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FIRST LINE AGENTS OF ANTI-EPILEPTIC DRUGs AND IT'S IMPURITIES

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ABSTRACT

Anti-epileptic drugs (AEDs) most commonly used for the treatment of epilepsy. Epilepsy is defined as a chronic neurological condition characterized by recent, unprovoked seizures. First-line drugs of AEDs are Valproic acid(VA), Lamotrigine(LTG), Topiramate(TPM). Lamotrigine is [3,5- diamino-6-(2,3-dichlorophenyl)-as-triazine] contains various impurities 2-[2,3-dichlorophenyl] -2- [guanidiny limino] acetonitrile [Schiff's base], 3- Amino-6-[2,3-dichlorophenyl]-1,2,4-triazin-5(4H)-one [Triazinone impurity], N-[5-Amino-6-[2, 3-dichlorophenyl]-1, 2, 4-triazin-3-yl]-2,3-dichloro benzamide [Mono benzoyl impurity], N-Guanidinyl-2, 3-dichlorobenzamide [Amide impurity], 3, 5-Bis [2,3-dichlorobenzamido]-6-[2,3-dichlorophenyl]-1,2,4-triazine [Dibenzoyl impurity]. Valproic acid is [di-N-propyl acetic acid] contains various impurities Pentanoic acid (valeric acid), (2RS)-2-Ethylpentanoic acid, (2RS)-2-(1-Methylethyl) pentanoic acid, 2, 2-dipropylpentanoic acid, Pentamide (valeramide), 2-Propylpantamide, 2, 2-Dipropylpantanamide. Topiramate is [2,3:4,5-Di-O-isopropylidene-β-D-fructopyranose sulfamate] contains various impurities 2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose, 2,3-O-(1-methylethylidene)-β-D-fructopyranose sulfamic acid, N-[(diethylamino)carbonyl]-2,3:4,5-bis-O-(1-methylethylidene)-β-D fructopyranose sulfamic acid.

Keywords: AEDs, Lamotrigine, Valproic acid, Topiramate and its impurities.

Introduction:

Aim:- The main aim of my review paper is brief knowledge on first line agents of antiepileptic drugs and its impurities along with their structures.

Antiepileptic Drug

AEDs most generally used for the treatment of epilepsy. They assistance switch seizures in around 7 out of 10 people. AEDs effort by altering the stages of chemicals in your brain. They do not treat epilepsy but can break seizures from happening. Common types of AEDs; sodium valproate, carbamazepine, lamotrigine, levetiracetam, topiramate.

New AEDs are better tolerated, have fewer drug interactions.[1] Novel antiepileptic drugs, mainly associated with an inhibition of voltage-dependent sodium channels are lamotrigine and oxcarbazepine.[2] TDM of AEDs is needed to improve the patient's clinical consequence by handling their medication routine through the help of measured drug concentration. The idea is built on the assumption that drug concentration compares well with clinical effects than the dose. TDM is extra significant for drugs by a narrow therapeutic range, where a relationship has been recognized among drug concentration and its therapeutic and toxic effects.[3] Epilepsy is defined as a chronic neurological condition characterized by recent, unprovoked seizures.[4]

Classification of AEDs:-

There are several Antiepileptic drugs approved for the treatment of seizures.[5]

Primary Generalized Tonic-Clonic seizures in that

1. **First–line agents** like Valproic acid, Lamotrigine, Topiramate

2. **Alternative agents** like Phenytoin, Carbamazepine, Phenobarbital

Mechanism of Action of AEDs

Blockade of voltage-gated sodium channels is the utmost common mechanism of action among currently available AEDs.[6] AEDs decrease membrane excitability by interacting with neurotransmitter receptors or ion channels.[7] The therapeutic arsenal for the treatment of seizures has extended significantly over the ancient era. Several of the innovative AEDs have clinical advantages over older, termed 'first-generation' AEDs in that they are additionally expectable in their dose-response profile and characteristically are related with less drug-drug interactions. In addition, many of the newer AEDs also have generation exceptional mechanisms of action related with previously obtainable agents. First-AEDs are proposed to have a combine of primary mechanisms of action. Sodium channel blockade and GABA potentiation equally result in a decrease of neuronal discharge. Additional current AEDs have

provided additional changes in drug targets, for example, specific GABA subunits and synaptic vesicle inhibition. Currently, there are some viable agents in the AED pipeline that extend the spectrum of effective MOA.[8] A combination of AEDs can produce different efficacies and side effects in either an additive, supra-additive or infra-additive fashion.[9]

Lamotrigine (*Lamictal, GlaxoSmithKline*)

Lamotrigine, an AED of the phenyltriazine class, is chemically unrelated to existing AEDs. Its chemical name is 3,5- diamino-6-(2,3-dichlorophenyl)-as-triazine, and its molecular weight is 256.09. (Fig.1)

Indication and Mechanism of Action

It is an effective adjunct to refractory partial and generalized epilepsy.[10] LTG is indicated as ancillary therapy for typical and atypical absence seizure and generalized epilepsy of Lennox–Gastaut syndrome in patients two years of age or older.[11] LTG is considered a broad-spectrum AED.[12]

MOA of lamotrigine is not completely unstated. LTG is a triazine, and examination has revealed that LTG discriminating stick sodium channels, balanced presynaptic neuronal membranes, and prevents glutamate release. Researchers have not confirmed that LTG has substantial effects on other neurotransmitters for example serotonin, norepinephrine, or dopamine. The theory of lamotrigine may interrelate with voltage-activated calcium-gated channels, contributing to its broad range of activity. LTG tails first-order kinetics through a half-life of 29 hours.[13] The other action of LTG, has a broader spectrum of action than other sodium channels AEDs for examples phenytoin.

There are several impurities present in Lamotrigine drug are as follows[14]

1. 2-[2,3-dichlorophenyl] -2- [guanidiny limino] acetonitrile [Schiff's base] (Fig.2)
2. 3- Amino-6-[2,3-dichlorophenyl]-1,2,4-triazin-5(4H)-one
3. N-[5-Amino-6-[2, 3-dichlorophenyl]-1, 2, 4-triazin-3-yl]-2,3-dichloro benzamide [Mono benzoyl impurity] (Fig.4)
4. N-Guanidinyl-2, 3-dichlorobenzamide [Amide impurity] (Fig.5)
5. 3, 5-Bis [2,3-dichlorobenzamido]-6-[2,3-dichlorophenyl]-1,2,4-triazine [Dibenzoyl impurity] (Fig.6)

Valproic Acid (*Depacon, Depakene*)

Valproic acid is also called as carboxylic acid. Its chemical name is di-N-propyl acetic acid, and the molecular weight is 144. (Fig.7)

Indication and Mechanism of Action

Valproic acid's prime use is as an anti-epilepsy medication, as well as in migraine,

mood, and nervousness disorders. Divalproex sodium is useful for treating a

wide range of seizure disorders such as Doose syndromes, absence seizures,

generalized seizures, partial epilepsy, and status epilepticus.[15] Valproate is oneof the most useful drugs against generalized absence epilepsy.[16] Research on the use of valproic acid in cancer therapy is still in its infancy and provides insight into new areas of its application. Also used in prophylaxis of sick headaches and bipolar illness.[17] MOA VA is a branched-chain fatty acid. As with other anticonvulsants, the MOA of valproic acid is not fully understood.[18] VA MOA with respect to its antiepileptic effect is related to increased concentrations of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) within the CNS through inhibition of GABA degradation or enhancement of GABA synthesis and release.[19] VA is approved for almost all types of seizures and is one of the widely used AEDs not only for epilepsy but also as a mood-stabilizing drug.[20] The anti-epileptic effects of valproic acid are complex and involve several MOA. Originally, the main MOA of valproic acid put forward was the inhibition of voltage-gated sodium channels. Valproic acid modulates neuronal hyperexcitability, especially by blocking the T-type calcium channel. The anti-epileptic action of valproic acid also results from its ability to strengthen the inhibitory action of GABA by binding to the GABA-A receptor and by causing an increase in brain concentrations of GABA by a weak inhibition of the two enzymes.[21]There are several impurities present in valproic acids are as fallows[22]

1. Pentanoic acid (valeric acid) (Fig.8)
2. (2RS)-2-Ethylpentanoic acid (Fig.9)
3. (2RS)-2-(1-Methylethyl) pentanoic acid (Fig.10)
4. 2, 2-dipropylpentanoic acid (Fig.11)
5. Pentamide (valeramide) (Fig.12) 6. 2-Propylpantamide (Fig.13)
7. 2, 2-Dipropylpantanamide (Fig.14)

Topiramate (*Topamax, Ortho- McNeil*)

Topiramate is designated chemically as 2,3:4,5-Di-O-isopropylidene-β-D-fructopyranose sulfamate. Its molecular weight is 339.36. (Fig.15)

Indication and Mechanism of Action

Topiramate is a useful adjunct in refractory partial or generalized seizures and other epileptic syndromes. It has demonstrated efficacy as adjunctive therapy in partial seizures[23], intractable seizures[24], Lennox Gastaut syndrome[25], infantile spasms[26], generalized epilepsy of infancy, and myoclonic-astatic epilepsy[27].In contrast to other AEDs, TPM has showed a modulatory outcome on potassium conductance. TPM-induced hyperpolarization and decline in input resistance is due to an increase in potassium conductance.[28] There are essentially four mechanisms by which antiepileptic drugs are believed to act. These are (1) alteration of voltage-gated sodium channels; (2) potentiation of GABA inhibition; (3) modulation of voltage- and receptor gated calcium ion channels; and (4) block of excitatory neurotransmission.[29] Topiramate, through a broad profile of action, might react at dissimilar levels: decreasing nociceptive

transmission through serotonergic alteration, and preventing cortical spreading depression.[30] The anti convulsant activities of TPM differ from those of other anti-epileptic drugs (AEDs) such as phenytoin (PHT) and carbamazepine (CBZ). It does exhibit the property of state and voltage-dependent blockade of neuronal Na^+ channels, as do the others, but in addition, TPM influences the activity of Ca^{2+}, $GABA_A$ receptors.[31]There are several impurities present in topiramate are as fallows[32]

1. 2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose (Fig.16)
2. 2,3-O-(1-methylethylidene)- β-D-fructopyranose sulfamic acid (Fig.17)
3. N-[(diethylamino)carbonyl]-2,3:4,5-bis-O-(1-methylethylidene)- β-D-fructopyranose sulfamic acid. (Fig.18)

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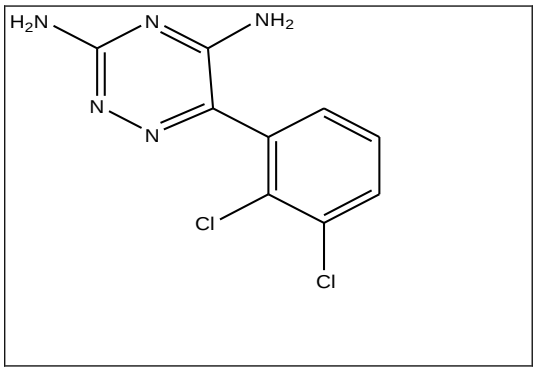
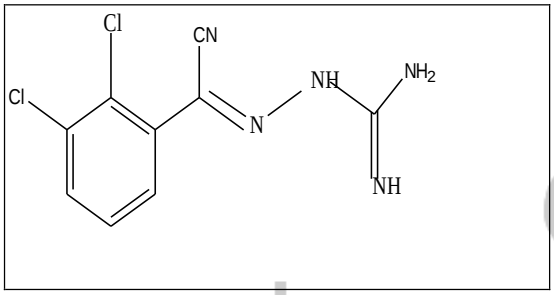
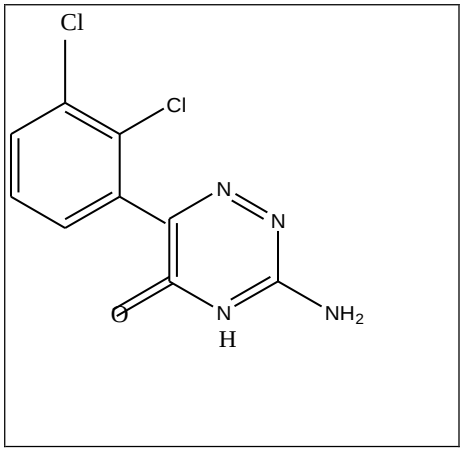
pharmaceutical formulations; JCS. 2016; 54(2):280-290.



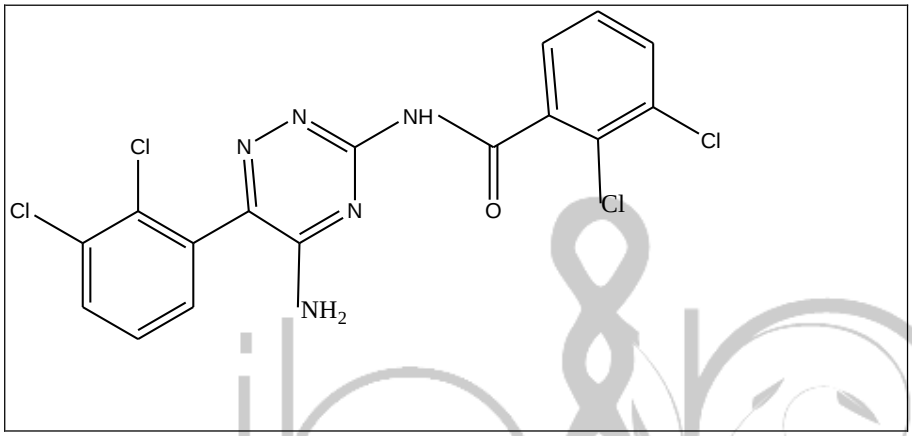
(Figure 1) Lamotrigine



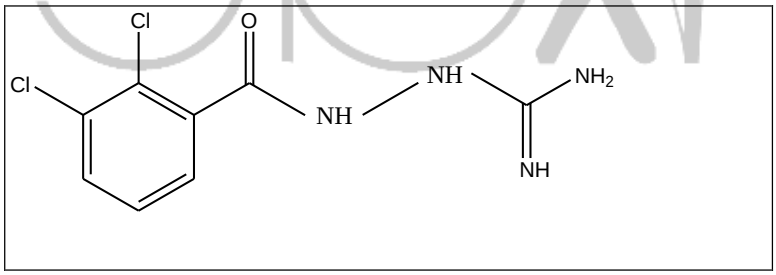
(Figure 2) 2-[2,3-dichlorophenyl] -2- [guanidiny limino] acetonitrile [Schiff's base]



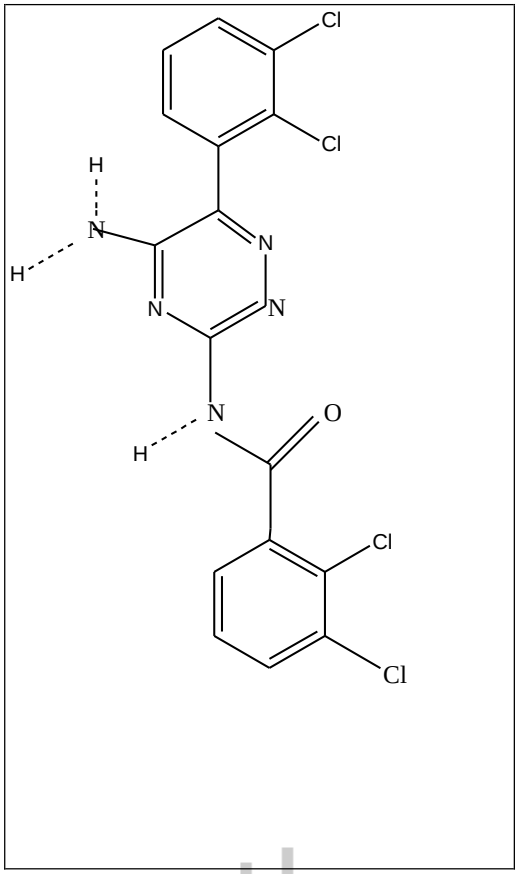
(Figure 3) 3- Amino-6-[2,3-dichlorophenyl]-1,2,4-triazin-5(4H)-one [Triazinone impurity]



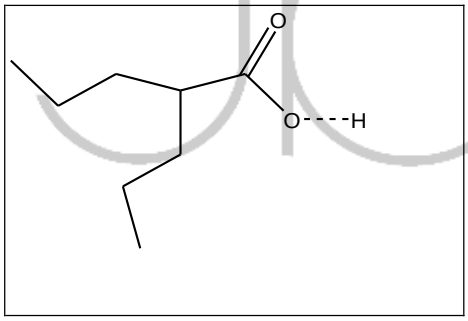
(Figure 4) N-[5-Amino-6-[2, 3-dichlorophenyl]-1, 2, 4-triazin-3-yl]-2,3-dichloro benzamide [Mono benzoyl impurity]



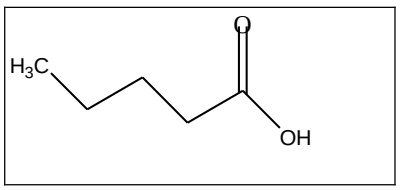
(Figure 5) N-Guanidinyl-2, 3-dichlorobenzamide [Amide impurity]



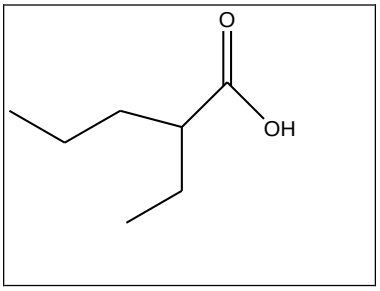
(Figure 6) 3, 5-Bis [2,3-dichlorobenzamido]-6-[2,3- dichlorophenyl]-1,2,4-triazine [Dibenzoyl impurity]



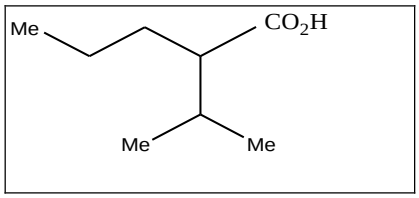
(Figure 7) Valproic acid



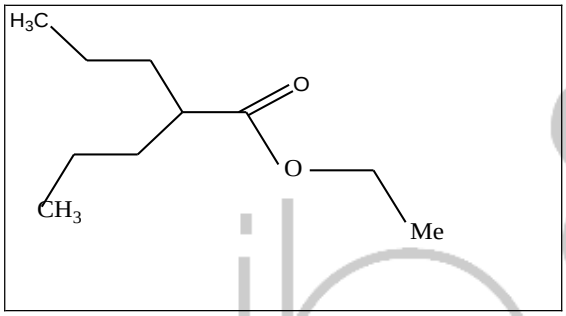
(Figure 8) Pentanoic acid (valeric acid)



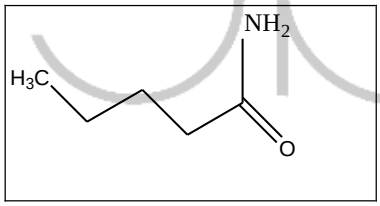
(Figure 9) (2RS)-2-Ethylpentanoic acid



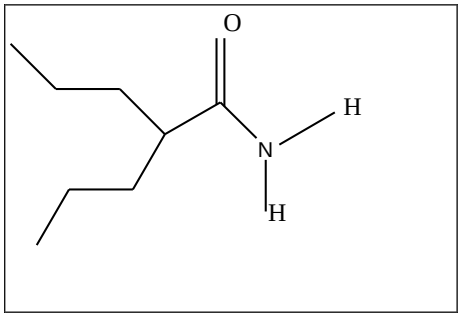
(Figure 10) (2RS)-2-(1-Methylethyl) pentanoic acid



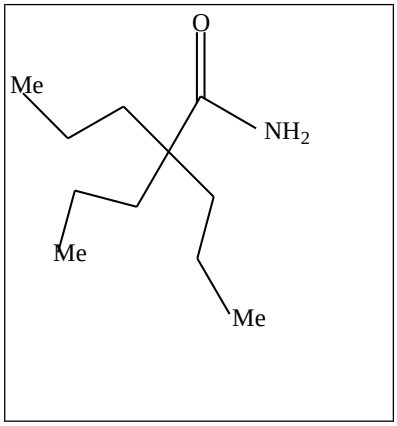
(Figure 11) 2, 2-dipropylpentanoic acid



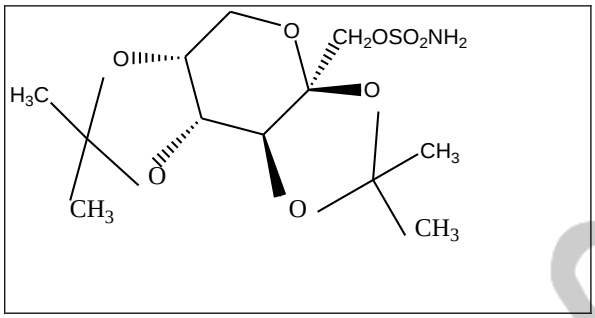
(Figure 12) Pentamide (valeramide)



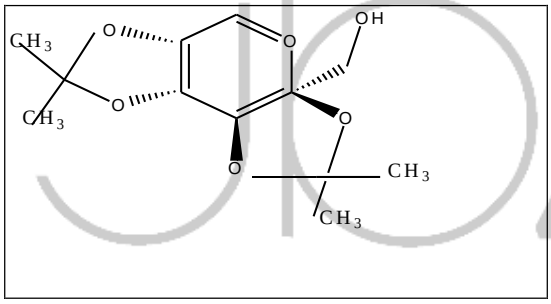
(Figure 13) 2-Propylpantamide



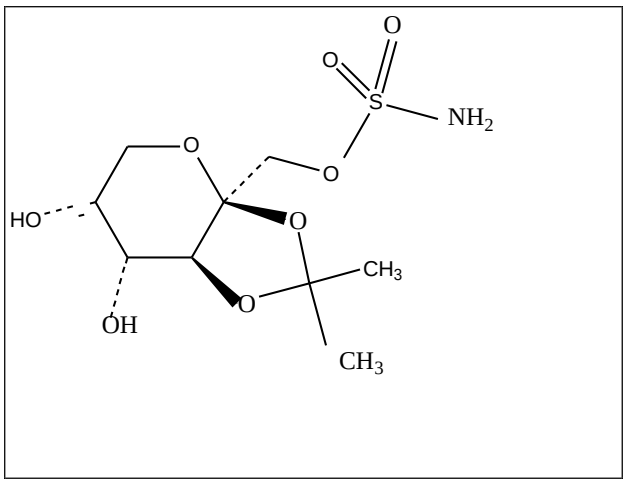
(Figure 14) 2, 2-Dipropylpantanamide



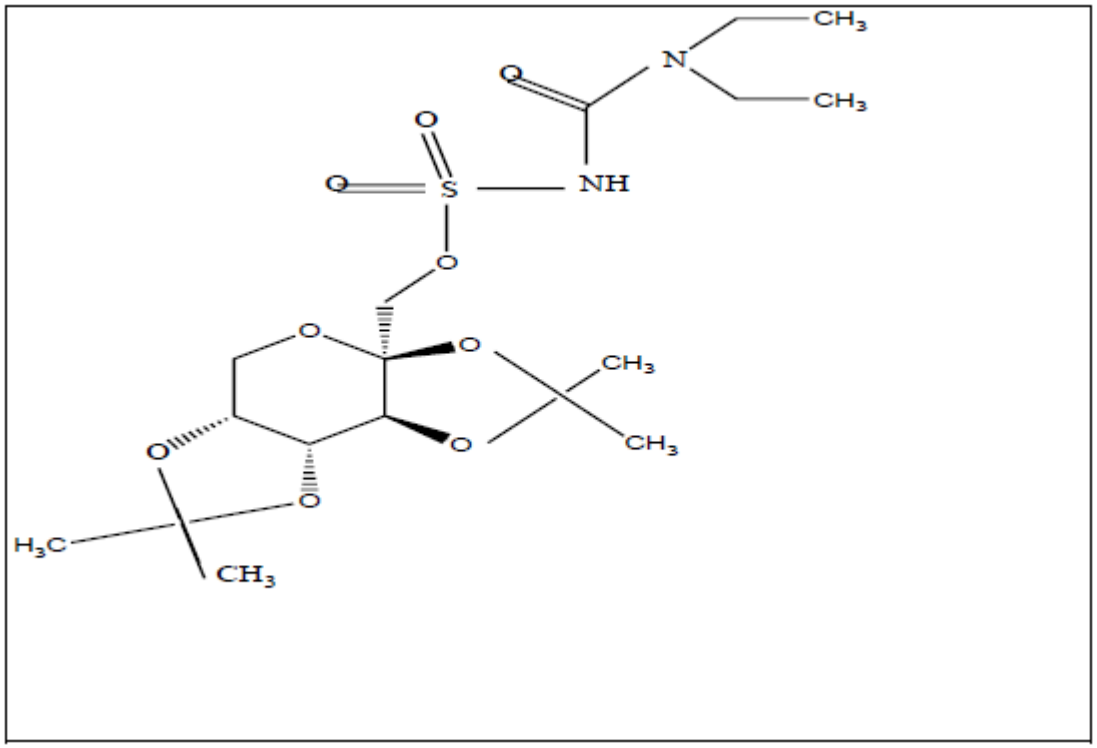
(Figure 15) Topiramate



(Figure 16) 2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose



(Figure 17) 2,3-O-(1-methylethylidene)- β-D-fructopyranose sulfamic acid



(Figure 18) N-[(diethylamino)carbonyl]-2,3:4,5-bis-O-(1-methylethylidene)- β-D-fructopyranose sulfamic acid.