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Synthesis of 4-(1-oxo-isoindoline) and 4-(5,6-dimethoxy-1-oxo-isoindoline)-substituted phenoxypropanolamines and their β_1-, β_2-adrenergic receptor binding studies

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Abstract

Phenoxypropanolamines with 1-oxo-isoindoline (**12**–**16**) and 5,6-dimethoxy-1-oxo-isoindoline groups (**17**–**20**) at the *para* position were synthesized. β_1, β_2-Adrenergic receptor binding affinities for the synthesized compounds were tested and compared with propranolol and atenolol. It was found that the incorporation of *para*-amidic functionality within the 1-oxo-isoindoline ring and 5,6-dimethoxy-1-oxo-isoindoline ring system led to a high degree of cardioselectivity in the phenoxypropanolamines. Two of the compounds **12** and **20** possessed β_1-adrenergic receptor affinity comparable with that of atenolol and both showed a better cardioselectivity than atenolol. Both **12** and **20** are undergoing further pharmacological evaluation.
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1. Introduction

Cardiovascular diseases are the major cause of deaths worldwide, even surpassing deaths due to cancer. Among these, hypertension is central to the pathogenesis of coronary artery disease (angina, myocardial infarction), heart failure, cerebral (stroke), and peripheral vascular diseases [1]. Pharmacological treatment of hypertension includes mainly the use of six drug classes: diuretics, β-adrenergic blocking agents, calcium antagonist, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, and α-adrenergic blockers [2].

As a part of our efforts [3–6] to develop β-adrenergic blocking agents with better activity and cardioselectivity than the existing β-blockers, we have synthesized a new series of phenoxypropanolamines based on the structure of practolol (**1**), a cardioselective agent. Use of cardioselective β-adrenergic blockers has been shown better suited for patients suffering from asthma and other bronchial disease than a non-selective β-adrenergic blocker [7,8]. Following the discovery of practolol with cardioselective action, numerous attempts were made by various researchers to develop β-adrenergic blocking agents with cardioselectivity. All these efforts led to the conclusion that significant cardioselectivity could be achieved either by an appropriate substitution in the *para*-position of the phenyl ring or by appropriate substitution of the side chain amino group [9]. Presence of *para*-amidic functionality in phenoxypropanolamines has been found to confer cardioselectivity [3,9]. It was also found that cardioselectivity could be conferred to phenoxypropanolamine type compounds by replacing isopropyl/*tert*-butyl groups with 3,4-dimethoxyphenylethyl moiety as the amino substituent [10,11].

In our previous study, we have reported the synthesis and β-adrenergic receptor binding of a series of phenoxypropanolamines (Fig. 1, **2a** and **2b**) with a *para*-amidic functionality [3]. Herein, we report the synthesis of phenoxypropanolamines with the *para*-amidic functionality incorporated in 1-oxo-isoindoline and 4-(5,6-dimethoxy-1-oxo-isoindoline) ring system (Fig. 1). Incorporation of *para*-amidic functionality with in the ring system leads to rigidification of the functionality, whose effect on receptor affinity and selectivity could be evaluated in this study. Also, the amino side chain substituent was varied from isopropyl/*tert*-butyl moiety to 3,4-dimethoxyphenylethyl moiety, with the aim of obtaining phenoxypropanolamines with good activity and cardioselectivity.

2. Materials and methods

2.1. Chemical synthesis

2.1.1. Materials

Melting points reported are uncorrected. ^{1}H NMR spectra were recorded on Bruker AC-300F, 300 MHz NMR instrument using tetramethylsilane (TMS) as the internal standard (chemical shifts in δ, ppm). IR spectra were recorded on Perkin-Elmer 882 spectrophotometer model. IR spectra were obtained with potassium

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