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Research paper

# Synthesis, vasorelaxant activity and 2D-QSAR study of some novel pyridazine derivatives

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ABSTRACT

Novel 3,6-disubstituted pyridazines were synthesized by facile method and screened for their vasorelaxant properties utilizing isolated thoracic rat aortic rings. Compounds **8a** and **11a** exerted potent vasorelaxant activity ($IC_{50}$ = 198 and 177 μM, respectively) relative to doxazosin mesylate (used reference standard, $IC_{50}$ = 226 μM), that, they may represent promising hits for treatment of cardiovascular disorders. The observed activity was validated by a statistically significant QSAR model (N = 32, n = 6, $R^2$ = 0.811782, $R^2_{cvOO}$ = 0.7153, $R^2_{cvMO}$ = 0.7209, F = 17.9708, $s^2$ = 9.65226 × $10^{-8}$) that was obtained employing CODESSA-Pro software.

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## 1. Introduction

Cardiovascular diseases (CVDs), in particular coronary heart disease and stroke, are the leading cause of mortality in the developed countries. According to the World Health Organization (WHO), 17 million people die every year by CVDs, accounting for almost one third of deaths worldwide per year [1]. Among cardiovascular disorders, hypertension is known as a silent killer as it is the most common risk factor that can cause coronary disease, myocardial infarction, stroke and sudden death. In addition, it is the major contributor to cardiac failure and renal insufficiency [2,3]. Moreover, hypertension is not only responsible for high morbidity and mortality, but it impacts negatively the quality of life of a huge number of people across the world. Therefore, prevention and treatment of hypertension is an important public health challenge. Over the past decades, great efforts have been made to discover many antihypertensive drugs that act through different mechanisms such as: diuretics [4], angiotensin-converting enzyme inhibitors [5,6], angiotensin II receptor blockers [6,7], calcium channel blockers [8], centrally sympathetic α2-adrenoreceptors stimulants [9], and drugs that prevent the action of peripheral sympathetic activity as β-adrenergic [10,11] and α-adrenergic blocking agents [12]. It is noteworthy that the reduction in blood pressure achieved with most of the aforementioned classes of drugs is directly or indirectly related to the relaxation of vascular smooth muscles; which makes vasorelaxation one of important strategies in controlling hypertension [13]. Several agents have been developed; however they are all associated with side effects such as fatigue, mood change, sleep disturbances, etc [14]. Therefore, there is a continuous need to explore and develop new vasorelaxant agents with minimal side effects.

The pyridazine nucleus represents a versatile scaffold to develop new pharmacologically active compounds. This heterocyclic system has a wide range of biological activities and can also be used to link other pharmacophoric groups [15–18]. For instance, the 6-(aryl or heteroaryl)pyridazinone derivatives represent an important core with a wide pharmacological profile that includes interesting activities on cardiovascular system, such as cardiotonic effects [19,20], antihypertensive activity [21] and platelet aggregation inhibition [22]. Zardaverine **I**, levosimendan **II** and motapizone **III** are some characteristic drugs bearing this pharmacophoric moiety [23–25] (Fig. 1). Most of the described pyridazinone derivatives, showing activity on cardiovascular system, possess aryl residues at position 6 of the pyridazine ring [23,26,27]. Interestingly, 3-hydrazinyl-6-phenylpyridazine **5a** which exhibited strong hypotensive properties, is the structural analog of the well known vasodilator hydralazine **IV** that possesses a phenyl ring attached to the pyridazine nucleus instead of being fused to it as in hydralazine [28] (Fig. 1). Encouraged by these findings; this work focused on design and synthesis of some phenylpyridazines substituted with a

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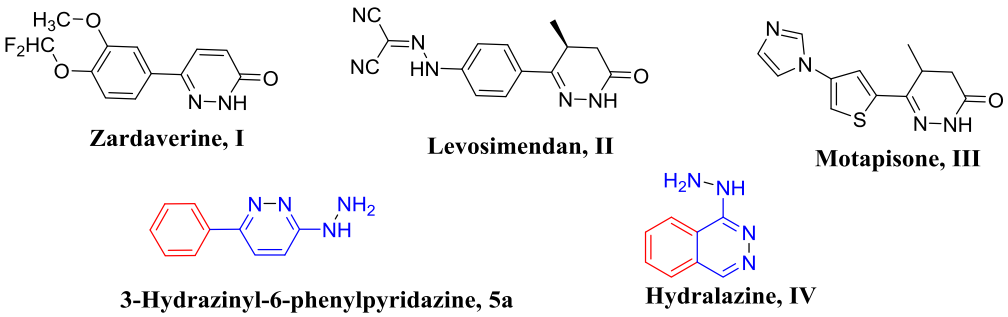


**Fig. 1.** Representative pyridazine based compounds with vasorelaxant activity.

heterocyclic ring, namely, pyrrolidine, imidazole or pyrazole, (general structure A, Fig. 2). These ring systems can be considered as pharmacophoric moieties in many vasorelaxant agents [9,19,21,25,29–31]. Moreover, 3-hydrazinyl-6-phenylpyridazine **5a** was used for further structural modification through derivatization of the hydrazine moiety into a semicarbazide group (general structure B), or an aryl hydrazone (general structure C, Fig. 2) in order to study their effect on the modulation of the activity. Additionally, quantitative structure–activity relationship (QSAR) studies were considered in the present work to validate the obtained vasorelaxant activity and detect the most important structural parameters controlling it.

## 2. Results and discussion

### 2.1. Chemistry

The targeted pyridazines were synthesized according to the general procedures outlined in Schemes 1 and 2. Thus, the 6-aryl-3(2H)pyridazinones **3a**–**d** were synthesized from the reaction of the appropriate acetophenone **1a**–**d** and glyoxilic acid **2** followed by cyclization with hydrazine hydrate [32]. Chlorination of **3a**–**d** with phosphorous oxychloride afforded 3-chloro-6-arylpyridazines **4a**–**d** which were further treated with hydrazine hydrate in absolute ethanol to obtain the 3-hydrazino derivatives **5a**–**d** [33]. The target compounds **6a**–**d** and **7a**–**c** were obtained from the precursor chloropyridazines **4a**–**d** through a nucleophilic substitution reaction with imidazole and pyrrolidine, respectively (Scheme 1). The structures of the obtained compounds **6a**–**d** were confirmed by $^1$H NMR which revealed three broad singlet signals at 7.30–7.32, 7.81–7.83 and 8.49–8.53 ppm corresponding to the imidazole protons, only the imidazole proton at C2 of compound **6b** appeared as a triplet at 7.83 ppm due to long range coupling with protons at C4, C5 of the imidazole ring. However, the pyridazine protons of **6a**–**d** appeared as two doublets at 7.59–7.68 and 7.97–8.24 ppm, while the phenyl ring protons of **6a** revealed two multiplets at 7.53–7.59 and 8.10–8.12 ppm. In case of the *p*-substituted derivatives **6b**, **6d**, two doublets appeared at the range 7.07–7.56 and 8.07 ppm. On the other hand, the *o*-substituted derivative **6c** showed doublet at 7.08 ppm corresponding to the proton at C3 that coupled with H of C4, two triplets of doublet at 7.18 and 7.49 ppm corresponding to protons at C5 and C4 which coupled with protons at C3, C4, C6 and C5, C6, C3, respectively, and one doublet of doublet at 8.04 ppm due to the proton at C6 that coupled with protons at C5 and C4. Moreover, the appearance of multiplet signals in the ranges 2.06–2.12 and a broad singlet at 3.63–3.65 ppm corresponding to the pyrrolidine protons attested the obtained compounds **7a**,**b**. Regarding compound **7c**, the pyrrolidine protons appeared as a multiplet at 1.98–2.01 ppm and a triplet at 3.56 ppm. Meanwhile, cyclocondensation of the hydrazine derivatives **5a**–**d** with acetylacetone in absolute ethanol afforded 3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-6-arylpyridazines **8a**–**d**. $^1$H NMR spectra of **8c**,**d** confirmed the obtained structure through the presence of three singlet signals at 2.34, 2.81–2.82 and 3.89–3.90 ppm corresponding to two methyl and one methoxy groups, respectively, in addition to a singlet attributed to the pyrazole proton at 6.08–6.09 ppm. Similarly, the reaction of **5a**–**d** with either ethoxymethylene malononitrile or ethyl ethoxymethylene cyanoacetate in absolute ethanol gave the 5-aminopyrazole derivatives **9a**–**d** and **10a**–**d**, respectively. The IR spectra of **9b**–**d** and **10b**–**d** showed the $NH_2$ stretching vibration as two bands at 3391–3285 and 3453–3312 cm$^{-1}$, in addition to the CN band at 2230-2210 cm$^{-1}$ in case of compounds **9b**–**d**. Moreover, $^1$H NMR spectra of **10b**–**d** revealed the triplet-quartet pattern of the $C_2H_5$ protons at 1.37–1.39 and 4.31–4.34 ppm along with two singlet signals at 7.60–7.62 and 7.82–7.84 ppm corresponding to $NH_2$ and pyrazole proton, respectively. The former signal for $NH_2$ was disappeared upon deuteration with $D_2O$. On the other hand, nucleophilic addition of hydrazines **5b**,**c** to the appropriate isocyanate in methylene chloride in the presence of triethylamine afforded the semicarbazides **11a**–**c**, whose structures were confirmed by the appearance of three NH bands at 3329–3300, 3250–3223 and 3138–3134 cm$^{-1}$ in the IR spectra. In addition, $^1$H NMR showed three singlet signals corresponding to three NH groups that were

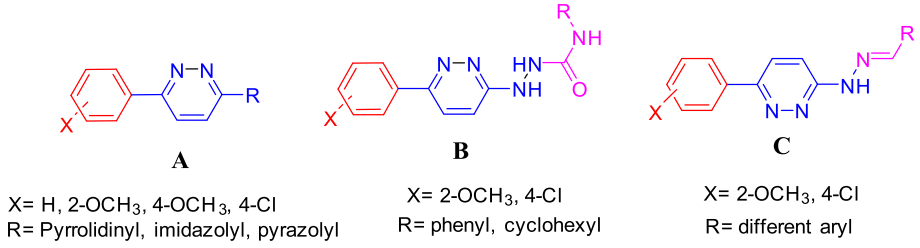


**Fig. 2.** General structures of the designed target compounds.

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