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OXCARBAZEPINE: A COMPUTATIONAL OVERVIEW WITH ITS CURRENT POTENTIAL

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ABSTRACT

The success of carbamazepine as a broad-spectrum anticonvulsant drug has led to its usage as a first line drug in treatment of partial and generalized tonic clonic seizures in children and adults. Due to its adverse effects on CNS and gastrointestinal, hepatic and endocrine disturbances, teratogenic effects, oxcarbazepine was developed to provide a compound chemically similar to carbamazepine which mimics its efficacy and overall safety along with improving its side-effect profile. In comparison to the parent drug, oxcarbazepine shows great reduction in hepatic microsomal enzyme induction as well as in autoinduction. This article gives an insight into various computed and physicochemical properties of oxcarbazepine as well as provides spectral information and predictions to support its structure.

KEYWORDS: Epilepsy, Anticonvulsant, seizures, Spectral information, Oxcarbazepine.

INTRODUCTION

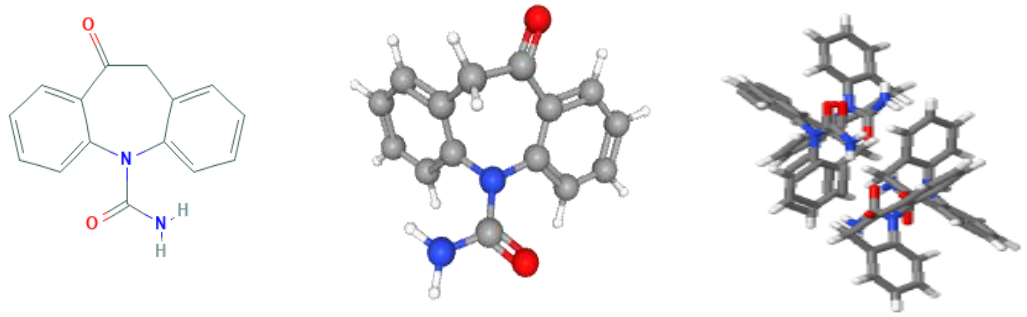
Epilepsy refers to a chronic disorder wherein recurrence of unprovoked seizures takes place. A seizure may be defined as a sudden electrical disturbance in the brain and may be classified as Generalized seizures (whole brain is affected) or Focal/ Partial seizures (a part of the brain is affected).[1] Epilepsy is not a disease, but a syndrome of different cerebral disorders of central nervous system (CNS), which is characterized by paroxysmal, excessive and hyper synchronous discharge of large number of neurons.[2] In an ongoing seizure, a person experiences abnormal behaviors, sensations and symptoms. The symptoms experienced include fatigue, rhythmic muscle contractions or spasms, aura, sensation of pins and needles, amnesia and loss of consciousness.[1] Diagnosis of seizures and type of epilepsy is based upon details including medical history, EEG, blood tests, brain imaging etc. Among the various tests enlisted EEG plays a central role in diagnosis and management of patients with epilepsy as it is an inexpensive and convenient way to determine abnormal cortical excitability which is the root of epilepsy.[3] In India, studies have reported the prevalence rate of epilepsy varying from 1710 to 9780 cases per million population.[4]

The treatment of epilepsy usually begins with medications, which may be followed by surgery or other type of treatments like therapies such as vagus nerve stimulation, ketogenic diet, deep brain stimulation etc.[5] Despite the optimal use of available anti-epileptic drugs (AEDs), many patients with epilepsy fail to experience seizure control and others do so only at the expense of significant toxic effects.[6] The limitations with the conventional AEDs highlighted the need for developing newer agents for epilepsies and the AED search has come a long way, particularly over the last two decades.

The anticonvulsant drug development, since 1993, has led to development of clinically efficient drugs for symptomatic relief of epilepsy such as - Felbamate (1993), Gabapentin (1994), Lamotrigine (1994), Fosphenytoin (1996), Topiramate (1996), Tiagabine (1997), Levetiracetam (1999), Zonisamide (2000) and, Oxcarbazepine (2000).[7] At present the available anticonvulsants do not extend absolute protection in controlling seizures and are linked with undesirable side effects. Therefore, there exists an urgent need for improved new agents for control of seizures.

OXCARBAZEPINE

Oxcarbazepine, having anticonvulsant property, is a dibenzazepine carboxamide derivative. It is a keto analogue of its parent drug carbamazepine, and is used in the therapy of partial seizures, either alone or in combination with other anticonvulsant agents.[8] The molecular structures and brand names (manufacturers) are shown in (Fig. 1, 2), computed and physio-chemical properties are listed in (Table 1, 2).



a) **b)** **c)**

Fig. 1: Oxcarbazepine structure; a) 2D structure; b) 3D structure; c) Crystal structure[8]

IUPAC Name: 5-Oxo-6H-benzo[b][1] benzazepine-1,1-carboxamide.

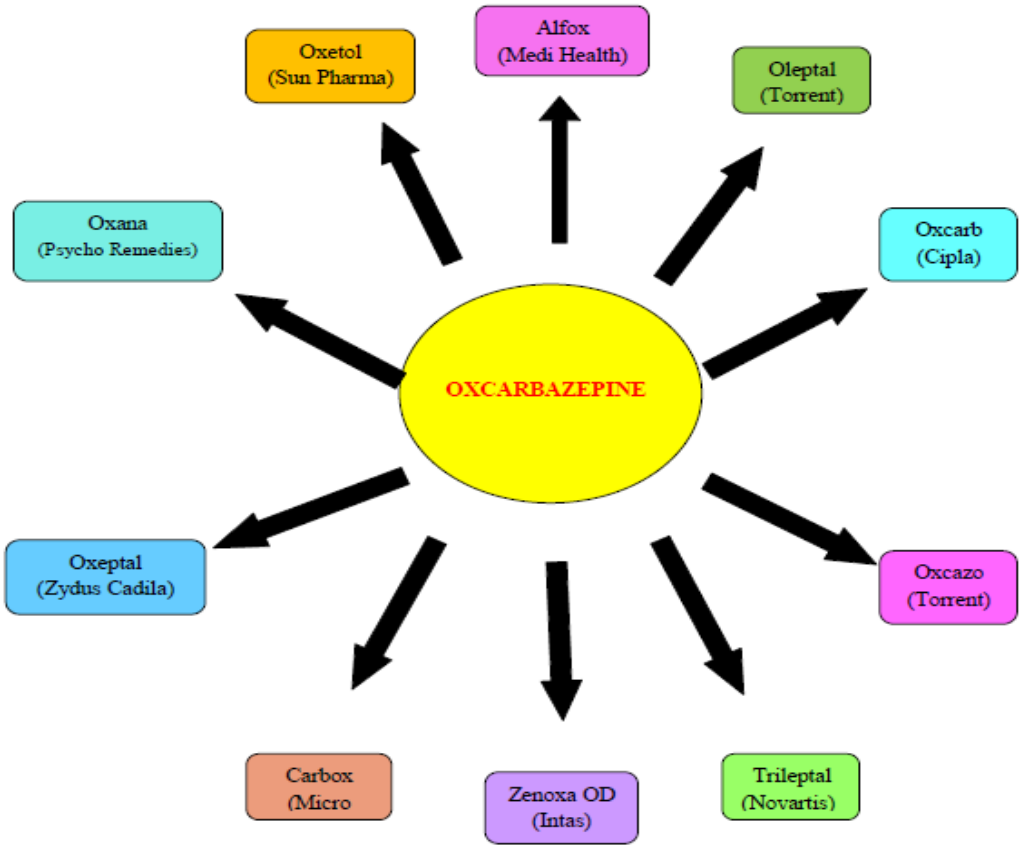
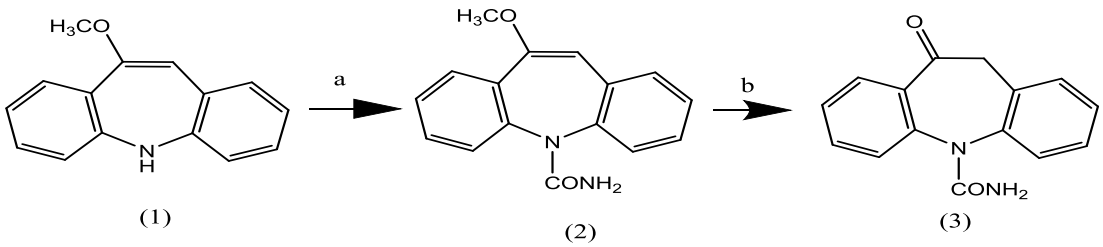


Fig. 2: Brand Names (Manufacturers).



Scheme 1: Synthetic route for oxcarbazepine.

Reagents and conditions: a) Sodium cyanate, Benzoic acid, toluene; b) Toluene, Dil. Hydrochloric acid.

Synthesis: 10-Methoxyiminostilbene (1) on treatment with sodium cyanate in presence of benzoic acid and toluene resulted in presence of benzoic acid and toluene resulted in 10-meth-oxycarbamazepine (2) which on treatment with toluene in dilute HCl gave oxcarbazepine.[9] (Scheme 1)

PHARMACODYNAMICS

Mechanism of Action: Oxcarbazepine is a prodrug and is rapidly converted into its active metabolite, 10-hydroxy derivative. The exact mechanism of action for antiepileptic effect is unclear but is thought to be working through blockade of voltage gated sodium ion channels. The opening and closing of these ion channels control the generation of action potential along a neuron. Thus, oxcarbazepine and its derivative are believed to inhibit these voltage gated sodium ion channels in their inactive states resulting in prolongation of the period for which the receptors remain unavailable for propagation of action potential. This facilitates stabilization of the hyper excited neuronal membranes, resulting in inhibition of neuronal firing causing prevention of seizure activity within the CNS. Anti-epileptic activity of oxcarbazepine is also anticipated to involve increased potassium conductance and modulation of voltage activated calcium channels.[8] (Fig. 3)

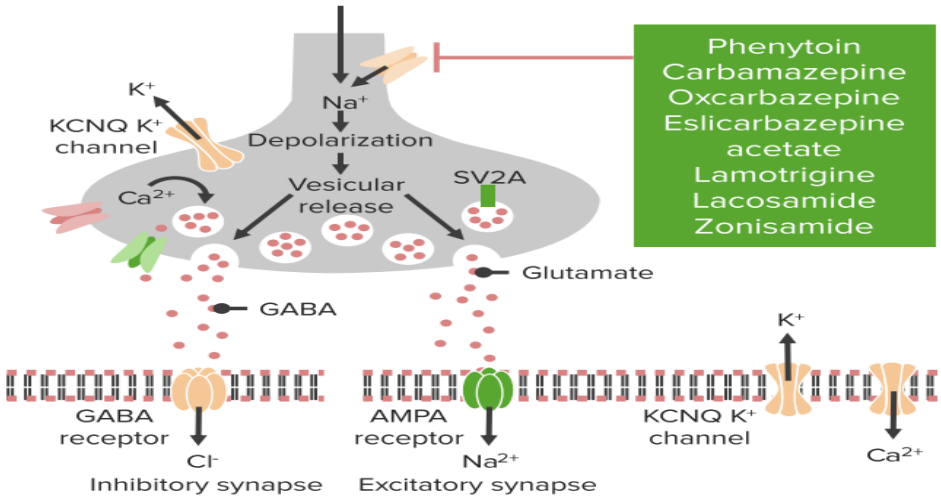


Fig. 3: Mechanism of action.[10]

PHARMACOKINETICS

Absorption

Oxcarbazepine is completely absorbed upon oral administration. A single dose of 600 mg results in a C_{max} value of 34 µmol/L and T_{max} of 4.5 hours of its active metabolite. Food does not affect its rate and extent of absorption. The bioavailability of its oral formulation is high. At constant state the peak concentration of the active metabolite is reached in 2 to 4 hours of drug administration. The plasma half-life of oxcarbazepine is around 2 hours whereas that of MHD is 8 - 10 hours.

Distribution

The detectable volume of distribution of oxcarbazepine is 49L whereas that of distribution of (R)- and (S)- forms of active metabolites are 31.7L and 23.6L respectively. The plasma clearance of oxcarbazepine is approximately 84.9L/h and that of its active metabolite is 2L/h. The plasma protein binding of the metabolite is 40%.

Metabolism

Oxcarbazepine is rapidly metabolized to its primary active metabolite, Monohydroxy derivative (MHD) which is produced through reduction by several enzymes of aldo-keto reductase group of cytosolic liver enzymes. This primary metabolite is important for majority of antiepileptic activity. It remains in plasma as racemate in an approx. ratio of 80% (S)- to 20%(R)-MHD. It further undergoes glucuronide conjugation to form metabolites for excretion and a small amount is oxidized to 10,11-dihydro-10,11-dihydroxycarbamazepine (DHD) as an inactive metabolite.

Excretion

More than 95% of Oxcarbazepine is present in urine with 1% as unchanged form. Almost 80% of the administered dose is excreted in urine as 49% of MHD glucuronide metabolites or 27% of unchanged MHD and 3% inactive DHD metabolite, 13% is conjugated oxcarbazepine and 1% unchanged parent drug. Less than 4 to 5 % goes through fecal elimination.

Side effects and toxicity[11]

1. Dizziness or drowsiness
2. Balance or co-ordination problems
3. Tremors or shaking
4. Hepatotoxicity
5. Neurotoxicity

Table 1: Computed Properties.[8]

S.No.	Properties*	Values*
1.	Molecular Formula	$C_{15}H_{12}N_2O_2$
2.	Molecular weight	252.27
3.	X LogP3-AA	1.7
4.	Hydrogen bond donor count	1
5.	Hydrogen bond acceptor count	2
6.	Rotatable Bond count	0
7.	Exact Mass	252.089877
8.	Monoisotopic Mass	252.089877
9.	Topological polar surface area	63.4Å^2
10.	Heavy atom count	19
11.	Formal charge	0
12.	Complexity	382
13.	Isotope atom count	0
14.	Defined atom stereocenter count	0
15.	Undefined atom stereocenter count	0
16.	Defined bond stereocenter count	0
17.	Undefined bond stereocenter count	0
18.	Covalently bonded unit count	1
19.	Compound is canonicalized	Yes

*Properties and values obtained from PubChem.

Table 2: Physio-chemical Properties.[8]

S.No.	Properties*	Values*
1.	Physical state	Solid
2.	Color/ form	White to faintly orange crystalline powder
3.	Melting point	215.5°C
4.	Solubility	Slightly soluble in chloroform, dichloromethane, acetone and methanol and practically insoluble in ethanol, ether and water
		7.6x10^{-9} mm Hg at 25°C
		1.5
5.	Vapor pressure	13.73
6.	Log P	153.8 Å^2
7.	pKa	1. Henry's law constant = 6.9 x 10^{-13} atm-cu m/mol at 25°C
8.	Collision cross section	2. Hydroxyl radical reaction rate constant = 2.8 x 10^{-11} cu
9.	Other experimental properties	cm/moles-sec at 25°C

*****Properties and values obtained from PubChem.

SPECTRAL INFORMATION

The IR values were theoretically deduced based on the structure of Oxcarbazepine. The hypothetical ^{1}H NMR and ^{13}C NMR spectrum was computed by ChemDraw Professional 16.0 (Fig. 4, 5). MS by King Draw chemical structure Editor version 2.5.4. (Fig. 6)

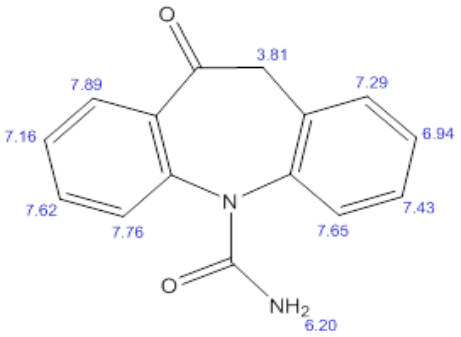


Fig. 4: ChemNMR ^{1}H Estimation.

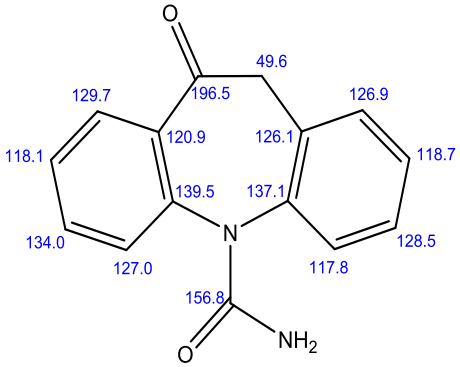


Fig. 5: ChemNMR ^{13}C Estimation.

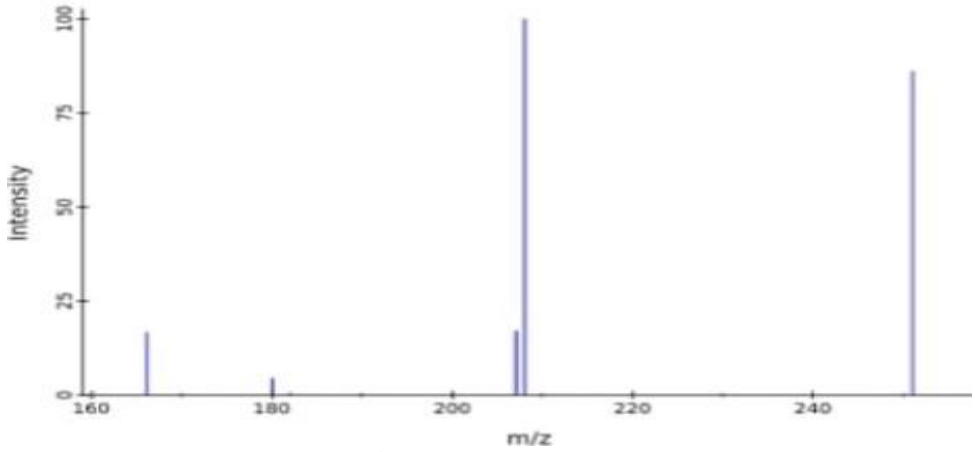


Fig. 6: Mass spectrum.

IR (KBr, cm^{-1}): 3350 (NH), 3030 (CH – Ar), 2020 (C – N), 1660 (C = O); ^{1}H NMR (300 MHz, DMSO, δ ppm): 3.81(s, 2H, CH_2), 6.20(bs, 2H, NH_2), 6.94 – 7.89(m, Ar – H); ^{13}C NMR (75 MHz, DMSO, δ ppm): 49.6, 117.8, 118.1, 118.7, 120.9, 126.1, 126.9, 127.0, 128.5, 129.7, 134.1, 137.1, 139.5, 156.8, 196.5; LCMS (m/ z): 251.08[M – H] –.

CURRENT POTENTIAL

Oxcarbazepine is a derivative of carbamazepine having a ketone substitution on 10^{th} position of dibenzoazepine ring. The drug is more efficacious in treatment of neuropathic pain in comparison to other antiepileptic drugs (AEDs), especially carbamazepine. Current evidence on Oxcarbazepine indicated it to possess analgesic potency, fewer drug to drug interaction, no air to induction of metabolism, improved tolerability by patients with better safety profile.[12]

Monotherapy with Oxcarbazepine is a suitable substitute for treatment of partial and generalized tonic – clonic seizures. The drug is also effectual in treatment of refractory partial seizures. It has been also reported that the use of Oxcarbazepine resulted in enhanced cognition and alertness in epileptic patients.[13,14] All these beneficial effects constitute to be a choice of drug in epilepsy.

CONCLUSION

Oxcarbazepine, a structural derivative of carbamazepine, is a valuable alternative where patients do not tolerate carbamazepine or suffer drug interactions. The beneficial pharmacokinetic properties and therapeutic potential of oxcarbazepine over other antiepileptic drugs, especially carbamazepine, favors to rate it as first line agent in the treatment of epileptic disorders. The computational study will be further useful for QSAR analysis.

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