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CHEMISTRY AND PATHOPHYSIOLOGY OF 1-(1,2-BENZISOXAZOL-3-YL) METHANESULFONAMIDE

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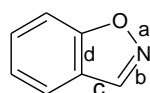
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Abstract: Zonisamide is a sulfonamide anticonvulsant approved for use as an adjunctive therapy in adults with partial-onset seizures. This may be a carbonic anhydrase inhibitor although this is not one of the primary mechanisms of action. This may act by blocking repetitive firing of voltage-gated sodium channels leading to a reduction of T-type calcium channel currents, or by binding allosterically to GABA receptors. This latter action may inhibit the uptake of the inhibitory neurotransmitter GABA while enhancing the uptake of the excitatory neurotransmitter glutamate. It is a synthetic 1,2-benzisoxazole-3-methanesulfonamide with anticonvulsant properties. The sulfamoyl group on zonisamide was expected to suppress seizures in a manner similar to another sulfonamide analogue, acetazolamide, through inhibition of carbonic anhydrase. However, this does not appear to be the primary mechanism of action since zonisamide requires much higher doses than acetazolamide to achieve equivalent titration in-vivo.

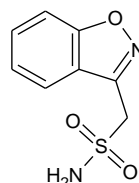
Studies with cultured neurons indicate that zonisamide blocks repetitive firing of voltage-sensitive sodium channels and reduces voltage-sensitive T-type calcium currents without affecting L-type calcium currents. Its dual mechanism of action may explain its efficacy in patients resistant to other antiepileptic drugs (AEDs). Zonisamide has a pharmacokinetic profile favorable for clinical use. It is rapidly and completely absorbed and has a long half-life (63–69 h in healthy volunteers) which allows twice-daily, or even once-daily, dosing. Zonisamide is not highly bound to plasma proteins. Consequently, it does not affect protein binding of other highly protein-bound AEDs. Furthermore, zonisamide does not induce its own metabolism and does not induce liver enzymes. However, since zonisamide is metabolized by cytochrome P450, liver enzyme-inducing AEDs will increase zonisamide clearance, and dosage adjustments may be necessary when it is used in combination with certain AEDs.

Keywords: sulphonamide, benzisoxazole, anticonvulsant, GABA receptor, AED

Chemistry: Zonisamide: CAS Registry Number: 68291-97-4. CA Index Name: 1,2-Benzisoxazole-3-yl methanesulfonamide. Zonisamide is benzo[d]isoxazol-3-yl methanesulfonamide moiety in which benzene ring is fused with isoxazole heterocyclic ring which is also called as 1,2-benzoxazole. Oxygen and Nitrogen hetero atoms are when placed in five-member ring that is called as oxazole in 1,3 position and when placed in 1,2 position that is called as isoxazole ring.^[1]



1,2-benzoxazole

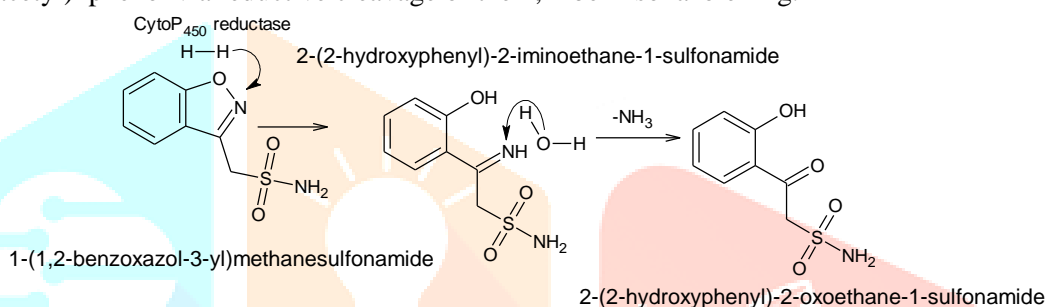


1-(1,2-benzoxazol-3-yl)methanesulfonamide

Face [d] of five membered heterocyclic ring is fused with one face of benzene ring so in nomenclature benzo[d]isoxazole is mentioned. Since the numbering in heterocyclic ring starts from the rule of oxa/thia/aza for Oxygen/Sulfur/Nitrogen so numbering starts from oxygen atom and hence the IUPAC becomes benzo[d]isoxazol-3-ylmethanesulfonamide. It has melting point: 161–163°C. It has water solubility: 0.8 mg/mL, LogP=0.5, pKa=10.2 (basic). Molecular Formula: C₈H₈N₂O₃S; Formula Weight: 212.22gm; Composition: C(45.28%), H(3.80%), N(13.20%), O(22.62%) S(15.11%)

Absorption: Variable, yet relatively rapid rate of absorption with a time to peak concentration of 2.8–3.9 hours. Bioavailability is close to 100% and food has no effect on the bioavailability of zonisamide but may affect the rate of absorption.^[2]

Metabolism: Zonisamide is metabolized mostly by the CYP3A4 isoenzyme, but also CYP3A7 and CYP3A5, to 2-(sulphamoylacetyl)-phenol via reductive cleavage of the 1,2-benzisoxazole ring.



Zonisamide molecule gets enzymatic reductive cleavage at O–N bonding of heterocyclic ring and after cleavage oxo moiety is converted into phenol [–OH] moiety, azo part of heterocyclic ring after cleavage becomes imino [C=NH] moiety which after hydration reaction becomes keto [C=O] and forms 2-(sulphamoylacetyl)-phenol [2-(2-hydroxyphenyl)-2-oxoethane-1-sulfonamide]. Zonisamide has logP= –0.1 and metabolised product has logP=0.49. So the polarity of drug changes from –0.1 to 0.49]

Pharmacokinetics: Zonisamide is rapidly and completely absorbed, with peak plasma concentrations occurring 2–4 h following 100– to 400 mg oral doses in healthy volunteers. The mean plasma elimination half-life is long—about 60 h in noninduced subjects after single and multiple doses, with ranges from 52 to 69 h reported.

Steady state plasma concentrations of zonisamide in placebo-controlled studies ranged from 1.9 to 55.3 µg/mL (median, 18 µg/mL) after 10–12 days of dosing. The plasma or serum levels of zonisamide have been shown to be linearly dose-related in adult and pediatric patients.^[3]

At zonisamide concentrations of 1.0–7.0 µg/mL, the drug is only about 40% bound to human plasma proteins. However, zonisamide has a high binding affinity for red blood cells (RBCs), and a marked concentration of zonisamide is observed in human red blood cells. The affinity of zonisamide for RBCs is 8 times higher than that for plasma proteins, and is dependent on the extracellular concentration of zonisamide. For plasma concentrations >5 µg/mL, the zonisamide plasma versus erythrocyte concentration relationship appears to be relatively linear due to a dominant passive-diffusion distribution process. Zonisamide undergoes acetylation to form N-acetyl zonisamide, and reduction to form the open ring metabolite, 2-sulfamoylacetyl phenol (SMAP)

Mode of action: Zonisamide is an antiseizure drug chemically classified as a sulfonamide and unrelated to other antiseizure agents. The precise mechanism by which zonisamide exerts its antiseizure effect is unknown, although it is believed that the drug blocks sodium and T-type calcium channels, which leads to the suppression of neuronal hypersynchronization (that is, seizure-form activity). It is also known to be a weak carbonic anhydrase inhibitor (similarly to the anticonvulsant topiramate). It is also known to modulate GABAergic and glutamatergic neurotransmission. It has half-life=63 hours.^[4]

The anticonvulsant activity of zonisamide, which shares pharmacological properties with phenytoin, carbamazepine, and sodium valproate, has been demonstrated in many animal and cultured neuron models, as well as in clinical studies. Like phenytoin and carbamazepine, zonisamide blocks the spread or propagation of seizure discharges. Zonisamide has been shown to prevent the tonic extensor components of maximal electroshock seizures in mice, rats, rabbits, and dogs; restrict the spread of focal seizures evoked by electrical stimulation of the visual cortex in cats; and prevent the propagation of seizures from the cortex to subcortical structures, which are evoked by cortical freezing in cats, and by electrical stimulation in visual cortex-kindled cats.^[5]

It is believed that zonisamide's effect on the propagation of seizure discharges involves blocking the repetitive firing of voltage-sensitive sodium channels, and reducing voltage-sensitive T-type calcium currents without affecting L-type calcium currents. These mechanisms stabilize neuronal membranes and suppress neuronal hypersynchronization, leading to the suppression of partial seizures and generalized tonic-clonic seizures in humans. Zonisamide possesses mechanisms of action that are similar to those of sodium valproate, e.g., suppression of epileptogenic activity and depression of neuronal responses. These mechanisms are thought to contribute to the suppression of absence and myoclonic seizures. Since zonisamide has a sulfamoyl group on its side chain, it was anticipated that the drug might exert its anticonvulsant effects in a manner similar to the related compound acetazolamide, which inhibits seizure activity, i.e. via inhibition of carbonic anhydrase. However, when zonisamide was compared with acetazolamide in vivo, zonisamide had only weak carbonic anhydrase inhibiting activity, requiring 100–1000 times higher doses than acetazolamide to achieve equivalent inhibition. Thus, carbonic anhydrase inhibition was ruled out as the primary mechanism of action of zonisamide. The presence of a methylene group on zonisamide's side chain may explain the differences in carbonic anhydrase inhibition. Unlike some other AEDs, zonisamide does not appear to affect the synaptic activity induced by γ -aminobutyric acid (GABA) or glutamate, as do other AEDs.^[6]

In summary, zonisamide is believed to exert anticonvulsant effects by blocking sustained, repetitive neuronal firing via a blockade of voltage-sensitive sodium and by reducing voltage-sensitive T-type calcium channels. Zonisamide has no effect on neuronal responses to GABA or glutamate, and its activity is not due to carbonic anhydrase inhibition.^[7]

Clearance: (a) 0.30 – 0.35 mL/min/kg [patients not receiving enzyme-inducing antiepilepsy drugs (AEDs)]

(b) 0.35 – 0.5 mL/min/kg [Concomitant administration of phenytoin and carbamazepine]

Toxicity: Symptoms of overdose include diminished breathing, loss of consciousness, low blood pressure, and slow heartbeat.

Drug interactions: Since zonisamide is not highly bound to plasma proteins, it does not affect protein binding of other highly protein-bound AEDs. Protein binding of zonisamide is unaffected in the presence of therapeutic concentrations of phenytoin, phenobarbital, or carbamazepine.^[8-9]

Since zonisamide is metabolized by the cytochrome P450 3A4, other drugs that induce or inhibit this enzyme may induce or inhibit zonisamide metabolism. Concomitant administration of phenytoin and carbamazepine increases zonisamide clearance from 0.32 to 0.51 mL/(min kg). The plasma elimination half-life of zonisamide is decreased to 27 h by phenytoin, to 38 h by phenobarbital and carbamazepine, and to 46 h by sodium valproate. The differential effects of phenytoin and carbamazepine were also documented in a study where zonisamide was administered to patients receiving phenytoin or carbamazepine as monotherapy. The area under the curve (AUC) of zonisamide was 20% higher in the carbamazepine group compared to the phenytoin group.^[10,11]

Conclusion: The pharmacokinetic profile of zonisamide is favorable for clinical treatment of seizures. Zonisamide is rapidly and completely absorbed. Its long plasma elimination half-life allows for twice-daily, or even once-daily, dosing. Its dual mechanism of action may account for its efficacy in patients resistant to other AEDs. Zonisamide does not affect protein binding of other highly protein-bound AEDs, such as phenytoin or carbamazepine. However, liver enzyme-inducing AEDs (such as phenytoin, carbamazepine, sodium valproate, or phenobarbital) will increase the plasma clearance of zonisamide, shorten its half-life, and lower its concentration/dose ratio. Therefore, dosage adjustments may be necessary to maintain therapeutic levels of the drug when it is used in combination with certain AEDs.

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Reference:

1. Grover ND, Limaye RP, Gokhale DV, Patil TR (2013). "Zonisamide: a review of the clinical and experimental evidence for its use in Parkinson's disease". *Indian Journal of Pharmacology*. 45 (6): 547–55.
2. Murata M, Hasegawa K, Kanazawa I (2007). "Zonisamide improves motor function in Parkinson disease: a randomized, double-blind study". *Neurology*. 68 (1): 45–50.
3. Grover ND, Limaye RP, Gokhale DV, Patil TR (2013). "Zonisamide: a review of the clinical and experimental evidence for its use in Parkinson's disease". *Indian Journal of Pharmacology*. 45 (6): 547–55.
4. Matsunaga S, Kishi T, Iwata N (2017). "Combination Therapy with Zonisamide and Antiparkinson Drugs for Parkinson's Disease: A Meta-Analysis". *Journal of Alzheimer's Disease: JAD*. 56 (4): 1229–1239.
5. Iwata Y, Irie S, Uchida H, Suzuki T, Watanabe K, Iwashita S, Mimura M (2012). "Effects of zonisamide on tardive dyskinesia: a preliminary open-label trial". *Journal of the Neurological Sciences*. 315 (1–2): 137–40.
6. Gadde KM, Franciscy DM, Wagner HR, Krishnan KR (2003). "Zonisamide for weight loss in obese adults: a randomized controlled trial". *Jama*. 289 (14): 1820–5.
7. Hasegawa H (2004). "Utilization of zonisamide in patients with chronic pain or epilepsy refractory to other treatments: a retrospective, open label, uncontrolled study in a VA hospital". *Current Medical Research and Opinion*. 20 (5): 577–80.
8. Bookheimer S, Schrader LM, Rausch R, Sankar R, Engel J (2005). "Reduced anesthetization during the intracarotid amobarbital (Wada) test in patients taking carbonic anhydrase-inhibiting medications". *Epilepsia*. 46 (2): 236–43.
9. Nakasa H, Nakamura H, Ono S, Tsutsui M, Kiuchi M, Ohmori S, Kitada M (1998). "Prediction of drug-drug interactions of zonisamide metabolism in humans from in vitro data". *European Journal of Clinical Pharmacology*. 54 (2): 177–83.
10. Stiff DD, Robicheau JT, Zemaitis MA (1992). "Reductive metabolism of the anticonvulsant agent zonisamide, a 1,2-benzisoxazole derivative". *Xenobiotica; The Fate of Foreign Compounds in Biological Systems*. 22 (1): 1–11.
11. Hemant Shah, Khushbu K. Patel, Pruthviraj Chaudhary and Dr. C. N. Patel (2020). Stability indicating analytical method development and validation for estimation of zonisamide in pharmaceutical dosage form, 9(5): 1204-1215.