SYNTHESIS AND EVALUATION OF TOXICITY AND BIOACTIVITY OF SALICYL AMIDE DERIVATIVES

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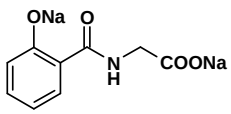
Abstract Salts of salicyl morpholide and salicyloyl glycine have been synthesized by the reaction of an amide with sodium/potassium phenolate or lithium hydroxide in inert solvent. The present study has been carried out to evaluate psychotropic activity and acute toxicity. The results of psychotropic activity reveal that amides possess significant psychotropic activity and low acute toxicity.

Keywords salicyl amides, psychotropic activity, acute toxicity

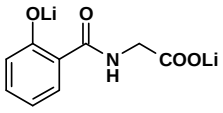
Introduction Derivatives of salicylic acid are known to possess a number of biological activities such as antimicrobial, antipyretic, anti-inflammatory, antithrombotic and analgesic [1]. Salicyl morpholide is known as an anti-inflammatory agent [2]. Salicyloyl glycine inhibits peptidyl α-hydroxylating monooxygenase (PHM) which is a potential target for the development of inhibitors as drugs for the treatment of human disease such as in cancer, rheumatoid arthritis, anxiety and depression [3].

Materials and Methods

Salicyl amides were synthesized following a procedures described earlier [4]. Water soluble forms of amides were prepared in the form of alkali metal salts. Salts of amides were synthesized by the reaction of an amide with sodium/potassium phenolate or LiOH in benzene. Purity of salts was checked by the Thin layer chromatography. Structures of amides were proved with ^{1}H NMR (300MHz) spectra.



I



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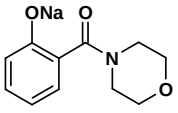

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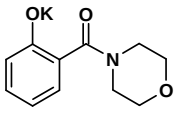
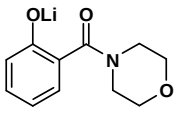


IV



V

Psychotropic activity study Albino rats of either sex were divided into 3 groups. Group I: control group – received 0.9 % NaCl solution (physiologic saline) in a constant volume of 1 ml/kg as vehicle, Group II: received the studied salt solution in dose of 10mg/kg, Group III: – in dose of 50mg/kg. Studied compounds were prepared in physiologic saline and administered intraperitonealy (i.p.). The open field exploration, the forced swimming test (FST), the elevated plus-maze and the passive (inhibitory) avoidance test were used in the study of psychotropic activity [5-8]. In the analgesic activity test, supramaximal intensity of impulse was as high as the animals could tolerate. The vocalization threshold was recorded.

Acute toxicity study White mice were used for toxicity study. The test material was administered i.p. at the dosage levels from 400 up to 3,000 mg/kg. Observations for pharmacotoxic signs and mortality were made at 24 h and daily thereafter for a total of 15 days.

Results and Discussion

A dose dependant effect of **I** at 10 mg/kg on the Inhibitory avoidance test showed a significant antiamnesic action. The results suggested a significant antidepressant activity for **II** as appeared in the FST. Additionally, **II** demonstrated a significant latency increase and time spent in unsafe side decrease indicating antiamnesic action at both doses on the Inhibitory avoidance test. **III** induced a dose dependent increase in the horizontal and vertical motility of the animals. Data demonstrated that animals treated with **III** (50 mg/kg) spent more time on the open arms and less on the center on the Elevated Pluz Maze test, suggesting a potential anxiolytic activity. **III** at the low dose tended to increase the latency and decreased the time spent in dark side on the Inhibitory avoidance test. These results suggested a potential antiamnesic activity for **III**. **IV** (50 mg/kg) induced a significant inhibition of the vertical motility in the open field. It can be concluded that **IV** has a mild sedative effect. **V** at 50 mg/kg increased the horizontal behavior in the open field and decreased immobility in the FST as compared to vehicle treated animals. The

results suggest a psychostimulant action. **V** at 10 and 50 mg/kg on the Inhibitory avoidance test demonstrated a significant latency increase and time spent in dark side decrease indicating good memory performance. **III** and **V** marked analgesic activity. Other data were not significant. In addition, our present investigation showed that all compounds are very safe for consumption with high LD_{50} values from 1.2 up to 2.5g/kg.

Conclusions

The studies indicated that the synthesized alkali metals salts of salicyl amides showed enhanced psychotropic activity with low acute toxicity.

References

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