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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and characterization of novel conjugates of 4-[3-(aryl/heteroaryl)-3-oxo-propenyl]-benzaldehyde with thiazole and thiazolidinones as possible voltage-gated sodium channel blockers

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Abstract A series of chalcones of thiazole and thiazolidinone (**3a–3j**) were synthesized, characterized and evaluated for anticonvulsant activity. The structures of all the new synthesized compounds were established by spectral and elemental analysis. The anticonvulsant activity was performed by maximal electroshock seizure (MES) in mice, and all the derivatives were found to be active. The compounds investigated for their ability to prevent chemically (isoniazid) induced seizures, when compared with phenytoin and diazepam. Results of the anticonvulsant activity revealed that among all the synthesized compounds, naphthalene and halo (4-fluoro-phenyl)-substituted ring serves as the lipophilic aryl portion. Thus, compound **3c** (95.61 % inhibition of the convulsions) and **3b** (66.07 % inhibition of the convulsions), with log *P* values of 3.40 and 2.70, respectively, exhibited potential anticonvulsant activity in MES and isoniazid-induced convulsion model at a dose of 50 mg/kg, respectively. Compound **3c** was also found to be least hydrolysed (1.92 %) in simulated gastric fluid (SGF). Thus, hydrolysis and most lipophilic character of compound **3c** made it a potent member of the series. Results showed that all the derivatives were more effective against MES model than isoniazid (INH) model. It can be promulgated that these compounds may act bind preferentially to the inactive form of the voltage-gated sodium channels (VGSCs) through blocking sustained high-frequency repetitive firing of action potentials, similar to phenytoin. Compound 3-(4-{[4-(4-methoxy-phenyl)-thiazol-2-yl]-hydrazonomethyl}-phenyl)-1-naphthalen-2-yl-propenone (**3c**) was found to be almost equipotent to phenytoin (97.32 % inhibition of the convulsions) in the MES model.

Keywords Chalcones · Conjugates · Thiazole · Thiazolidinone · MES · INH

Introduction

It is estimated that up to 28–30 % of patients are poorly treated with the available antiepileptic drugs (AEDs) (Tripathi *et al.,* 2011). Also, their use is often limited by adverse effects such as drowsiness, ataxia, gingival hyperplasia, hirsutism, gastrointestinal disturbance, hepatotoxicity and megaloblastic anaemia and even life-threatening condition (Siddiqui *et al.,* 2010). During the past decade, several new drugs were approved, e.g. felbamate, fosphenytoin, gabapentin, lamotrigine, vigabatrin and zonisamide. The search for new anticonvulsant drugs continues to be an active area of investigation in medicinal chemistry (Aggarwal and Mishra, 2005). Chalcones are natural biocides (Karthikeyan *et al.,* 2007) and are unique templates, with an aromatic ketone that forms the central core for a variety of important biological compounds (Singh *et al.,* 2011). One of the main objectives of organic and medicinal chemistry is the design, synthesis and production of molecules having value as human therapeutic agents (Verma and Saraf, 2008).

Thiazoles are important nitrogen–sulphur containing five-membered, heterocyclic compounds. Their chemistry has recently received considerable attention as precursors, thus making them useful materials in drug research. The diverse

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