SHORT COMMUNICATIONS

Synthesis and evaluation of Clenbuterol/Rimiterol Analogues

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Received 21 July 1994

Two compounds were synthesised by combining the structural features of bronchodilators Clenbuterol and Rimiterol. Two clenbuterol analogues with only one chlorine atom on aromatic nucleus were synthesised to ascertain whether activity is retained and also to establish a new route of synthesis. All compounds were tested for smooth muscle relaxant property in different test systems and one of them exhibited bronchodilator activity comparable to that of Isoproterenol.

ISOPROTERENOL is a potent bronchodilator, but it exhibits a short duration of action. The short duration of action is mainly due to metabolic inactivation by enzymes such as catachol o-methyl transferase[1] and monoamine oxidase[2]. Structural modifications of isoproterenol led to long acting bronchodilators such as Clenbuterol[3] and Rimiterol[4].

In the present study two new bronchodilators were synthesised by incorporating the essential structural features of both clenbuterol and Rimiterol. It led to the synthesis of (4- acetamido-3-chlorophenyl)-2-piperidyl methanol (A-1) and (4-amino-3-chlorophenyl)-2-piperidyl methanol hydrochloride (A-2). Two clenbuterol analogues were also synthesised to ascertain whether both the chlorine atoms as present in clenbuterol are essential for activity and to establish a new route of synthesis. The compounds synthesised were 1-(4-acetamido-3-chlorophenyl)-2- isopropylaminoethanol (A-3) and 1-(4-acetamido-3-chlorophenyl)-2- tertiarybutylaminoethanol (A-4).

(4-acetamido-3-chlorophenyl)-2-piperidylmeth anol was synthesised from o-chloroacetanilide by Fridel-Crafts acylation in presence of picolinyl chloride and anhydrous aluminium chloride, followed by catalytic reduction of the pyridyl ketone intermediate. The reduction was achieved by dissolving the intermediate in 25% acetic acid and treating the solution with Adam's catalyst and hydrogen gas (40 lbs/in^2) in a Burger Parr reduction flask at room temperature. Hydrolysis of the acetamido group with concentrated hydrochloric acid gave the free aromatic amine in the form of its hydrochloride salt.

1-(4-acetamido-3-chlorophenyl)-2-tertiarybutyl aminoethanol and the corresponding isopropylamino analogue were synthesised from o-chloracetanilide by acylation using chloroacetyl chloride and anhydrous aluminium chloride, followed by amination with t- butylamine/isopropylamine and then reduction of the keto group with sodium borohydride.

The compounds were evaluated for smooth muscle relaxant property in isolated test systems such as guinea pig tracheal chain and rat uterus preparations. Isoproterenol was used as the standard drug for comparison. The compounds were further tested on the isolated guinea pig atrium to ascertain their degree of selectivity for the beta$_2$ receptor. The ED_{50} values determined are as follows.

*For Correspondence

Compound	Tracheal chain ED_{50} in mcg.	Rat uterus ED_{50} in mcg
A - 1	2.19	2.45
A - 2	4.36	4.37
Isoproterenol	2.09	2.75
A - 3	8.91	9.33
A - 4	4.00	7.24
Isoproterenol	2.13	1.51

In conclusion, all compounds exhibited beta adrenegic receptor stimulant activity and compound A-1 was as potent as Isoproterenol. All the compounds showed a high degree of selectivity for the $beta_2$ receptor sub-type, however, they also exhibited a small degree of cardiac beta receptor blocking activity at the doses studied.

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Synthesis and Antimicrobial activity of some new Imidazolones having Thymolmoiety

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Received 4th October 1994

Some new-1-(2'-Isopropyl-4'-nitroso-5' methyl phenoxy-acetamido)- 2-methyl/phenyl-4-arylidene-5-imidazoli-nones were prepared by reaching 4-nitroso hydrazinocarbonyl methyl thymol with preformed azalactone. The structure of the compounds have been confirmed by IR, PMR and elemental analysis. The products were screened for their antimicrobial activity. Some of the products exhibited comparable antimicrobial activity with standard drugs at same concentration.

IMIDAZOLONE[1-4] derivatives have wide range of biological activities as thymol[5-7] derivatives have been found to possess a broad pharmacological spectrum.

Reaction to acetic anhydride, aromatic aledhydes with hippuric acid or acetyl glycine in the presence of sodium acetate has been known to produce azalactone[8] (I). I on refluxing with 4- nitroso hydrazinocarbonyl methyl thymol[9] in 1:1 ratio in the presence of pyridine yielded the title compound (II) (**Table- I**). The latter was synthesised by condensation of 4-nitrosothymol and ethyl-chloro acetate followed by the reaction with hydrazine-hydrate.

The melting points were uncorrected. The IR(KBr) spectra were recorded on a Shimadzu-435