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ABSTRACT BOOK

SYNTHESIS AND PHARMACOLOGICAL CHARACTERIZATION OF CONFORMATIONALLY RESTRICTED RETIGABINE ANALOGUES AS NOVEL NEURONAL KV7 CHANNELS ACTIVATORS

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The Kv7 K^+ channels play a fundamental role in controlling neuronal excitability, representing an attractive pharmacological target for the treatment of different neurological disorders, particularly epilepsy.[1,2] Retigabine, the only antiepileptic drug approved for human use, acts as Kv7.2/7.3 agonist. However, it has been withdrawn from the market due to the formation of unsafe oxidized metabolites.[3] In order to improve both chemical and metabolic stability, we designed and synthesized three series of conformationally restricted analogues of retigabine (Figure 1). The pharmacological effects of these series were investigated by electrophysiological and patch-clamp experiments. The indole-based derivatives **23a** (EC_{50} = 0.08 ± 0.04 μM) and **24a** (EC_{50} = 0.63 ± 0.07 μM) acted as potent Kv7.2 agonists with improved potency and efficacy than retigabine (EC_{50} = 0.93 ± 0.43 μM).

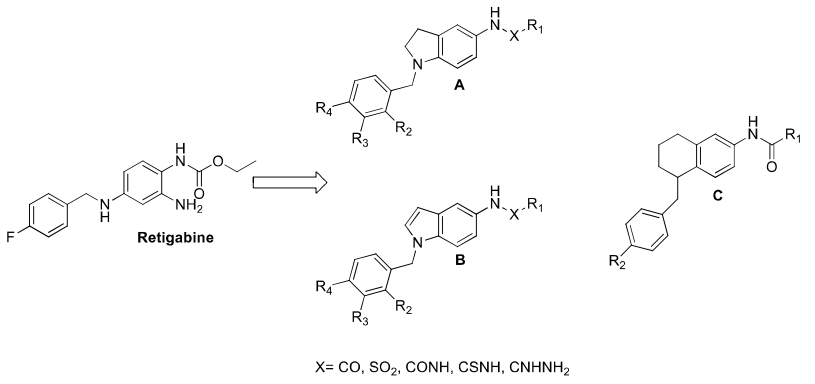

Figure 1. Design and synthesis of conformationally restricted analogues of retigabine.

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