterm labor (Table 20).



(348)

AVP is excitatory in the ventral hippocampus, either directly or by potentiation of glutamatergic responses. An inhibitory effect has been observed in C_{A1}. AVP may be involved in the formation of long-term potentiation and thus learning and memory. However, AVP is proconvulsive, may augment the formation of drug tolerance and dependence, and affects cardiovascular regulatory processes.

OT receptors in the hypothalamus are regulated by steroids. OT systems in the CNS are involved in homeostasis, reproduction, and related behavior. OT is also excitatory to neurons in the CNS at nanomolar concentrations (86), but relatively little is known about neuronal mechanisms and pharmacology.

3. Economic Aspects

Neuroregulators comprise a large portion of clinically effective human therapeutic agents in use as of this writing. Thus as an aggregate group, neuroregulators have an estimated global market in excess of $50–100 billion per year. The histamine H_2 blockers, cimetidine, and ranitidine have aggregate sales in their ethical and generic forms in excess of $6 billion/yr. The antidepressant drug market is approaching $5.0 billion; sales of drugs for Parkinson's disease are $1.0 billion; anxiolytics are $2 billion; drugs for pain, $5.0 billion; manic depression, $330 million; Alzheimer's, $1.0 billion, with sales for an effective agent in the $3–4 billion range; and other dementias $750 million. Sales of antipsychotic drugs are $1.5 billion; drugs for eating disorders and

obesity, $310 million; migraine, $1 billion; attention hyperactivity deficit disorder, $460 million; epilepsy, $850 million; hearing loss, $1.1 billion; insomnia, $250 million; drug and alcohol abuse, $36 million, with sales for an effective agent in excess of $2 billion; neurotrauma, $180 million; and cardiovascular diseases, eg, hypertension, $5 billion.

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