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ORIGINAL ARTICLE

Design and synthesis of novel 4-substituted 1,4-dihydropyridine derivatives as hypotensive agents

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KEYWORDS

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Abstract Calcium-channel blockers have an important role in the treatment of several cardiovascular disorders. Derivatives of 1,4-dihydropyridines are one of the most potent calcium antagonists. In this study a series of novel 1,4-dihydropyridine calcium channel blockers of general formula diethyl 4-(4-substituted phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate were synthesized and tested for hypotensive activity, including electrocardiographic and effect on heart rate. Compound diethyl 4-(4-benzyloxy phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (DHP I) and diethyl 4-(2-(2-chlorobenzyloxy) phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (DHP III), were the most potent in this series. All synthesized compounds lowered rat blood pressure significantly in comparison with DMSO as control and nifedipine was used as positive control.

1. Introduction

One of the most important goals in organic and medicinal chemistry is the design and synthesis of molecules that have value as therapeutic agents. In this regard, heterocyclic compounds have proven to be versatile support structures that offer a high degree of structural diversity (Weiner, 1988).

1,4 Dihydropyridines exhibit various activities such as the calcium channel antagonists (Triggle, 2007) and the heterocyclic ring is the common feature for various pharmacological activities such as antihypertensive, antianginal (Love et al., 1974; Bossert et al., 1981; Breitenbucher and Figliozz, 2000), antitumor (Boer and Gekeler, 1995), anti-inflammatory (Briukhanov, 1994; Bahekar et al., 2002), antitubercular (Wachter and Davis, 1998), analgesic (Gullapalli and Ramarao, 2002), and antithrombotic (Sunkel et al., 1990; Onohandkinura, 1981). It binds to L-type channel and also shows action by binding to N-type channel (Triggle, 1999). Other activities are found to be reported such as vasodilation (Wilson and Giswold, 2003), anticonvul-

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sant (Tusell et al., 1993), stress protective effect (Tarasenko et al., 2002), cardio depressant activity (Budriesi et al., 2008), antibacterial (Chhillar et al., 2006), antileishmanial agents (Pandey et al., 2010), cystic fibrosis transmembrane conductance regulator activity (Cateni et al., 2009), mineralocorticoid receptor antagonist activity (Arhancet et al., 2010), neuroprotection properties (Leon et al., 2008), HIV-1 protease inhibitors (Hilgeroth and Lilie, 2003), Alzheimer's disease (Contelles et al., 2009), antifertility agent (Waghmare et al., 2011).

Calcium-channel blockers have an important role in the treatment of several cardiovascular disorders (Mirkhani et al., 1999; Parmley et al., 1996). They have been widely used for hypertension, angina pectoris, heart failure and Raynaud's disease (Safak and Simsek, 2006; Epstein et al., 2007).

Structurally diverse group of compounds are known to be effective as calcium channel antagonists (Goldmann and Stoltefuss, 1991). The most potent class of antagonists comprises derivatives of 1,4-dihydropyridine of which nifedipine is used widely today (Haria and Wagstaff, 1995; Hadizadeh et al., 2007). Dihydropyridines act by inhibiting the influx of calcium ion into the vascular smooth muscle cells via L-type calcium channels (Meredith and Elliott, 2004). Their useful effects in management of cardiovascular disorders are due to their ability to relax vascular smooth muscles.

In angina pectoris, such drugs decrease the resistance in systemic and coronary arterial beds, thereby reducing cardiac oxygen requirement and increasing cardiac oxygen supply, respectively.

In this paper, we describe the design and synthesis of 4-substituted 1,4-dihydropyridine derivatives and its hypotensive effect on measuring rat blood pressure using invasive in vivo technique on canulation with right carotid artery system.

1.1. Drug design

Work done in our laboratory on QSAR studies on dihydropyridines by selecting a series reported by Chang et al., (Chang et al., 2010), was used for carrying out the present study on antagonism of 4-substituted 1,4-dihydropyridine-3,5-dicarboxylates towards voltage-dependent L-type Ca^{2+} channels $Ca_V1.3$ and $Ca_V1.2$. Work done in our laboratory on QSAR studies on DHP, shows the developed MLR (Abraham et al., 2003), model reveals that the descriptor T_T_N_2 negatively contributes to the biological activity. T_T_N_2 is an Alignment Independent (AI) descriptor that signifies the count of the number of any atoms (single double or triple bonded) separated from the nitrogen atom (single, double or triple bonded) by a distance of two bonds in a molecule. The next descriptor SsssCHcount is inversely proportional to the activity. This descriptor defines the total number of –CH group connected with three single bonds. The descriptor, $SdCH_2$count is also negatively contributing to the biological activity. It is the total number of $–CH_2$ group with double bond. The descriptor T_T_O_6 is positively contributing to the activity. It is the count of the number of any atoms (single, double or triple bonded) separated from any other oxygen atom (single, double or triple bonded) by a distance of six bonds in a molecule. The last descriptor, rotatable bond count is negatively contributing to the activity. On the basis of these QSAR inferences the ligands were designed that accomplish the requirements. Among the several designed analogues only top four molecules that were predicted to be active were selected for synthesis.

2. Materials and methods

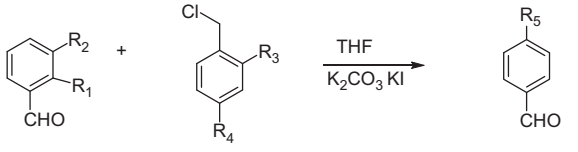
Melting points were determined by open capillary tubes using VEEGO VMP-D digital melting point apparatus and are uncorrected. FTIR spectra of the powdered compounds were recorded using KBr on a JASCO FTIR 4100 series and are reported in cm^{-1} and ^1H NMR spectra were recorded on a Varian Mercury YH300 (300 MHz FT NMR) spectrophotometer using TMS as an internal reference (Chemical shift represented in dppm). Purity of the compounds was checked on TLC plates using silica gel G as stationary phase and iodine vapours as visualizing agent.

2.1. General procedure for the preparation of compounds ALD I–ALD III

As shown in Scheme I (Lin et al., 2005; Chang et al., 2001) (Fig. 1), the starting substituted phenol (0.1 mol) was dissolved in THF (100 ml). To the solution was added substituted benzyl chlorides (0.13 mol), K_2CO_3 (20 g), and KI (26 g). The resulting mixture was stirred under reflux for 6 h. The solvent was removed in vacuum. Water (100 ml) was added and the mixture was extracted with $CHCl_3$, dried over $MgSO_4$, and evaporated. The residue was purified by recrystallization to yield respective derivatives.

2.2. Procedure for the synthesis of 4-oxo-4H-chromene-3-carbaldehyde (ALD IV)

As shown in Scheme II (Lacova et al., 1998) (Fig. 2), dry dimethylformamide (121 ml) in a three-necked flask, $POCl_3$ (0.49 mol) was added slowly with intensive stirring at 50 °C. Heating and stirring were continued for 2 h at 45–55 °C. The solution of 2-hydroxyacetophenone (0.12 mol) in DMF (25 ml) was then slowly added under stirring at 50 °C. The stirring was continued for 2 h at 55–60 °C. After cooling the mix-



Scheme I

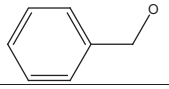
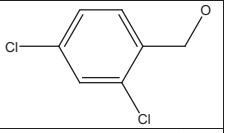
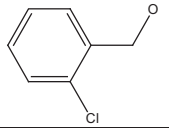
Aldehydes	R_1	R_2	R_3	R_4	R5
ALD I	OH	H	H	H	
ALD II	H	OH	Cl	Cl	
ALD III	H	OH	Cl	H	

Figure 1 Scheme I for synthesis of DHP.