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Benzopyran Sulfoxide Derivatives as New Potassium Channel Activator

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Abstract: The sulfoxide derivatives of benzopyran were synthesized and their biological activity were measured.

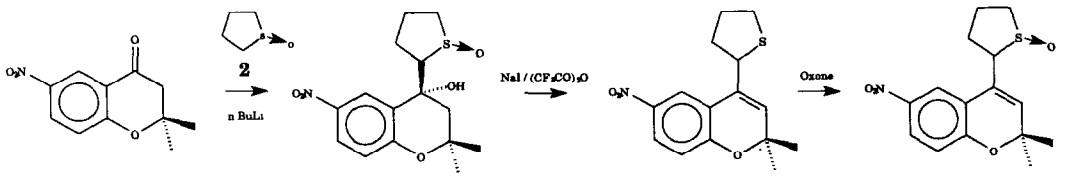
Potassium channel activators have attracted considerable attention due to their potential use for the treatment of hypertension and asthma, etc.[1] The benzopyran type of potassium channel activators known to date can be divided, on the basis of the substituent at C-4, into two groups, a cyclic amide (cromakalim type)[2] and a pyridine N-oxide (Ro 31-6930 type)[3].

From the structure-activity relationship of the known compounds, it is apparent that an amide oxygen (cromakalim) or a pyridine N-oxide oxygen (Ro 31-6930) seems to be indispensable for biological activities. In both cases they are electron rich oxygens. However, the nature of the interaction involving with these atoms is not clear. We have been interested in other functionality such as a sulfoxide to find out whether it has a similar function as an amide or a pyridine N-oxide group. In this Letter we would like to report on the synthesis and biological activity of the sulfoxide derivatives.

The synthesis started with a chromanone **1** which can be prepared by the known procedure.[4] When **1** was reacted with the anion of the sulfoxide **2** generated by n-BuLi, the adduct **3**[5] was produced. The dehydration of the hydroxyl group was accomplished by the treatment of **3** with NaI in trifluoroacetic anhydride. Under this condition, the sulfoxide group was also reduced to the corresponding sulfide **4** which was oxidized selectively by oxone to **5**[5].

The biological activity of the compounds **3** & **5** was measured for their relaxation activity of smooth muscle using a canine mesentric artery and their EC_{50} values are summarized in Table 1.

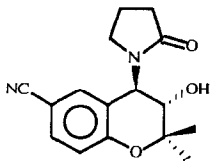
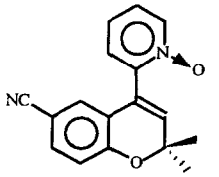
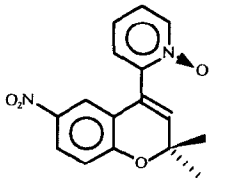
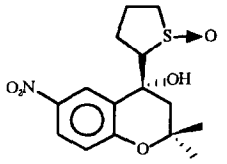
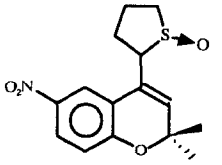
The sulfoxide **5** was found to be about 30 times less potent than the corresponding pyridine N-oxide **6**, but was found to be as potent as cromakalim. On the other hand the compound **3** was quite less active (6 times less active than **5**).



1 **3** **4** **5**

In conclusion we have demonstrated that the sulfoxide derivative is still effective as a potassium channel activator, although the activity is substantially less active than the corresponding pyridine N-oxide.

Table 1

Compound	Structure	EC_{50}*
cromakalim		1.96×10^{-6}
Ro 31-6930		2.22×10^{-7}
6		6.18×10^{-8}
3		1.22×10^{-5}
5		1.96×10^{-6}

* EC_{50} value is the molar concentration for 50% relaxation of canine mesentric artery

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5 The compound **3** is a mixture of diastereoisomers and **5** is a racemic mixture. The separation of isomers will be carried out in due course.