SYNTHESIS AND BIOLOGICAL ACTIVITY ON RAT AORTA RING OF OPEN ANALOGUES OF CROMAKALIM BEARING A THIOUREA MOIETY

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Introduction & Objectives:

The cromakalim skeleton (Fig 1) has been used as a model in a new pharmacological investigation, which led to some potassium channel openers (PCOs) having potential interesting therapeutic applications in various diseases, especially in hypertension and asthma. Biological data previously collected revealed that several ring-closed compounds of general formula **(I, II, Fig 1)** exhibited a marked myorelaxant activity on vascular smooth muscle (rat aorta) and reduced insulin secretion from rat pancreatic β-cells.[1-3]

To discover new potent and vascular smooth muscle selective PCOs, a series of ring-opened analogues **(A1-14, Fig 1)** structurally related to cromakalim were prepared and evaluated on rat aorta rings (myorelaxant effect).

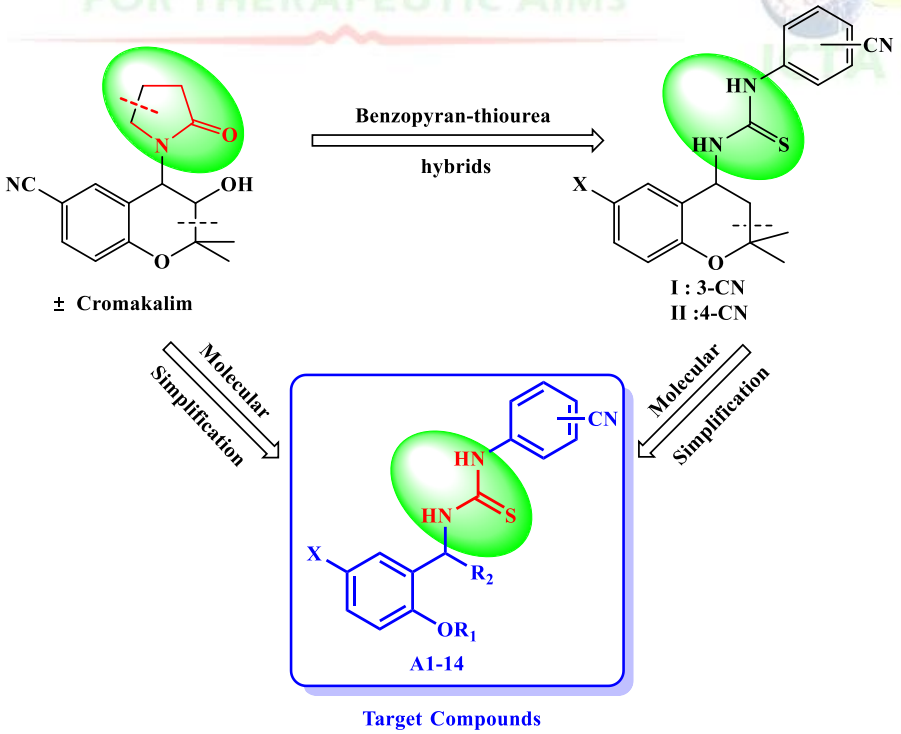

Figure 1: Design of ring-opened cromakalim analogues (**A1-14**).

Methodology (Material and methods):

Fourteen compounds **(A1-14)** were synthesized and purified; these derivatives are characterized by the presence of a thiourea function. Confirmation of chemical structures was performed by usual spectroscopic methods of analysis (SM-ESI, ^{1}H NMR, ^{13}C NMR) and elemental analyses. The vasodilator effect of compounds was examined on aorta rings precontracted with 30 mM KCl, removed from adult fed Wistar rats (180-300 g) and their activity was compared to that of the reference potassium channel openers (±)-cromakalim, diazoxide and of previously reported cromakalim analogues.[3,4]

Results and Discussion:

The pharmacological results indicated that most of the thiourea derivatives were markedely active on rat aortic rings. The introduction of a methyl group on the benzylic carbon atom, which mimicked the chiral center of cromakalim, dramatically increased the vasodilator activity. Indeed, the best active compound showed an EC_{50} value of 1.5 ± 0.4 µM (5), and was almost 15-fold more active than diazoxide. Structure-activity relationships indicated that the most pronounced activity was obtained with molecules bearing a cyano group on the para-phenyl ring of the arylthiourea moiety.[4]

Conclusion:

In conclusion, the present results clearly revealed that the molecular simplification of dihydrobenzopyrans, by opening the pyran ring and introducing arylthiourea moieties led to a new class of compounds expressing identical biological effects than their ring-closed analogues. Furthermore, we succeeded to develop novel analogues of cromakalim that are much more active on the aorta rings tissue than the reference molecule diazoxide.[4]

Keywords: ring-opened cromakalim analogues, thiourea, potassium channel openers, relaxant activity, aortic rings, hypertension.

References

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