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# A REVIEW ON GAMMA-AMINOBUTYRIC ACID (GABA) AND ITS RECEPTORS

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## ABSTRACT

The inhibitory neurotransmitter, γ-aminobutyric acid (GABA), activates a variety of receptors in all areas of the central nervous system (CNS). GABA acts at inhibitory synapses in the brain by binding to specific transmembrane receptors in the plasma membrane of both pre and postsynaptic neuronal processes. There are three classes of GABA receptors. $GABA_A$ and $GABA_C$ receptors are ionotropic in nature (i.e., their activation results in enhanced membrane ion conductance) and $GABA_B$ receptor is metabotropic type of receptor (i.e., their activation results in increased intracellular levels of second messenger). GABA is present in high concentrations (millimolar) in many brain regions. The $GABA_A$ receptor is a complex structure and includes the five major binding domains. These include binding sites localized in or near the Cl− channel for GABA, benzodiazepines, barbiturates and picrotoxin as well as binding sites for the anesthetic steroids. $GABA_B$ receptors ($GABA_B$) are metabotropic transmembrane receptors for gamma-aminobutyric acid (GABA) that are linked via G-proteins to potassium channels. These $GABA_B$ receptors are activated by baclofen. In addition to the $GABA_B$ receptors there is a distinct class of ligand gated ion channels that are activated by GABA, referred to as the $GABA_C$ receptor. The $GABA_C$ receptors are activated by cis-aminocrotonic acid (CACA), which is not recognised by either the $GABA_A$ or $GABA_B$ receptors. $GABA_C$ receptors are expected to mediate the lateral inhibition of light responses and have been shown to inhibit transmitter release at bipolar cell terminals. The pharmacology of these novel subtypes of GABA receptors may yield important therapeutic agents.

**KEY WORDS : Gama-aminobutyric acid (GABA), Ionotropic, Metabotropic, Baclofen, Cis-aminocrotonic acid (CACA)**

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# INTRODUCTION

## GAMMA-AMINOBUTYRIC ACID (GABA)

GABA is the major inhibitory amino acid transmitter of the mammalian central nervous system and it is present in some 25-50% of all neurones[1]. γ –aminobutyric acid (GABA) is the chief inhibitory neurotransmitter in mammalian central nervous system and it plays an important role in regulating the neuronal excitability throughout the nervous system.

Several amino acids are found in high concentrations in brain, and some have been established as neurotransmitters. *L-Glutamic* acid (glutamate) is the major neurotransmitter for fast excitatory synaptic transmission, whereas the γ –aminobutyric acid (GABA) is considered as a major neurotransmitter for fast inhibitory synaptic transmission. Glycine is a secondary rapid inhibitory neurotransmitter, especially in the spinal cord[2, 3]. GABA acts at inhibitory synapses in the brain by binding to specific transmembrane receptors in the plasma membrane of both pre and postsynaptic neuronal processes.This binding causes the opening of ion channels to allow the flow of either negatively charged chloride ions into the cell or positively charged potassium ions out of the cell. Depending on which ion channels open, the membrane potential is either hyperpolarized or repolarized. This action results in a negative change in the transmembrane potential, usually causing hyperpolarization. Neurons that produce GABA as their output are called GABAergic neurons, and have chiefly inhibitory action[4]. Most of the early studies, carried out with iontophoretic application of GABA in the CNS, indicated that it generally produced inhibitory hyperpolarizing responses on neurones, which were blocked competitively by the alkaloid bicuculline. The hyperpolarizing response is due to an increase in the chloride conductance of the neuronal membrane allowing chloride ions to flow down their electrochemical gradient into the cell.However, in the late 1970s, Bowery and his colleagues, in attempts to identify GABA receptors on peripheral nerve terminals, noted that GABA application reduced the evoked release of noradrenaline in the rat heart and that this effect was not blocked by bicuculline. This action of GABA was mimicked by baclofen, 4- amino-3-(4-chlorophenyl) butanoic acid, a compound that had no effect on chloride conductance in central neurones. The new receptor was named $GABA_B$ to differentiate it from its more familiar cousin, which was termed $GABA_A$.The $GABA_C$ receptor had a rather more difficult birth.

In an attempt to discover which conformation of GABA was responsible for activating the receptor, Johnson and his colleagues synthesised a number of conformationally restricted analogues of GABA and noted that cis-4-aminocrotonic acid (CACA), which has a partially folded conformation, depressed the firing of cat spinal neurones in a bicuculline insensitive manner. These depressant effects could not be reproduced by baclofen[5], suggesting pharmacology distinct from that of either $GABA_A$ or $GABA_B$ receptors. This receptor is known as $GABA_C$. The DNAs that encode these receptor proteins have now been identified, providing not only a facile means for their molecular characterisation but also a significant stimulus for our attempts to understand their physiological importance.

## SYNTHESIS, RELEASE, UPTAKE AND METABOLISM OF GABA

GABA is formed in vivo by a metabolic pathway referred to as the GABA shunt.The GABA shunt is a closed-loop process with the dual purpose of producing and conserving the supply of GABA. GABA is present in high concentrations (millimolar) in many brain regions.The first step in the GABA shunt is the transamination of α-ketoglutarate, formed from glucose metabolism in the Krebs cycle by GABA α-oxoglutarate transaminase (GABA-T) into l-glutamic acid[6]. Glutamic acid decarboxylase (GAD) catalyzes the decarboxylation of glutamic acid to form GABA.GAD is expressed only in GABAergic neurons and in certain peripheral tissues

which are also known to synthesize GABA. Like most neurotransmitters, GABA is stored in synaptic vesicles and is released in a $Ca^{2+}$ dependent manner upon depolarization of the presynaptic membrane. Following release into synaptic cleft, GABA's actions are terminated principally by reuptake into presynaptic terminals and/or surrounding glial cells[7].In the nerve terminal, GABA is stored in vesicles by a unique sodium-independent, ATP-dependent transport system that is selective for GABAergic neurons[8, 9]. This uptake system is biochemically and pharmacologically distinct from the neuronal and glial membrane high-affinity transport system and is driven by an electrochemical proton gradient[10-12]. GABA in vesicles and, perhaps, in the cytoplasm is released into the synaptic cleft upon depolarization of the terminal by a calcium dependent mechanism. After release, GABA diffuses across the synaptic cleft to interact with postsynaptic GABA receptors. GABA is inactivated by diffusion and by a high-affinity, sodium-dependent transport system into synaptic terminals and glial cells.The reuptake of GABA occurs via highly specific transmembrane transporters which have recently been shown to be members of a large family of $Na^+$ dependent neurotransmitter transporters. GABA uptake is temperature- and ion-dependent[13] (both $Na^+$ and $Cl^-$ ions are required for optimal uptake).GABA is also metabolized by GABA-T to form succinic semi-aldehyde. This transamination will regenerate glutamate when it occurs in the presence of a-ketoglutarate. Succinic semialdehyde is oxidized by succinic semi-aldehyde dehydrogenase (SSADH) to succinic acid which then re-enters the Krebs cycle[13].

**Synthesis of GABA by GABA shunt[41]**

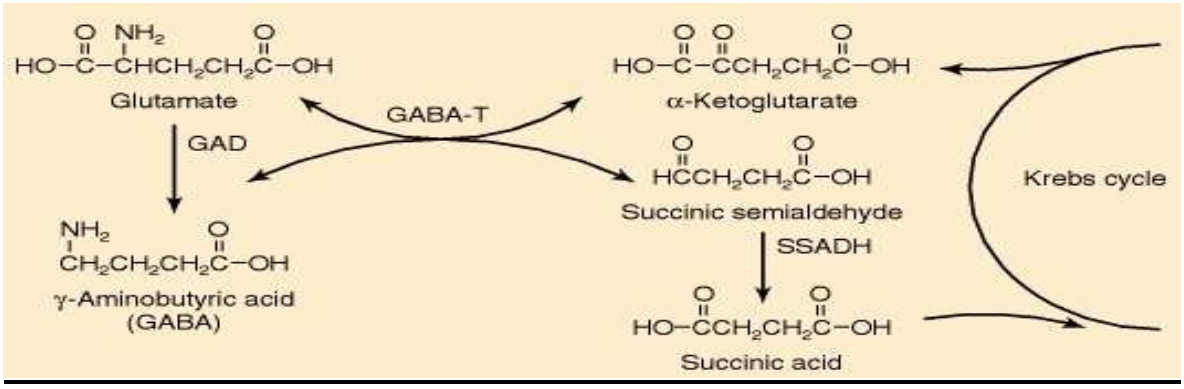


**Figure 1**

***GABA shunt is a closed-loop process with the dual purpose of producing and conserving the supply of GABA. The first step in the GABA shunt is the transamination of α-ketoglutarate, formed from glucose metabolism in the Krebs cycle by GABA α-oxoglutarate transaminase (GABA-T) into l-glutamic acid[6]. Glutamic acid decarboxylase (GAD) catalyzes the decarboxylation of glutamic acid to form GABA.GAD is expressed only in GABAergic neurons and in certain peripheral tissues which are also known to synthesize GABA.***

## GABA RECEPTORS - PHYSIOLOGY AND PHARMACOLOGY

The GABA receptors are a class of receptors that respond to the neurotransmitter gamma-aminobutyric acid (GABA), the chief inhibitory neurotransmitter in the vertebrate central nervous system. There are three classes of GABA receptors.$GABA_A$ and $GABA_C$ receptors are ionotropic (i.e., their activation results in enhanced membrane ion conductance),$GABA_B$ receptor is metabotropic (i.e., their activation results in increased intracellular levels of second messenger)[14, 15].$GABA_A$and $GABA_C$ receptors

are ionotropic receptors leading to increased Cl- ion conductance, whereas $GABA_B$ receptors are metabotropic receptors which are coupled to G proteins and thereby indirectly alter membrane ion permeability and neuronal excitability.GABA receptors were widely distributed in mammalian brain and are in high concentration in cerebral cortex, hippocampus, basal ganglia, thalamus, cerebellum, and brainstem[16].

## $GABA_A$ RECEPTOR

The $GABA_A$ receptor is one of ligand-gated ion channels responsible for mediating the effects of Gamma-Amino Butyric Acid (GABA)**.**The rapid chloride current defined a physiologic receptor mechanism termed the $GABA_A$ receptor, also pharmacologically defined by the antagonist bicuculline, as well as picrotoxin, and the agonist muscimol. Thus, the $GABA_A$ receptor is a chloride channel regulated by GABA binding, and it is now grouped in the superfamilyof ligand-gated ion channel receptors**,** which includes the well-characterized nicotinic acetylcholine receptor, present at the skeletal neuromuscular junction[17, 18].

In Ionotropic $GABA_A$ receptors, binding of GABA molecules to their binding sites in the extracellular part of receptor triggers the opening of a chloride ion-selective pore. The increased chloride conductance drives the membrane potential towards the reversal potential of the $Cl^-$ ion which is about –65 Mv in neurons, inhibiting the firing of new action potentials[19].

The $GABA_A$ receptors are the major players in CNS function and relevance to psychopharmacology. Activation of the $GABA_A$ receptor by agonist results in an increase in $Cl^-$ ion conductance via the receptor-gated ion channel or pore. This increase in $Cl^-$ ion conductance, which requires the binding and cooperative interaction of two molecules of GABA, is actually due to an increase in the mean open time of the $Cl^-$ ion channel itself[20]. (GABA activates the $GABA_A$ receptor at low micromolar concentrations, suggesting that it must be highly compartmentalized within nervous tissue). The increase in $Cl^-$ ion conductance observed following activation of $GABA_A$ receptors results in a localized hyperpolarization of the neuronal membrane and therefore leads to an increase in the "threshold" required for excitatory neurotransmitters to depolarize the membrane in order to generate an action potential. This decrease in neuronal membrane "excitability" results in the inhibitory actions of GABA.

## MOLECULAR STRUCTURE OF $GABA_A$ RECEPTORS

The $GABA_A$ receptor is a complex structure and includes the five major binding domains. These include binding sites localized in or near the $Cl^-$ channel for GABA, benzodiazepines, barbiturates and picrotoxin as well as binding sites for the anesthetic steroids. These binding domains modulate receptor response to GABA stimulation. In addition, other drugs, including volatile anesthetics, ethanol and penicillin, have been reported to have an effect on this receptor[21]. An integral part of this complex is the $Cl^-$ channel.The GABA-binding site is directly responsible for opening the $Cl^-$ channel. A variety of agonists binds to this site and elicits GABA-like responses. One of the most useful agonists is the compound muscimol, a naturally occurring GABAanalogue isolated from the psychoactive mushroom *Amanita muscaria.* It is a potent and specific agonist at $GABA_A$ receptors and has been a valuable tool for pharmacological and radioligand-binding studies[22, 23]. Other GABA agonists include isoguvacine, 4,5,6,7-tetrahydroisoxazolo-[5,4-*c*]py-ridin-3-ol (THIP), 3-aminopropane-sulfonate and imidazoleacetic acid[23]. The classical $GABA_A$-receptor antagonist is the convulsantbicuculline, which reduces current by decreasing the opening frequency and mean open time of the channel. It is likely that bicuculline produces its antagonistic effects on $GABA_A$ receptor currents by competing with GABA for binding to one or both sites on the $GABA_A$ receptor.

**Structural model of the $GABA_A$ benzodiazepine receptor—chloride ($Cl^-$) ionophore complex[41]**

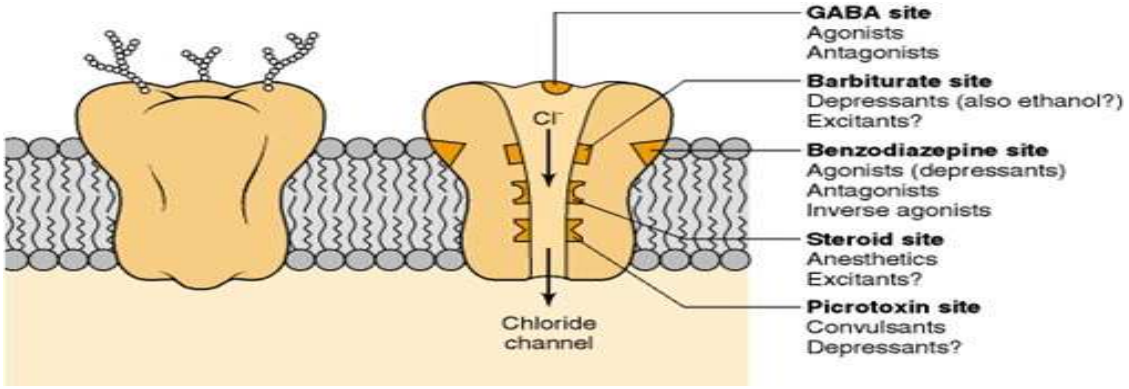


**Figure 2**

***The cut-away view of the $GABA_A$demonstrates targets for a variety of compounds that influence the receptor complex. No specific drug receptor location is implied.***

## $GABA_A$ RECEPTOR IS THE MAJOR MOLECULAR TARGET FOR THE ACTION OF MANY DRUGS IN THE BRAIN

Among these are benzodiazepines, intravenous and volatile anesthetics and possibly ethanol. Benzodiazepine receptor-binding sites copurify with the GABA-binding sites[24]. In addition, benzodiazepine receptors are immune precipitated with antibodies that were developed to recognize the protein containing the GABA-binding site[25]. This indicates that the benzodiazepine receptor is an integral part of the $GABA_A$ receptor $Cl^-$ channel complex.

Benzodiazepine agonists represent the newest group of agents in the general class of depressant drugs, which also includes barbiturates, that show anticonvulsant, anxiolytic and sedative—hypnotic activity. Well-known examples include diazepam and chlordiazepoxide, which often are prescribed for their anti-anxiety effects[26]. The mechanism of action of benzodiazepine agonists is to enhance GABAergic transmission. From electrophysiological studies, it is known that these benzodiazepines increase the frequency of channel opening in response to GABA, thus accounting for their pharmacological and therapeutic actions. In addition, the benzodiazepine site is coupled allosterically to the barbiturate and picrotoxin sites[27]. Benzodiazepine receptors are heterogeneous with respect to affinity for certain ligands. A wide variety of nonbenzodiazepines, such as the β-carbolines, cyclopyrrolones and imidazopyridines, also bind to the benzodiazepine site.

Barbiturates comprise another class of drugs commonly used therapeutically for anesthesia and control of epilepsy. Phenobarbital and pentobarbital are two of the most commonly used barbiturates. Phenobarbital has been used to treat patients with epilepsy since 1912. Pentobarbital is also an anticonvulsant, but it has sedative side effects. Barbiturates at pharmacological concentrations allosterically increase binding of benzodiazepines and GABA to their respective binding sites[27]. Measurements of mean channel open times show that barbiturates act by increasing the proportion of channels opening to the longest open state (9 millisec) while reducing the proportion opening to the shorter open states (1 and 3 millisec), resulting in an overall increase in mean channel open time and $Cl^-$ flux.

Channel blockers, such as the convulsant compound picrotoxin, cause a decrease in mean channel open time. Picrotoxin works by preferentially shifting opening channels to the briefest open state (1 millisec). Thus, both picrotoxin and

barbiturates appear to act on the gating process of the $GABA_A$ receptor channel, but their effects on the open states are opposite to each other. Experimental convulsants like pentylenetetrazol and the cage convulsant*t*-butyl bicyclophosphorothionate (TBPS) act in a manner similar to picrotoxin, preventing $Cl^-$ channel permeability. The antibiotic penicillin is a channel blocker with a net negative charge. It blocks the channel by interacting with the positively charged amino acid residues within the channel pore, consequently occluding $Cl^-$ passage through the channel.

There have been numerous studies on the role of $GABA_A$ receptors in anesthesia. A considerable amount of evidence has been compiled to suggest that general anesthetics, including barbiturates, volatile gases, steroids and alcohols, enhance GABA-mediated $Cl^-$ conductance. A proper assessment of this phenomenon requires not only a behavioral assay of anesthesia but also *in vitro* models for the study of receptor function. In this regard, not only electrophysiological methods but also neurochemical measurements of $Cl^-$ flux and ligand binding have been useful. For example, a strong positive correlation exists between anesthetic potencies and the stimulation of GABA-mediated $Cl^-$ uptake. This is seen with barbiturates and anesthetics in other chemical classes[28].

Comparison of ligand-gated ion channels that vary in sensitivity to anesthetic modulation, using the chimera and site-directed mutagenesis approach, has identified two amino acids in the membrane-spanning domains that are critical for anesthetic sensitivity[29]. Direct evidence of ethanol augmentation of $GABA_A$ receptor function, measured either by electrophysiological techniques or agonist-mediated $Cl^-$ flux, has been reported[28, 30]. The similarity between the actions of ethanol and sedative drugs such as benzodiazepines and barbiturates that enhance GABA action suggests that ethanol may exert some of its effects by enhancing the function of $GABA_A$ receptors. Ethanol potentiation of $GABA_A$ receptor function appears to be dependent upon the cell type tested and the method of assay. This suggests that the ethanol interaction may be specific for certain receptor subtypes and/or that it may be an indirect action.

## $GABA_B$ RECEPTORS

GABA also activates metabotropic $GABA_B$ receptors, which are widely distributed within the central nervous system and also in peripheral autonomic terminals.$GABA_B$ receptors ($GABA_B$) are metabotropic transmembrane receptors for gamma-aminobutyric acid (GABA) that are linked via G-proteins to potassium channels[31].

Their activation causes an inhibition of both basal and stimulated adenylatecyclase activity together with a decrease in $Ca^{2+}$ and an increase in $K^+$ conductance in neuronal membranes. The receptors are activated by baclofen, used in the treatment of spasticity, baclofen being the active isomer. There is evidence that $GABA_B$receptor agonists may be useful in the treatment of pain and to reduce the craving for drugs of addiction. There is limited information on the therapeutic potential of $GABA_B$receptor antagonists but there is support for the idea that they may prove valuable in the treatment of absence epilepsy and as cognition enhancers.

$GABA_B$ receptors are coupled indirectly to $K^+$ channels. When activated, these receptors can decrease $Ca^{2+}$ conductance and inhibit cAMP production via intracellular mechanisms mediated by G proteins. $GABA_B$ receptors can mediate both postsynaptic and presynaptic inhibition. Presynaptic inhibition may occur as a result of $GABA_B$ receptors on nerve terminals causing a decrease in the influx of $Ca^{2+}$, thereby reducing the release of neurotransmitters[32].

$GABA_B$receptors couple to Ca2+ and K+ channels via G proteins and second messenger systems [33,34]. They are selectively activated by baclofen and are antagonized by phaclofen and 2-hydroxy saclofen. GABA, receptors do not respond to the known GABA, receptor modulators.

## $GABA_C$ RECEPTORS

In addition to the $GABA_B$ receptors there is a distinct class of ligand gated ion channels that are activated by GABA, referred to as the $GABA_C$ receptor. It is a subclass of ionotropic GABA receptors, insensitive to typical allosteric modulators of $GABA_A$ receptor channels such as benzodiazepines and barbiturates, was designated $GABA_C$ receptor[35]. The natural agonist GABA is about an order of magnitude more potent at the $GABA_C$ receptors than at the most common of the $GABA_A$ receptors.

The $GABA_C$ receptors are activated by cis-aminocrotonic acid (CACA), which is not recognised by either the $GABA_A$ or $GABA_B$ receptors, suggesting that they recognise the partially folded conformation of GABA. GABA receptors are not blocked by bicuculline and do not recognise the benzodiazepines, barbiturates or the neuroactive steroids but, like $GABA_A$ receptors are blocked by picrotoxin, while 1,2,5,6-tetrahydropyridine-4-yl methyl phosphinic acid (TPMPA) appears to inhibit $GABA_C$ receptors selectively[36].Native responses of the $GABA_C$ receptor type occur in retinal bipolar or horizontal cells across vertebrate species.$GABA_C$ receptors are exclusively composed of ρ (rho) subunits that are related to $GABA_A$ receptor subunits. Although the term "$GABA_C$ receptor" is frequently used, $GABA_C$ may be viewed as a variant within the $GABA_A$ receptor family[37].

### CACA (CIS-AMINOCROTONIC ACID) AS A SELECTIVE GABA, RECEPTOR LIGAND

CACA is much more selective as a GABA, receptor ligand than the more potent TACA, which interacts strongly with a variety of macromolecules that recognize GABA. Unlike TACA, CACA is at best, a very weak GABA, receptor agonist and is neither a substrate for, nor an inhibitor of GABA, 2-oxoglutarate aminotransferase in extracts of rat brain mitochondria. In addition, it does not influence the activity of glutamate decarboxylase in rat brain extracts[38]. CACA is a weak substrate for a transporter that transports GABA, p-alanine and nipecotic acid in glial cells isolated from guinea-pig retina[39]. This is consistent with the idea that CACA, p-alanine, nipecotic acid and GABA are substrates for a common transporter that may be related to the GAT-3 transport protein cloned from rat CNS. CACA is tenfold weaker as a substrate for the transporter than as a partial agonist for GABA, receptors[39].

The most potent competitive antagonists of GABA, responses are 3-APMPA [3-aminopropyl (methyl) phosphinic acid], 3-APPA (3-aminopropyl phosphinic acid) and 3-APA (3-aminopropyl phosphonic acid).

Recent evidence indicates that $GABA_C$ receptors are composed of the recently discovered p subunit. In 1991, Cutting and colleagues cloned the pl subunit from a human cDNA library. This was the first member of a new family of GABA-receptor subunits and is expressed at high levels in the retina. $p_1$ and $p_2$ share 74% amino acid sequence identity, but only 30-38% when compared with other GABA-receptor subunits[40].

$GABA_C$ receptors display characteristic activation, desensitization, conductance and gating properties that distinguish them clearly from $GABA_A$ receptors.$GABA_C$ receptors are expected to mediate the lateral inhibition of light responses and have been shown to inhibit transmitter release at bipolar cell terminals.

## CONCLUSION

Interest in the receptors for GABA, the major inhibitory transmitter in the CNS, has been developed, with varying degrees of enthusiasm, over the past 40 years. We now have agonists and antagonists which allow us to differentiate, experimentally at least, between responses mediated by the three pharmacologically distinct receptor families with which they interact. The possible mechanism of action of $GABA_A$ and $GABA_C$ receptors which are ionotropic receptors include the increased Cl- ion conductance, whereas for $GABA_B$ receptors (metabotropic receptors) which are coupled to G proteins and thereby altering indirectly membrane ion permeability and neuronal excitability. The information base is most extensive for the

GABA receptors, driven largely by observations that these proteins are the targets for a number of drugs with significant clinical importance. The expansion continues with the conviction that this almost bewildering complexity can be harnessed for the next generation of pharmacological agents with a more restricted profile of activity. The developments over the past 7 years or morehave delivered a promissory note that is producing significant investment and many hold real conviction in their future.

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