Discovery of lesser neurotoxic and effective anticonvulsant agents active in four animal models of seizure

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Background and Objective: Epilepsy is the most common primary neurological disorder known, affecting 0.4-0.8% of the population and up to 50 million people worldwide.[1] Aryl semicarbazones have documented increasing advances in antiepileptic drug design and were found to act by blocking the voltage-gated sodium ion channels.[2] They do not possess the dicarboximide group as found in conventional drugs like barbiturates, hydantoins and oxazolidinediones which may be associated with toxicity and side effects. Hence, the main objective of the present work is to design and synthesize novel aryl semicarbazones with potential anticonvulsant activity with lesser neurotoxicity.

Methods: A series of disubstituted aryl semicarbazones were prepared and characterized using spectral data. The compounds were screened for anticonvulsant properties in the maximal electroshock seizure (MES), subcutaneous pentylenetetrazole (scPTZ), strychnine (scSTY) and picrotoxin (scPIC) seizure threshold tests in mice. Neurotoxicity was determined using the rotorod test in mice. The compounds were also studied for behavioral despair and depression using actophotometer and porsolt's swim pool test respectively.

Results: All of the compounds showed anti-MES activity. In particular, seven compounds emerged as wide-spectrum active anticonvulsants being active in all the four animal models of seizure. The ED_{50} of the most potent compound was 17.74 ± 1.66 mg/kg. These compounds were also found to be less neurotoxic (TD_{50} > 300 mg/kg) compared to the standard anticonvulsant agents.

Conclusion: Overall, the experimental findings demonstrate the wide-spectrum anticonvulsant activity and lesser neurotoxicity of the reported aryl semicarbazones. Some prototypes also showed lesser central nervous system side effects.

References

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