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Regioselective synthesis and molecular modeling study of vasorelaxant active 7,9-dioxa-1,2-diaza-spiro[4.5]dec-2-ene-6,10-diones

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Vasodilation
Molecular modeling

ABSTRACT

Nitrilimines (PhC^{-}:N^{+}:NR′) generated in situ from hydrazonoyl chlorides **2a,b** reacted regioselectively with 5-arylidene-2,2-dimethyl[1,3]dioxane-4,6-diones **1a-f** to afford 1,3,4-triaryl-8,8-dimethyl-7,9-dioxa-1,2-diaza-spiro[4.5]dec-2-ene-6,10-diones **3a-l**. In vitro vasodilation activity screening of the synthesized compounds using isolated thoracic aortic rings of male Wister rats pre-contracted with norepinephrine hydrochloride revealed considerable vasodilation activity; compounds **3f** and **3j** had IC_{50} (concentration necessary for 50% reduction of maximal norepinephrine hydrochloride induced contracture) of 0.325, 0.321 mM, respectively. Molecular modeling, including fitting to a 3D-pharmacophore model using Discovery studio 2.1 programs and their docking into optimized α_1-AR homology models as α_1-AR antagonist showed high-docking score and fit values. The experimental in vitro vasodilation activity of compounds **3a-l** was consistent with the molecular modeling.

1. Introduction

Despite the significant progress in its prevention and treatment, cardiovascular diseases remain the main cause of worldwide mortality, with an increasing number of deaths [1]. Hypertension and atherosclerosis are central to the pathogenesis of coronary artery diseases (ischemia, angina, myocardial infarction), heart failure, cerebral (stroke) and peripheral vascular disease [2]. Therapeutic intervention is the most common therapy to control hypertension and reduce hypertension-related organ damage. Recent progress includes new antihypertensive drugs with three main categories: (1) diuretics and adrenergic receptor blockers; (2) calcium channel blockers and (3) inhibitors targeting the renin-angiotensin system (RAS), namely angiotensin converting enzyme (ACE) inhibitors and angiotensin type-1 (AT_1) receptor antagonists [3]. However, no ideal antiarrhythmic or hypotensive treatment exists without side effects, which include fatigue, mood change, sleep disturbances, dry mouth, blurry vision or impotence. It is urgent to search for new agents with minimal side effects [4].

The present work describes the synthesis of dioxa-diaza-spiro[4.5]decanes by 1,3-dipolar cycloaddition reactions of nitrilimines to [1,3]dioxane-4,6-diones possessing an exocyclic olefinic linkage including regioselectivity. Vasodilation is expansion of blood vessels by relaxation of smooth muscle cells within their walls, especially large and smaller arterioles and large veins. When vessels dilate, the flow of blood is increased due to a decrease in vascular resistance. Therefore, dilation of arterial blood vessels (mainly arterioles) leads to a decrease in blood pressure. This work is a continuation of our investigations in this area searching for bioactive hits easily prepared from accessible starting materials and facile synthetic approaches [5,6]. Molecular modeling is attempted to validate the observed pharmacological properties and distinguish the obtained structure-activity relationships.

Adrenoceptors (AR) are classified into α-AR and β-AR [7]. α-ARs play a pivotal role in the regulation of a variety of physiological processes, particularly within the cardiovascular system and are divided into two main subtypes α_1- and α_2-ARs [2,8]. The α_1- and

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α_2-ARs are located in the vascular smooth muscle cell membrane, and upon stimulation by an appropriate agonist, mediate vasoconstriction. The simultaneous occurrence of both receptor subtypes on vascular smooth muscles indicate that α_1- and α_2-ARs could contribute to the maintenance of peripheral arterial tone and may play an important role in resistance seen in hypertension. α_1-ARs modulate intercellular biochemical processes in response to changes in extracellular concentrations of the neurotransmitter norepinephrine and the circulating hormone epinephrine [9–11]. Compounds acting as antagonists at various post-junctional α_1-ARs are frequently used in the therapy of high blood pressure, prazosin being the most common drug [8]. α_1-AR antagonists are also used in the treatment of benign prostatic hyperplasia, lower urinary tract symptoms and cardiac arrhythmia [11,12].

2. Results and discussion

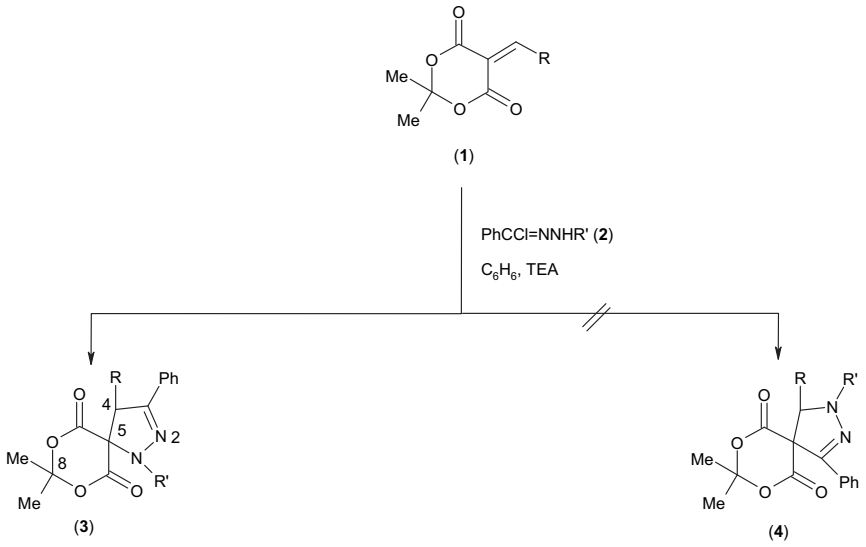
2.1. Chemistry

Nitrilimines ($PhC^-:N^+:NR'$) generated in situ by dehydrohalogenation of the corresponding hydrazonoyl chlorides **2a, b** using triethylamine underwent 1,3-dipolar cycloadditions with various 5-arylidene-2,2-dimethyl[1,3]dioxane-4,6-diones **1a-f** under reflux in benzene to afford single products (TLC). The isolated products were established to be 1,3,4-triaryl-8,8-dimethyl-7,9-dioxa-1,2-diaza-spiro[4.5]dec-2-ene-6,10-diones **3a-l** rather than their regio-isomers 7,9-dioxa-2,3-diaza-spiro[4.5]dec-1-ene-6,10-diones **4**, based on their spectroscopic (IR, ^{1}H NMR, ^{13}C NMR) and elemental analysis data (Scheme 1).

The IR spectra of **3a-l** reveal the presence of strong carbonyl stretching vibration bands at ν = 1791–1744 cm^{-1}. ^{1}H NMR spectra of **3a-l** show the pyrazolinyl *H*-4 as a sharp singlet signal at δ = 5.33–5.68, in addition to the methyl singlet signals at δ = 1.72–1.88. The chemical shift values for pyrazolinyl *H*-4 is evidence for the deduced regio-isomeric form; many other similar spiro analogues such as spiro[2*H*-indene-2,3′-[3*H*]pyrazole]-1,3-diones reveal characteristic pyrazolinyl *H*-4′ signals at δ = 5.14–5.48 [13]. Additionally, pyrazolinyl *H*-4 of regio-isomeric form **4** was expected to appear at $\delta > 6.5$ [14]. The ^{13}C NMR spectra of **3a-l** provide a strong evidence for the structures shown by exhibiting the characteristic *HC*-4 and *C*-5 (spiro-carbon) at δ = 57.9–67.1 and 74.4–76.8, respectively in accord with many similar spiro-ring systems [13–18]. The methyl carbons (δ = 29.3–30.1), carbonyl carbons (δ = 160.5–165.6) and quaternary *C*-8 (δ = 107.1–108.6) are also well recognized.

2.2. Vasodilation properties

Screening of the vasodilation activity of the synthesized 7,9-dioxa-1,2-diaza-spiro[4.5]dec-2-ene-6,10-diones **3a-f,h-l** was investigated in vitro using isolated thoracic aortic rings of male Wister rats pre-contracted with norepinephrine hydrochloride



1a, R = 4-ClC_6H_4
1b, R = 4-FC_6H_4
1c, R = 4-$H_3COC_6H_4$
1d, R = 4-$(CH_3)_2NC_6H_4$
1e, R = 2-thienyl
1f, R = 5-methyl-2-furanyl

2a, R' = Ph
2b, R' = 3-ClC_6H_4

3a, R = 4-ClC_6H_4, R' = Ph
3b, R = 4-ClC_6H_4, R' = 3-ClC_6H_4
3c, R = 4-FC_6H_4, R' = Ph
3d, R = 4-FC_6H_4, R' = 3-ClC_6H_4
3e, R = 4-$H_3COC_6H_4$, R' = Ph
3f, R = 4-$H_3COC_6H_4$, R' = 3-ClC_6H_4
3g, R = 4-$(CH_3)_2NC_6H_4$, R' = Ph
3h, R = 4-$(CH_3)_2NC_6H_4$, R' = 3-ClC_6H_4
3i, R = 2-thienyl, R' = Ph
3j, R = 2-thienyl, R' = 3-ClC_6H_4
3k, R = 5-methyl-2-furanyl, R' = Ph
3l, R = 5-methyl-2-furanyl, R' = 3-ClC_6H_4

Scheme 1.