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Original article

Rational design, synthesis and QSAR study of vasorelaxant active 3-pyridinecarbonitriles incorporating 1*H*-benzimidazol-2-yl function

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ABSTRACT

A variety of 2-alkoxy-4-aryl-6-(1*H*-benzimidazol-2-yl)-3-pyridinecarbonitriles **4a**–**r** were prepared via either regioselective reaction of 3-aryl-1-(1*H*-benzimidazol-2-yl)-2-propen-1-ones **3** with malononitrile or ylidenemalononitriles **6** with 2-acetyl-1*H*-benzimidazoles **1** in the presence of sodium alkoxide in the corresponding alcohol. All the synthesized compounds showed significant vasodilation properties using isolated thoracic aortic rings of rats pre-contracted with norepinephrine hydrochloride standard technique. Compounds **4d**, **4p**, **4l**, and **4f** exhibited remarkable activity compared with prazosin hydrochloride, which was used as a reference standard in the present study. QSAR studies revealed a good predictive and statistically significant 3 descriptor model (r^2 = 0.913, $r^2_{adjusted}$ = 0.8808, $r^2_{prediction}$ = 0.7911).

1. Introduction

Cardiovascular and cerebrovascular disorders are the main reason for morbidity and death in recent years. These include coronary heart diseases, hypertension, and peripheral artery diseases in addition to others [1]. Hypertension is the most common cardiovascular disease that represents the major risk factor for endothelial dysfunction, metabolic syndrome, renal dysfunction, congestive heart failure, coronary artery disease, and stroke [2]. Hypertension affects approximately billions of people all around the world. Hypertension is defined as repeatedly elevated systolic and/or diastolic blood pressure above 140/90 mm Hg [3]. Consistent control of blood pressure is of crucial importance and should be achieved throughout the 24 h dosing interval where, uncontrolled hypertension is associated with acute end-organ damage [4] as congestive heart failure [5] or renal failure as in type-2 diabetes patients [6]. Drugs currently used for hypertension include diuretics [7]; drugs that prevent the action of peripheral sympathetic activity as β-adrenergic [8,9] and α-adrenergic [10] blocking agents; centrally sympathetic α_2-adrenoceptors [11]; angiotensin-converting enzyme inhibitors [12,13]; angiotensin II receptor blockers [13,14] and calcium channel blockers [15]; in addition to drugs directly dilating the blood vessels (arterial dilators) [16]. Relaxation of vascular smooth muscles is considered one of the main strategies for treatment of hypertension [17]. Several agents have been developed; however they are all associated with side effects such as fatigue, mood change, sleep disturbances, dry mouth, blurry vision, impotence etc. [1]. Therefore, there is a continuous need to explore, search and develop new vasorelaxant agents with minimal side effects.

One of the most known vasodilatory active heterocycles are nicotinate esters. Where many nicotinate analogs are well known as vasodilating active agents such as, micinicate '*cis*-3-pyridinecarboxylic acid, 2-oxo-1-phenyl-2-[(3,3,5-trimethylcyclohexyl)oxy]ethyl ester', hepronicate '3-pyridinecarboxylic acid, 2-hexyl-2-[[(3-pyridinylcarbonyl)oxy]methyl]-1,3-propanediyl ester' and inositol nicotinate '*myo*-inositol hexa-3-pyridinecarboxylate' [18]. In continuation of our reports directing toward developing vasorelaxant active agents [19–23], it is intended in the present work to describe synthesis as well as vasodilation properties of novel 3-pyridinecarbonitriles incorporating 1*H*-benzimidazol-2-yl function. Interest in developing these agents could be attributed to the fact that, 3-pyridinecarbonitriles are recognized as bio-isosteric forms of nicotinate analogs (3-pyridinecarboxylates),

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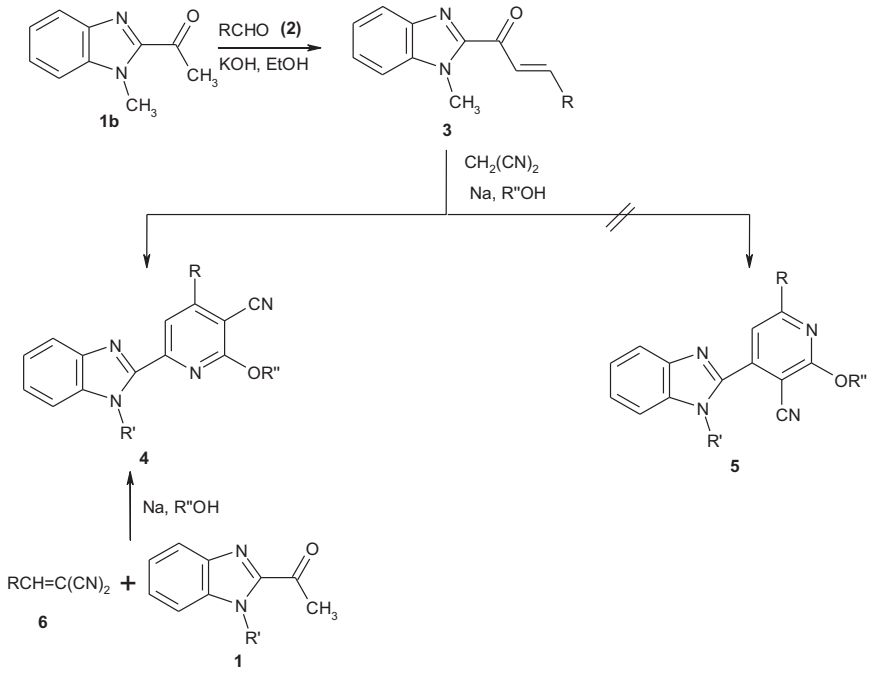
where only the cyano group replaces the acid/ester function. This may develop enhanced pharmacological active agents with higher potency and fewer side effects. Recent publications describing vasorelaxant properties of 4,4′-[1,2-ethanediylbis(oxy-2,1-phenylene)]bis(2-alkoxy-6-aryl-3-pyridinecarbonitriles) also support the present investigation [24]. Bioactivity and applications as pharmaceutical active agents and agricultural materials of pyridinecarbonitriles also prompted the present study [25,26]. Additionally, 4-amino-3-pyridinecarbonitriles were reported as PKCθ inhibitor [27–33]. PKCθ, a novel isoform, is crucial for the activation and survival of T cells [34–36]. Proof-of-concept studies with mice where the PKCθ gene was deleted or 'knocked out' validated that the inhibition of this kinase could have therapeutic utility in diseases such as multiple sclerosis [37,38], arthritis [39], asthma [40,41], inflammatory bowel disease [42], and transplant rejection [43,44]. Pyridinecarbonitriles analogs were also reported as fluorescent materials useful as security markers for treatment of paper [45–47]. Moreover, benzimidazole containing-compounds were reported to exhibit promising pharmacological properties such as antihypertensive [48] and vasodilation [49] in addition to antitumor [50–53], anti-inflammatory [54], antibacterial [55,56], and antiviral [57–59] activity. Additionally, quantitative structure–activity relationships (QSAR) will be also considered in the present study not only to explore the controlling factors governing the observed pharmacological properties of the synthesized analogs, but also to validate the observed activity.

2. Results and discussion

2.1. Chemistry

Reaction of 3-aryl-1-[(1-methyl-1*H*-benzimidazol)-2-yl]-2-propen-1-ones **3a**,**b** with malononitrile in the presence of sufficient amount of sodium alkoxide in the corresponding alcohol afforded only one product which structure was assigned to be either 2-alkoxy-4-aryl-6-[(1-methyl-1*H*-benzimidazol)-2-yl]-3-pyridinecarbonitriles **4** or their isomeric form 2-alkoxy-6-aryl-4-[(1-methyl-1*H*-benzimidazol)-2-yl]-3-pyridinecarbonitriles **5**, based on the observed spectroscopic (IR, ^{1}H NMR, ^{13}C NMR, MS) and elemental analysis data (Scheme 1). Formation of **4a**–**r** via reaction of ylidenemalononitriles **6a**–**h** with 2-acetyl-1*H*-benzimidazoles **1a**,**b** in the presence of sufficient amount of sodium alkoxide in the corresponding alcohol not only adds good support for the assumed structures but also confirms that the reaction of 2-propen-1-ones **3** with malononitrile proceeds in a regioselective



1a; R' = H
1b; R' = Me

2a, 3a; R = 4-ClC$_6$H$_4$
2b, 3b; R = 4-H$_3$COC$_6$H$_4$

6a; R = Ph
6b; R = 4-ClC$_6$H$_4$
6c; R = 2,4-Cl$_2$C$_6$H$_3$
6d; R = 4-FC$_6$H$_4$
6e; R = 4-H$_3$CC$_6$H$_4$
6f; R = 4-H$_3$COC$_6$H$_4$
6g; R = 2-thienyl
6h; R = 5-methyl-2-furanyl

4a; R = Ph, R', R" = Me
4b; R = Ph, R' = Me, R" = Et
4c; R = 4-ClC$_6$H$_4$, R' = H, R" = Me
4d; R = 4-ClC$_6$H$_4$, R', R" = Me
4e; R = 4-ClC$_6$H$_4$, R' = Me, R" = Et
4f; R = 2,4-Cl$_2$C$_6$H$_3$, R', R" = Me
4g; R = 2,4-Cl$_2$C$_6$H$_3$, R' = Me, R" = Et
4h; R = 4-FC$_6$H$_4$, R', R" = Me
4i; R = 4-FC$_6$H$_4$, R' = Me, R" = Et
4j; R = 4-H$_3$CC$_6$H$_4$, R', R" = Me
4k; R = 4-H$_3$CC$_6$H$_4$, R' = Me, R" = Et
4l; R = 4-H$_3$COC$_6$H$_4$, R', R" = Me
4m; R = 4-H$_3$COC$_6$H$_4$, R' = Me, R" = Et
4n; R = 2-thienyl, R', R" = Me
4o; R = 2-thienyl, R' = Me, R" = Et
4p; R = 5-methyl-2-furanyl, R' = H, R" = Me
4q; R = 5-methyl-2-furanyl, R', R" = Me
4r; R = 5-methyl-2-furanyl, R' = Me, R" = Et

Scheme 1. Synthetic routes of compounds **4a**–**r**.