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Exploration of diphenylalkyloxadiazoles as novel cardiac myosin activator

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ABSTRACT

To explore novel cardiac myosin activator, a series of diphenylalkyl substituted 1,3,4-oxadiazoles and 1,2,4-oxadiazoles have been prepared and tested for cardiac myosin ATPase activation *in vitro*. In all cases, three carbon spacer between the oxadiazole core and one of the phenyl ring was considered crucial. In case of 1,3,4-oxadiazole, zero to two carbon spacer between oxadiazole core and other phenyl ring are favorable. Phenyl ring can be replaced by cyclohexyl moiety. In case of 1,2,4-oxadiazole, zero or one carbon spacer between the oxadiazole and other phenyl ring are favorable. Introduction of hydrogen bonding donor (NH) group at the 2nd position of the 1,3,4-oxadiazole enhances the activity. Substitutions on either of the phenyl rings or change of phenyl ring to other heterocycle are not tolerated for both the oxadiazoles. The prepared oxadiazoles showed selective activation for cardiac muscle over smooth and skeleton muscles.

Heart failure (HF) affects at least 26 million people worldwide and is increasing in prevalence.[1,2] In 2013, HF was the most common cause of death worldwide (15% of deaths worldwide).[3] The health expenditures for controlling HF are considerable and will increase dramatically with an ageing population.[4,5] Despite the significant advances in therapies and prevention of HF, mortality and morbidity are still high and quality of life of HF patients are very poor.[6]

Decreased systolic function is a central factor in the pathogenesis of heart failure.[7,8] Acutely decompensated chronic heart failure concerns about 70% of patients with acute heart failure syndromes,[9] and at least half of the patients with heart failure have low ejection fraction (40% or less),[10] thus leading to systolic heart failure.[11] Systolic dysfunction is better characterized as a decrease in cardiac contractility that can be measured by a reduction in the left ventricular ejection fraction.[12–14] Safe medical therapy to improve cardiac function of heart failure patients with reduced ejection fraction is still challenging.[15] Most current therapies are focused on blockade of neurohormonal activation using inhibitors of the renin-angiotensin pathway, β-adrenergic blockers, and aldosterone antagonists and do not improve the contractile function of the heart.[16,17]

Currently available inotropes such as adrenergic receptor agonists, phosphodiesterase inhibitors and calcium sensitizers are used in the treatment of systolic heart failure. Unfortunately, these drugs have adverse effects such as, increased intracellular concentrations of calcium and cAMP, contributing to increased heart rate, hypotension, and mortality.[18–21] To address these limitations cardiac myosin activators are being developed, which directly work at the level of the cardiac sarcomere activating the actin-myosin cross-bridges, the smallest force-producing unit involved in the contraction mechanism.[15,22–25] The selective cardiac myosin activator, omecamtiv mecarbil (OM), is currently undergoing clinical trials.[26] Unlike prior agents that increased intracellular cAMP and calcium and decrease ejection time, OM increased myocardial contraction and stroke volume without increasing oxygen consumption, thereby increasing myocardial efficiency.[27,28] Although OM is currently undergoing clinical trials, a broader range of drugs that can improve cardiac function is urgently required.

Recently our group discovered flexible 3-phenylpropyl urea scaffold as novel cardiac myosin activator with good cardiac myosin ATPase activation *in vitro* and *in vivo*.[29] For example, 1-benzyl-3-(3-phenylpropyl)urea (**1**, cardiac myosin ATPase activation (CMA) at 10 μM = 53.3%; fractional shortening (FS) = 30.04%; ejection fraction (EF) = 18.27%) and 1-phenethyl-3-(3-phenylpropyl)urea (**2**, CMA at 10 μM = 51.1%; FS = 18.90%; EF = 12.15%) showed potent activity (Fig. 1). Further, the lead compounds **1** and **2** were optimized to improve the activity and found **3** (CMA at 10 μM = 91.6% FS = 17.62%; EF = 11.55%), **4** (CMA at 10 μM = 52.3% FS = 38.96%; EF = 24.19%) and **5** (CMA at 10 μM = 47.6% FS = 23.19%; EF = 15.47%) as novel cardiac myosin activators (Fig. 1).[30]

In continuation, the present work aim to investigate possible isosteric replacement of the urea scaffold. Hence, oxadiazoles (1,3,4-oxadiazoles and 1,2,4-oxadiazoles) have been designed and synthesized as selective cardiac myosin activators for the treatment of systolic heart

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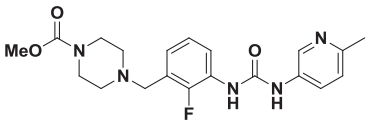
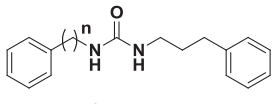


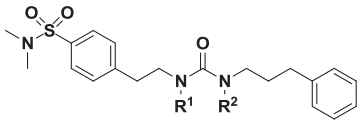
omecamtiv mecarbil
inotrope- *cardiac myosin activator*

Cardiac myosin ATPase activation % at 10 uM	Fractional shortening % increase	Ejection Fraction % increase
58.0	20.32	13.35



1: n = 1
2: n = 2

	Cardiac myosin ATPase activation % at 10 uM	Fractional shortening % increase	Ejection Fraction % increase
1; n = 1	53.3	30.04	18.27
2; n = 2	51.1	18.90	12.15



	Cardiac myosin ATPase activation % at 10 uM	Fractional shortening % increase	Ejection Fraction % increase	Ventricular cell contractility (% change at 5 μM)
3; R^1 = H; R^2 = H	91.6	17.62	11.55	47.9 + 3.2
4; R^1 = CH_3; R^2 = H	52.3	38.96	24.19	45.5 + 2.4
5; R^1 = H; R^2 = CH_3	47.6	23.19	15.47	63.5 + 2.2

Fig. 1. Novel urea analogs as cardiac myosin activator.

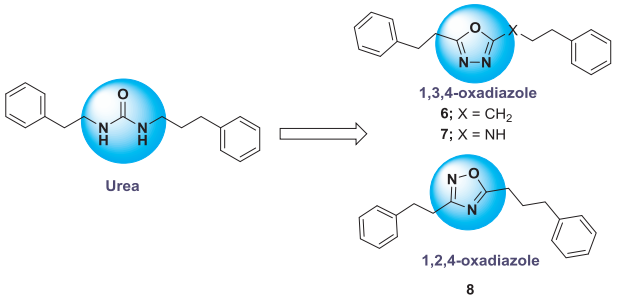
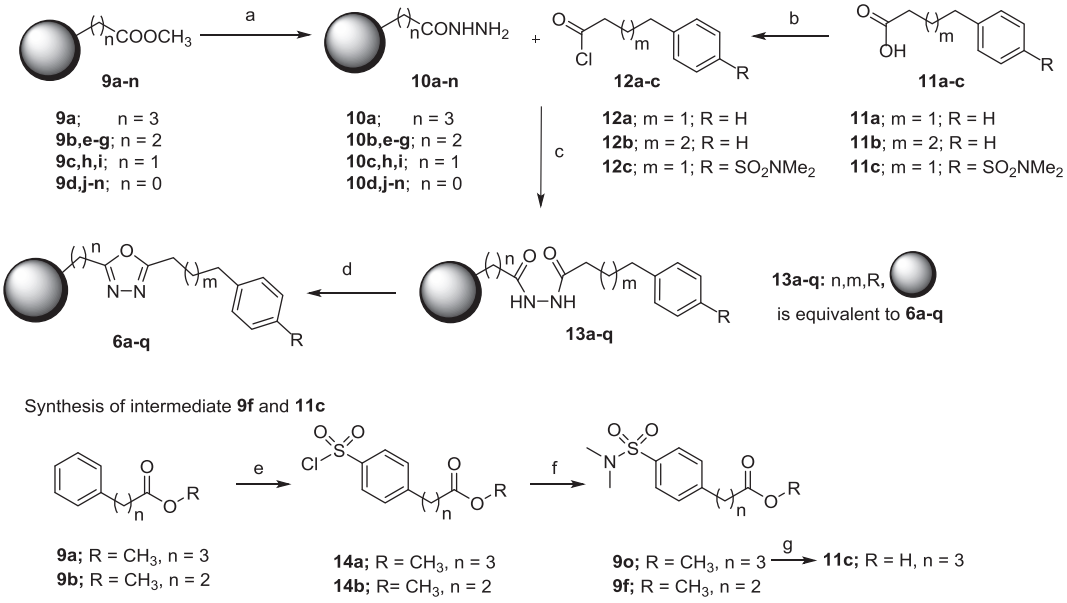


Fig. 2. Isosteric replacement of urea with oxadiazoles for novel cardiac myosin activator.

failure (Fig. 2).

Scheme 1 represents the synthesis of compounds **6a–q**. The reaction of various carboxylic esters **9a–n** with hydrazine hydrate in presence of catalytic amount of pyridine in ethanol under reflux condition yielded the hydrazide intermediate **10a–n**. The reaction of **10a–n** with the acid chlorides **12a–c** derived from the corresponding carboxylic acids **11a–c** afforded the dihydrazide intermediates **13a–q** in good yield. The intermediates **13a–q** on cyclodehydration reaction in presence of refluxing phosphorous oxychloride yielded 1,3,4-oxadiazoles **6a–q**. The *N,N*-dimethylsulfonamido substituted carboxylic esters **9o** and **9f** were synthesized from **9a** and **9b** by chlorosulfonation at *para* position to give **14a** and **14b** followed by the treatment of *N,N*-dimethylamine, respectively. The hydrolysis of **9o** with LiOH/H_2O yielded **11c**.

Scheme 2 represents the synthesis of compounds **7a-f**. The



Scheme 1. Preparation of 1,3,4-oxadiazoles **6a–q**. *Reagents and conditions;* a) $NH_2NH_2{\cdot}H_2O$, pyridine, EtOH, reflux, 10 h b) $SOCl_2$, DCM, reflux, 3 h; c) TEA, DCM, 0 °C, 2 h; d) $POCl_3$, reflux, 3 h; e) $ClSO_3H$, DCM, 0 °C to RT, 3 h; f) $NH(CH_3)_2$.HCl, $NaHCO_3$, THF, 40 °C, 5 h; g) LiOH, H_2O THF, RT, 3 h; ●, n, m of **6a–q** are denoted in Table 1.