EVALUATION OF ANTICONVULSANT ACTIVITY OF BIS-(3-ARYL-3-OXO-PROPYL)ETHYLAMINE HYDROCHLORIDES AND 4-ARYL-3-ARYLCARBONYL-1-ETHYL-4-PIPERIDINOL HYDROCHLORIDES

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Anticonvulsant activity of bis-Mannich bases, bis (3-aryl-3-oxo-propyl)ethylamine hydrochlorides ¹, ², and their corresponding structural and non-classical isomers, 4-aryl-3-arylcarbonyl-1-ethyl-4-piperidinols ³, ⁴ was evaluated. Alterations in anticonvulsant activity depending on modifications in chemical structure were followed. Aryl part was phenyl in ¹ and ³, or 2-thienyl in ² and ⁴. Anticonvulsant activity was determined by maximal electroshock (MES) and subcutaneous metrazol (scMet) tests. Rotorod toxicity test was used for neurological deficits according the literature [1].

None of the compounds was effective in scMet, while they were found protective in MES at different dose levels and time points. Neurotoxicity is not observed in any of the synthesized compounds which were administered in mice in the dose range of 30-300 mg/kg within ½ h and 4 h But Measurement could not be realized when Compound ² and ⁴ were administered at 300 mg/kg and Compound ¹ at 100 mg/kg dose and above, since the mice died within 20 min. The results of MES were as follows:

Compound [dose level (mg/kg), time (h)]: ¹ [30 (½ h)]; ² [30 (½ h), 100 (½ h)]; ³ [30 (½ h), 100 (½ h, 4h), 300 (½ h, 4h)]; ⁴[100 (½ h)]. ³ was the only compound which was effective at 4h in MES screening.

Replacement of phenyl ring in ¹ by thiophene in ² improved the anticonvulsant activity in ², while it decreased the anticonvulsant activity in ⁴. While it was a useful modification to convert bis Mannich base to the corresponding piperidinol in ¹, it was not useful in ² since conversion caused loss of anticonvulsant activity observed at 30 mg/kg in ². In conclusion, ³ seemed to be candidate compound for further synthesis and in vivo studies to develop effective agents against grand mal seizures for its potential anticonvulsant activity in MES at both ½ h and 4 h without neurotoxicity.