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SUBSTITUTED QUINAZOLINE A POTENTIAL DRUG CANDIDATE: AN OVERVIEW

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ABSTRACT

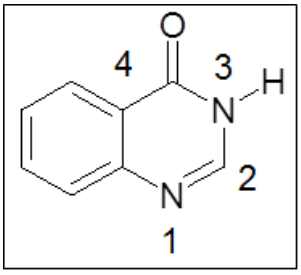
Heterocycles are among the most frequently encountered scaffolds in drug and pharmaceutically relevant substances. A heterocyclic core is propitious for variations of substitution pattern during Structure Activity Relationship (SAR). Quinazoline (German-Chinazolin) was first proposed by Weddige. Ketoquinazoline (Quinazolinone) is most important. Quinazoline-4(3*H*)-ones and its derivatives are versatile nitrogen heterocyclic compounds which have long been known as a promising class of biologically active compounds. Quinazolinone are excellent reservoir of bioactive substances. The stability of the Quinazoline nucleus has inspired medicinal chemists to introduce many bioactive moieties to this nucleus to synthesize new potential medicinal agents. Quinazoline and condensed Quinazoline exhibit potent central nervous system (CNS) activities like anti-anxiety, analgesic, anti-inflammatory and anticonvulsant. Quinazolin-4(3H)-ones with 2, 3-disubstitution is reported to possess significant analgesic, anti-inflammatory and anticonvulsant activities. The synthesis of new compounds which will exert more desired effects with fewer side effects has become an important goal for medicinal chemists.

KEYWORDS: Quinazoline, anti-inflammatory, analgesic.

INTRODUCTION

Heterocycles are among the most frequently encountered scaffolds in drug and pharmaceutically relevant substances.

Quinazoline (German-Chinazolin) was first proposed by Weddige. Keto-quinazoline (Quinazolinone) is most important. Quinazoline is 1, 3-diazanaphthalene. It is also known as 5, 6-benzopyrimidine and its 4-oxo derivative is called 4(3*H*)-quinazolinone.[1, 2, 3]



IUPAC: Quinazoline-4(3*H*)-ones.

Benzene Ring fused with six membered heterocyclic ring containing two Nitrogen atom Paal and Bush suggested the numbering of Quinazoline ring system, which is currently used.

Quinazolinones are always high melting crystalline solids, insoluble in water and in most organic solvents but soluble in aqueous alkali. Stability of the ring system: The ring system in quinazolinone is exceedingly stable in oxidation, reduction, hydrolysis reactions and other treatment designed to break the ring. There is no report of degradation of quinazolinone by simple chemical oxidation.

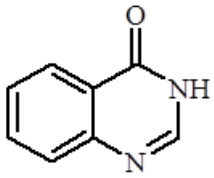
Quinazoline-4(3*H*)-ones and its derivatives are versatile nitrogen heterocyclic compounds which have long been known as a promising class of biologically active compounds. Quinazolinone are excellent reservoir of various bioactive substances. The versatility in pharmacological activities and stability of the quinazoline nucleus has inspired medicinal chemists to introduce many bioactive moieties to this nucleus to synthesize new potential medicinal agents.

Quinazoline and quinazolinone derivatives have continued to attract a widespread interest for a long time due to their diverse pharmacological activities such as antibacterial[4,5], antitubercular[6], antifungal[7], hypoglycemic[8] and anti tumour.[9]

During literature survey for our ongoing medicinal chemistry research program, we found that quinazolines and condensed quinazolines exhibit potent central nervous system (CNS) activities like analgesic, anti-inflammatory[12] and anticonvulsant.[13] Quinazolin-4(3*H*)-ones

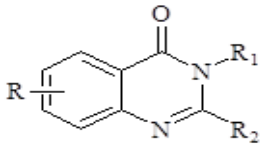
with 2, 3-disubstitution is reported to possess significant analgesic, anti-inflammatory and anticonvulsant activities.[10]

Quinazolin-4(3*H*)-ones are also important building blocks in the synthesis of natural and pharmacological compounds. The Quinazoline skeleton, when selectively functionalized, is a building block for the preparation of numerous alkaloids and substances with pronounced biological activities.

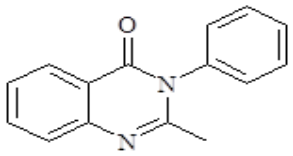


4(3*H*)quinazolinone

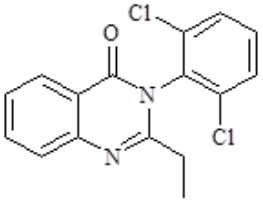
During the past years various approaches toward the synthesis of quinazolin-4(3*H*)-ones derivatives have been explored. 2, 3-Disubstituted-3*H*-quinazolin-4-ones (I) are a privileged structure present in many biologically active compounds such as Methaqualone (II) (sedative-hypnotic), chloroqualone (III) (antitussive) and piriqualone (IV) (anticonvulsant).



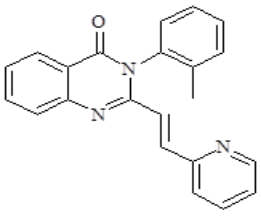
2,3-disubstituted 3*H*-quinazolin-4-one (I)



Methaqualone (II)



Chloroqualone (III)



Piriqualone (IV)

Recently 2-phenylquinazolin-4(3*H*)-one and its derivatives were synthesised by using various green chemistry approaches and principles like microwave assisted synthesis, solid phase synthesis, solvent free reactions, ultrasonic radiations.

We report here the synthesis of several newer derivatives of quinazolinone by incorporating different substituted acetamide at the ring nitrogen of 2-phenylquinazolin-4(3*H*)-one. Up to

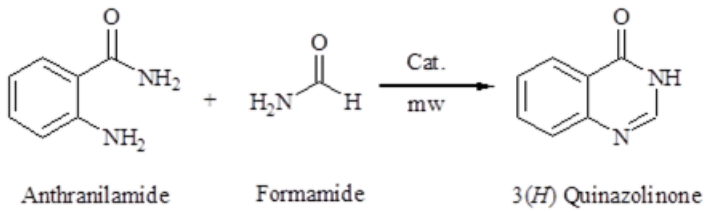
now, a great number of various procedures have been proposed for the synthesis of quinazolin-4-ones in the past few years. Using microwave instrument, this reaction could be easily and rapidly performed in very good yields, providing a large quantity of various quinazolin-4-one acetamide derivatives which can be employed as useful bioactive compounds.

We also report a facile and efficient method for the synthesis of 2-phenylquinazolin-4(3*H*)-one by the condensation reaction of anthranilic acid, benzoyl chloride to form 2-phenyl-4*H*-benzoxazin-4-one as an intermediate and ammonium acetate was added to this reaction mixture to generate ammonia in-situ as a source of nitrogen.

1.1.1. Survey of synthetic methods for Building Blocks

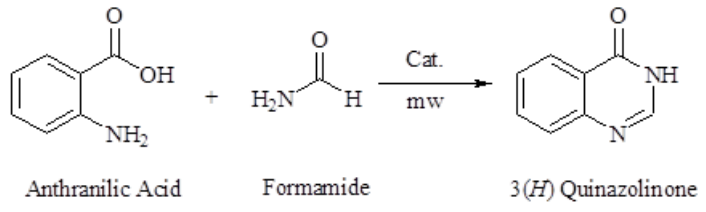
The competition in the field of drug discovery has helped to know, identify speed of synthesis as top priority in drug development. In accordance with the significance of quinazolin-4(3*H*)-ones, various synthetic methods have been developed for the construction of this kind of fused heterocycles. Many quinazolines can be prepared from 2-aminobenzaldehyde, 2-aminophenyl ketones or anthranilic acid and it's derivatives. Typically, quinazolin-4(3*H*)-ones are prepared from an anthranilic acid or its derivative. Niementowski reaction is the formation of 2-alkyl-4(3*H*) quinazolinone by condensation of anthranilic acid or substituted anthranilic acid and amides.

Scheme 1[11]



Anthranilamide Formamide 3(*H*) Quinazolinone

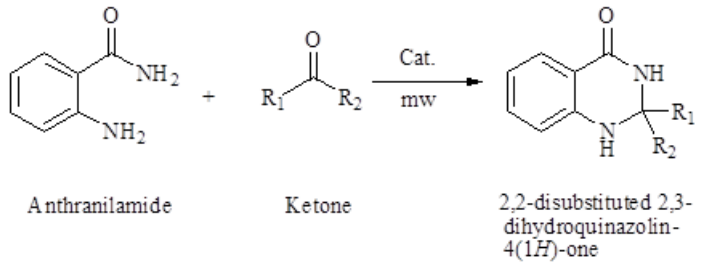
Scheme 2[12]



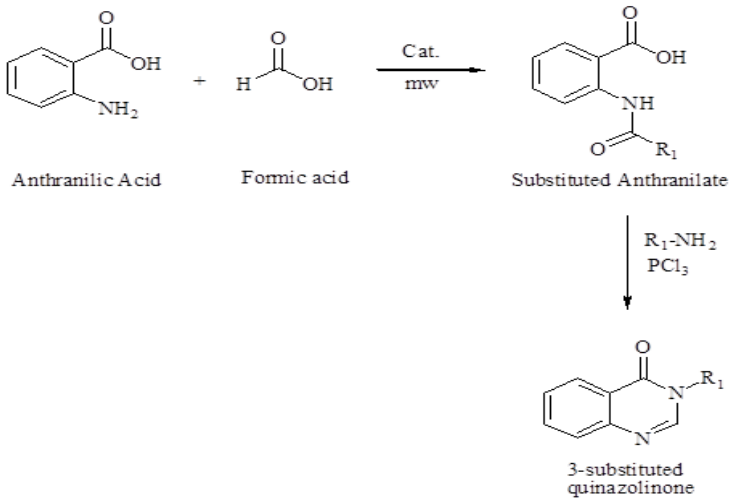
Anthranilic Acid Formamide 3(*H*) Quinazolinone

Scheme 3[13]

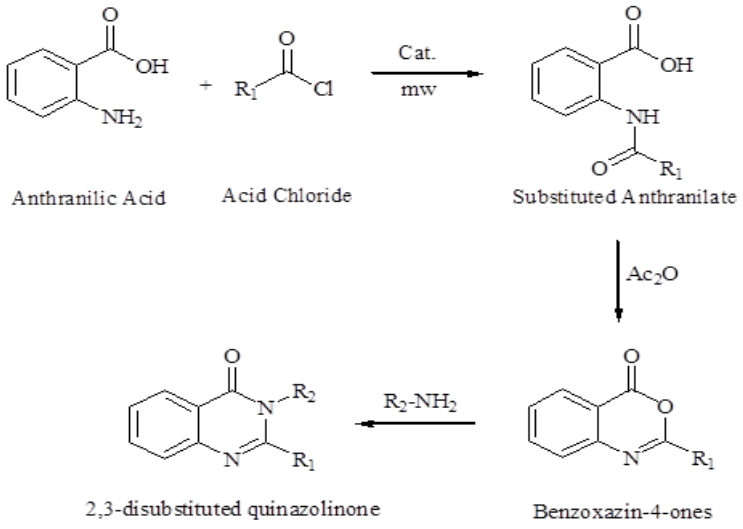
Due to the superior performance in the Niementowski reaction, anthranilamide was selected as the substrate and was subjected to reaction with different kinds of ketones. As a result, different 2, 2-disubstituted 2, 3- dihydroquinazolin-4(1*H*)-ones were obtained in yields ranging from 66 to 95%.



Scheme 4[14]

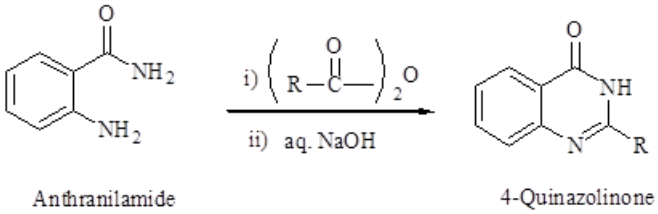


Scheme 5[15]



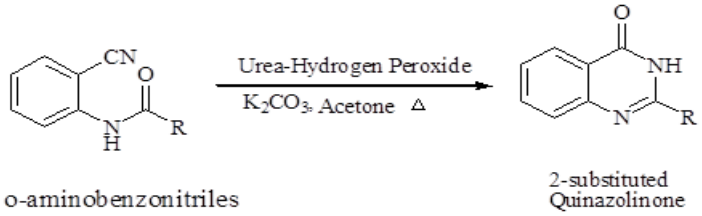
Scheme 6[17]

4-Quinazolinones with 2-substitution can be produced simply and quickly. Carboxylic acid quinazolinone derivatives can be conveniently synthesized by reacting anthranilamide with a range of anhydrides including benzoic anhydride, succinic anhydride, glutaric anhydride and diethyl oxalate, followed by a cyclization using aqueous sodium hydroxide.



Scheme 8[18]

A further simple way to form substituted quinazolin-4(3*H*)-ones is by Oxidative hydration of *o*-aminobenzonitriles using urea-hydrogen peroxide (UHP) that will help in cyclization.



Scheme 9[19]

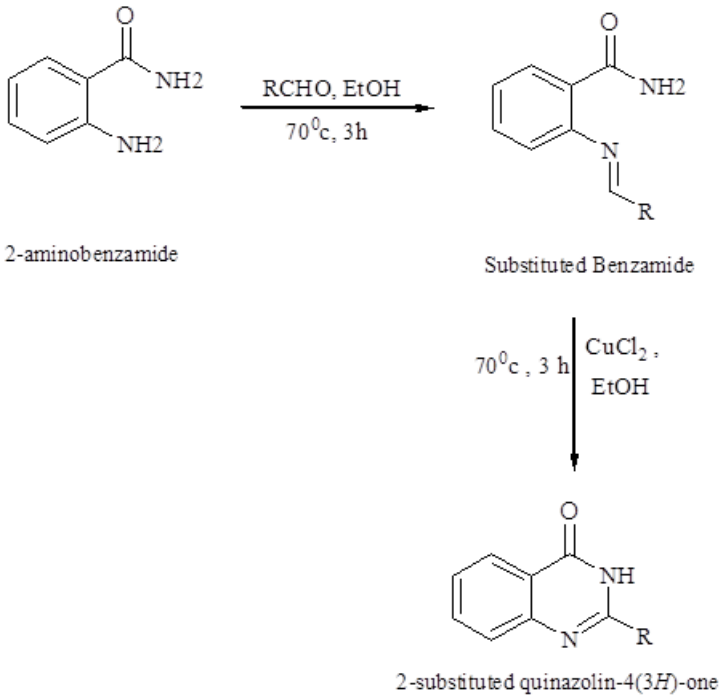
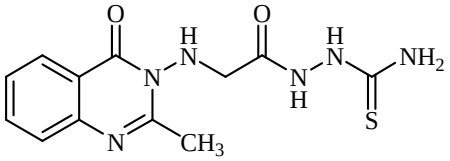
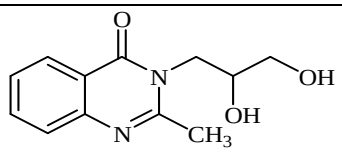
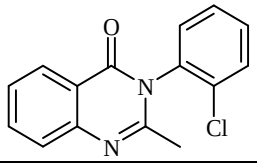
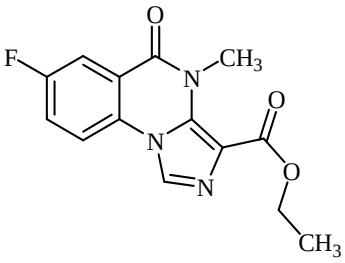
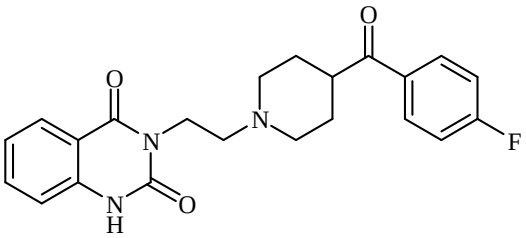
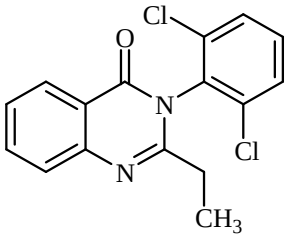
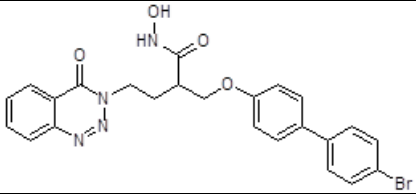
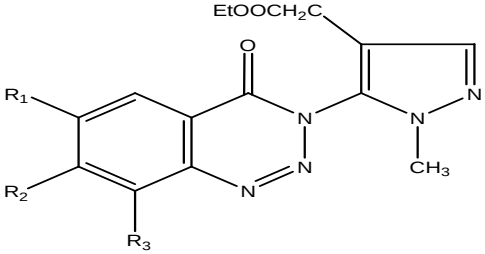


Table 1: Biological Profile of Quinazoline Derivatives.

Sr. No.	Name of drug	Structure of Drug	Biological activity
1	1-[3-Amino acetyl-2- methyl quinazolin-4-onyl]-thio-semicarbazide[4]		Anticonvulsant
2	Diproqualone[5]		Anxiolytic Anti-rheumatic
3	Mecloqualone[6]		Anxiolytic
4	Flumazenil[7]		Benzodiazepine Antagonist
5	Ketanserin[8]		Psychotropic
06	Chloroqualone[9]		Anticancer agent
07	2-(4'-Cyanobiphenyl-4-yloxymethyl)-4-(4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl) butyrohydroxamic acid[10]		Antiarthritic Drugs, Oncolytic Drugs
08	l-methyl-5 [6,7,8-substituted-4(3H) -oxo-1,2,3-benzotriazin-3-yl] - lH-pyrazole-4-acetic acid.[11]		Analgesic, Anti-inflammatory activity

Pharmacological Activity

Convulsion: A CNS disorder

Convulsion is a medical condition where a body muscle is contract and relax rapidly and repeated by resulting in a uncontrolled shaking of the body.

Seizure is a physical findings or changes in behaviour that occur after an episode of abnormal electrical activity in the brain.

Epilepsy (from the Ancient Greek (epilepsia) — "to seize") is a common chronic neurological disorder characterized by recurrent unprovoked seizures.

Anticonvulsants are a diverse group of pharmaceuticals used in the treatment of epileptic seizures.

These seizures are transient signs and/or symptoms of abnormal, excessive or synchronous neuronal activity in the brain.[30] About 50 million people worldwide have epilepsy, with almost 90% of these people being in developing countries. Epilepsy is more likely to occur in young children or people over the age of 65 years, however it can occur at any time. As a consequence of brain surgery epileptic seizures may occur in recovering patients. Epilepsy is usually controlled, but cannot be cured with medication, although surgery may be considered in difficult cases. However, over 30% of people with epilepsy do not have seizure control even with the best available medications.

However these studies may be given the significant risk epileptiform seizures pose to children and the distinct possibility of death and devastating neurological sequela secondary to seizures. Anticonvulsants are more accurately called **antiepileptic drugs** (abbreviated "AEDs"), sometimes referred to as **antiseizure drugs.** While an anticonvulsant is a fair description of AEDs, it neglects to differentiate the difference between convulsions and epilepsy. Convulsive non-epileptic seizures are quite common and these types of seizures will not have any response to an antiepileptic drug. In epilepsy an area of the cortex is typically hyperirritable that can often be confirmed by completing an EEG.

Antiepileptic drugs function to help reduce this area of irritability and thus prevent epileptiform seizures.

1. Types of convulsions

International classification of seizure types

This classification is based on observation (clinical and EEG) rather than the underlying pathophysiology or anatomy.

1.1 Partial seizures (Older term: focal seizures)

A. Simple partial seizures - consciousness is not impaired

B. Complex partial seizures - consciousness is impaired (Older terms:

Temporal lobe or psychomotor seizures)

C. Partial seizures evolving to secondarily generalized seizures

1.2 Generalized seizures

A. Absence seizures (Older term: petit mal)

B. Myoclonic seizures

C. Clonic seizures

D. Tonic seizures

E. Tonic–clonic seizures (Older term: grand mal)

F. Atonic seizures

1.3 Unclassified epileptic seizures

1.4 Phases of convulsion

(1) Tonic flexion: Powerful flexion i.e. bending of fore limbs.

(2) Tonic extension: Firstly force limbs & then hind limbs stretch slowly kward in a powerful, sustained contraction.

(3) Clonic convulsions: Flexor & extensor movements occur alternatively.

Contraction of one set of muscle is followed by relaxation of other, gives rise to jerks.

(4) Stupor: Long term maintenance of animal in same position.

(5) Recovery / Death.

1.5 Etiology of convulsions

The diagnosis of epilepsy usually requires that the seizures occur spontaneously. Nevertheless, certain epilepsy syndromes require particular precipitants or triggers for seizures to occur. These are termed reflex epilepsy. Photosensitive epilepsy can be limited to seizures triggered by flashing lights. Other precipitants can trigger an epileptic seizure in patients who otherwise would be susceptible to spontaneous seizures. Finally, other

precipitants can facilitate, rather than obligately trigger, seizures in susceptible individuals. Emotional stress, sleep deprivation, sleep itself, heat stress, alcohol and febrile illness are examples of precipitants cited by patients with epilepsy. Notably, the influence of various precipitants varies with the epilepsy syndrome.[30] Likewise, the menstrual cycle in women with epilepsy can influence patterns of seizure recurrence.[31] There are different causes of epilepsy that are common in certain age groups.

During late infancy and early childhood, febrile seizures are very common. There may be other causes like CNS infections and trauma. During childhood well defined epilepsy syndromes are generally seen.

During adolescence and adulthood, the causes are more likely to be secondary to any CNS lesion and idiopathic epilepsies are less common. Other causes associated with these age groups are trauma, CNS infections, brain tumours, illicit drug use and alcohol withdrawal. In older adults, cerebrovascular disease is a very common cause. Other causes are CNS tumours, trauma and other degenerative diseases like Alzheimer's are common to the older age group.

Sign and Symptoms of Epilepsy

Epilepsy is characterized by recurrent, disorganized, abnormal electrical firing in brain cells, which can disrupt normal functioning of the brain. This disruption can cause recurrent seizures, which is the main symptom of epilepsy. While these seizures are usually caused by abnormal electrical activity in the brain, they can manifest very differently from person to person. For instance, one type of seizure may cause a brief loss of consciousness, whereas another seizure type may cause uncontrollable jerking of the entire body.

- Weakness
- Anxiety
- Staring
- Purposeless or Repetitive movements
- Loss of consciousness
- Contraction or Jerking of body muscles

1.6 Clinical management of convulsions

Epilepsy is usually treated with medication prescribed by a physician; primary caregivers, neurologists and neurosurgeons all frequently care for people with epilepsy. However, it has been stressed that accurate differentiation between generalized and partial seizures is

especially important in determining the appropriate treatment.[70] In some cases the implantation of a stimulator of the vagus nerve, or a special diet can be helpful. Neurosurgical operations for epilepsy can be palliative, reducing the frequency or severity of seizures; or, in some patients, an operation can be curative.

The goal for individual patients is, of course, no seizures and no side effects and the job of the physician is to aid the patient to find the best balance between the two during the prescribing of anticonvulsants. Most patients can achieve this balance best with mono therapy, the use of a single anticonvulsant medication. Some patients, however, require polypharmacy; the use of two or more anticonvulsants.

Mainly epilepsy is managed or controlled by following ways:

- Surgical treatment
- Other treatment
- Pharmacologic treatment

1.7 Classification of anticonvulsants

In the following list, the dates in parentheses are the earliest approved use of the drug.

I. Aldehydes:

e.g. Paraldehyde

II. Aromatic allylic alcohols:

e.g. Stiripentol

III. Barbiturates:

e.g. Phenobarbital, Methylphenobarbital, Metharbital, Barbexaclone

IV. Benzodiazepines:

e.g. Diazepam, Barbexaclone, Clonazepam, Clorazepate, Lorazepam, Nitrazepam

V. Bromides e.g. Potassium bromide

VI. Carbamates e.g. Felbamate

VII. Carboxamides e.g. Carbamazepine, Oxcarbazepine

VIII. Fatty acids The valproates — valproic acid, sodium valproate and divalproex sodium (1967). e.g. Vigabatrin, Progabide

IX. Fructose derivatives

e.g. Topiramate

X. Gaba analogs

e.g. Gabapentin, Pregabalin

XI. Hydantoins e.g. Ethotoin, Phenytoin, Mephenytoin, Fosphenytoin

XII. Oxazolidinediones

e.g. Paramethadione, Trimethadione, Ethadione

XIII. Propionates e.g. Beclamide

XIV. Pyrimidinediones e.g. Primidone, Pyrrolidines, Brivaracetam, Levetiracetam, Seletracetam

XV. Succinimides e.g. Ethosuximide, Phensuximide, Mesuximide

XVII. Triazines e.g. Lamotrigine

XVIII. Ureas e.g. Pheneturide, Phenacemide

XIX. Valproylamides (amide derivatives of valproate)

e.g. Valpromide, Valnoctamide

1.8 Side effects

In some patients, anticonvulsants may produce usually mild side effects. Headache, nausea, and unusual tiredness and weakness are the most frequently reported side effects of anticonvulsants. Other general side effects of anticonvulsants that do not usually require medical attention include:

- Mild coordination problems
- Mild dizziness
- Abdominal pain or cramping
- Sinus pain
- Sleeplessness or nightmares
- Change in appetite
- Mild feelings of anxiety
- Feeling of warmth
- Tingling or prickly feeing on the skin, or in the toes and fingers
- Mild tremors
- Diarrhoea or constipation
- Eartburn or indigestion
- Aching joints and muscles or chills
- Unpleasant taste in mouth or dry mouth

Many of these side effects disappear or occur less frequently during treatment as the body adjusts to the medication. However, if any symptoms persist or become too uncomfortable, the prescribing physician should be consulted.

Other, uncommon side effects of anticonvulsants can be serious or may indicate an allergic reaction. A patient taking any anticonvulsant who experiences one or more of the following symptoms should contact the prescribing physician immediately:

- Rash or bluish, purplish, or white patches on the skin
- Jaundice (yellowing of the skin and eyes)
- Bloody nose or unusual bleeding
- Hallucinations (seeing visions or hearing voices that are not present)
- Sores in the mouth or around the eyes
- Ringing or vibrations in the ears
- Depression or suicidal thoughts
- Mood or mental changes, including excessive fear, anxiety, hostility
- Severe tremors
- Prolonged numbness in the extremities
- General loss of motor skills
- Persistent lack of appetite
- Altered vision

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