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Original article

Synthesis, bioassay, and QSAR study of bronchodilatory active 4*H*-pyrano[3,2-*c*]pyridine-3-carbonitriles

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ABSTRACT

A statistically significant QSAR model describing the bioactivity of bronchodilatory active 4*H*-pyrano[3,2-*c*]pyridine-3-carbonitriles ($N = 41$, $n = 8$, $R^2 = 0.824$, $R^2_{cv} = 0.724$, $F = 18.749$, $s^2 = 0.0018$) was obtained employing CODESSA-Pro software. The bronchodilatory active 4*H*-pyrano[3,2-*c*]pyridine-3-carbonitriles **17**–**57** were synthesized through a facile approach *via* reaction of 1-alkyl-4-piperidones **1**–**4** with ylidenemalononitriles **5**–**16** in methanol in the presence of sodium. The bronchodilation properties of **17**–**57** were investigated *in vitro* using isolated guinea pig tracheal rings pre-contracted with histamine (standard method) and compared with theophylline (standard reference). Most of the compounds synthesized exhibit promising bronchodilation properties especially, compounds **25** and **28**.

1. Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are both prevalent respiratory diseases that affect millions of people all over the world [1]. Asthma affects about 300 million people worldwide, and is characterized by an increase in inflammatory cell population in the epithelium and submucosa of the airways [2]. There are two main effects of asthma pathophysiology: (i) airway inflammation and (ii) smooth muscle dysfunction which has led to two categories of medicine used in asthma treatment: anti-inflammatory drugs and bronchodilators. To treat the inflammatory component of asthma, inhaled corticosteroids are used, whereas inhaled β_2-agonists are the most effective bronchodilators, offering proven benefits in reducing this disease [3,4]. COPD is the fourth leading cause of death and is projected to rise to third place by 2020 [5]. COPD is most commonly associated with cigarette smoking but other risk factors include air pollutants and occupational dust. This debilitating disease is characterized by a progressive airflow limitation that is only partially reversible. Treatment guidelines emphasize the use of bronchodilators at all stages of the disease with a combination of long-acting bronchodilators recommended for patients with moderate to severe COPD [6].

The present work reports the synthesis and bronchodilation properties of novel 4*H*-pyrano[3,2-*c*]pyridine-3-carbonitriles. Our interest in these compounds stems from our previous program directed towards investigation of bio-active agents [7] especially those characterized by vasodilation properties [8,9]. Our recent publication on the vasorelaxant properties of 4*H*-pyrano[3,2-*c*]pyridine-3-carbonitriles in isolated thoracic aortic rings of rats pre-contracted with norepinephrine hydrochloride [9], stimulated an investigation of the muscle relaxant properties of the analogs described in this paper, as bronchodilations. Whereas, the receptors assumed to be involved in both pharmacological mode of actions are somewhat correlated (α/β-adrenoceptors), the selectively of the

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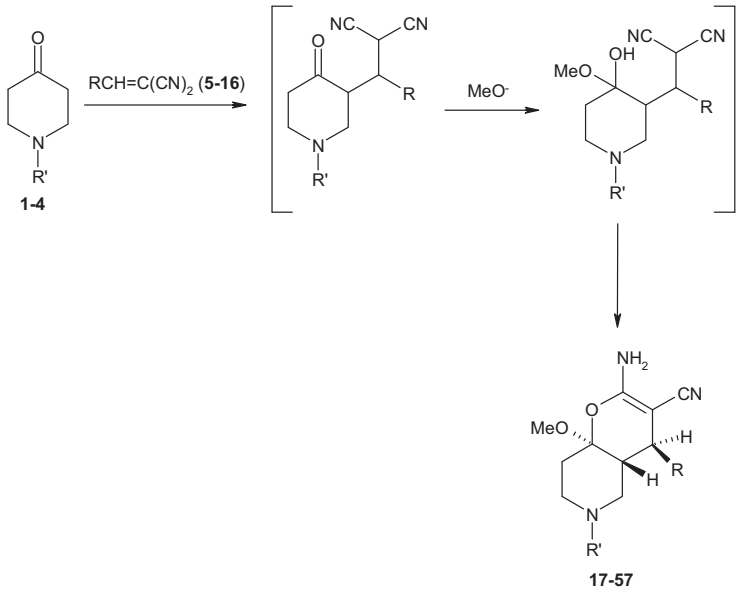
effective agents is questionable. Publications reporting the smooth muscle relaxation and vasodilation properties of pyrano[3,2-*c*] pyridines also motivated the present work [10–12]. Quantitative structure–activity relationship (QSAR) studies are also considered in the present work for validating the observed pharmacological properties of the investigated bronchodilatory compounds and also for determining the most important structure parameters controlling activity.

2. Results and discussion

2.1. Chemistry

The targeted analogs were prepared following our recently published procedure [9] *via* the reaction of 1-alkyl-4-piperidones **1**–**4** with ylidenemalononitriles **5**–**16** in methanol in the presence of sufficient sodium to afford the 6-alkyl-2-amino-4-aryl-



1, R' = Me
2, R' = Et
3, R' = 1-Propyl
4, R' = Benzyl

5, R = Ph
6, R = 2-naphthyl
7, R = 4-BrC_6H_4
8, R = 4-ClC_6H_4
9, R = 2,4-$Cl_2C_6H_3$
10, R = 4-FC_6H_4
11, R = 4-$H_3CC_6H_4$
12, R = 4-$H_3COC_6H_4$
13, R = 3,4-$(H_3CO)_2C_6H_3$
14, R = 4-(1-Piperidinyl)phenyl
15, R = 4-(4-Morpholinyl)phenyl
16, R = 2-Thienyl

17, R = Ph, R' = Me
18, R = Ph, R' = Et
19, R = Ph, R' = 1-Propyl
20, R = Ph, R' = Benzyl
21, R = 2-naphthyl, R' = Me
22, R = 2-naphthyl, R' = Et
23, R = 2-naphthyl, R' = 1-Propyl
24, R = 2-naphthyl, R' = Benzyl
25, R = 4-BrC_6H_4, R' = Me
26, R = 4-BrC_6H_4, R' = Et
27, R = 4-BrC_6H_4, R' = 1-Propyl
28, R = 4-ClC_6H_4, R' = Me
29, R = 4-ClC_6H_4, R' = Et
30, R = 4-ClC_6H_4, R' = 1-Propyl
31, R = 4-ClC_6H_4, R' = Benzyl
32, R = 2,4-$Cl_2C_6H_3$, R' = Me
33, R = 2,4-$Cl_2C_6H_3$, R' = Et
34, R = 2,4-$Cl_2C_6H_3$, R' = 1-Propyl
35, R = 2,4-$Cl_2C_6H_3$, R' = Benzyl
36, R = 4-FC_6H_4, R' = Me
37, R = 4-FC_6H_4, R' = 1-Propyl

Scheme 1. Synthetic pathway towards pyrano[3,2-*c*]pyridines.