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Efficient syntheses, crystal structure, thermal and biological evaluation of amlodipine 4-chlorobenzoyl, 4-chlorobenzene and 2,5-dichlorobenzene sulfonamide derivatives

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ABSTRACT

An efficient synthesis of new **A-2**, **A-3**, and **A-4** analogues from amlodipine (**A-1**) has been achieved. All synthesized compounds were investigated by elemental analysis, FTIR, EIMS, and ^{1}H NMR techniques. Crystal structures of **A-2** and **A-3** were determined by single crystal X-ray diffraction method. Compound **A-2** crystallizes in a monoclinic space group $C2/c$ having unit cell parameters $a = 23.8754(9)$ Å, $b = 8.6725(3)$ Å, $c = 30.5777(12)$ Å, $\beta = 90.673(2)^\circ$, and $V = 6331.0(4)$ Å^3, whereas **A-3** crystallizes in a triclinic space group $P\bar{1}$ having unit cell parameters $a = 8.2968(3)$ Å, $b = 9.3112(4)$ Å, $c = 18.1359(7)$ Å, $\alpha = 100.692(2)^\circ$, $\beta = 98.316(3)^\circ$, $\gamma = 102.747(2)^\circ$, and $V = 1317.39(9)$ Å^3. These compounds showed that C—H···O and N—H···O hydrogen bonds stabilize the crystal packing. The results of thermal analysis of all products were consistent with the proposed stoichiometry and compounds were found thermally stable up to 200 °C. The compounds were tested for direct free radical scavenging effect toward α, α-Diphenyl-1-picryl hydrazide (DPPH$^\bullet$) and 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS$^{\bullet+}$) radical cation in aqueous phosphate-buffered saline of pH 7.4 and showed significant in vitro antioxidant potential. Antiurease activity was also performed; **A-2** and **A-4** showed excellent results with dose independency.

1. Introduction

Amlodipine (**A-1**) ((*R,S*)-3-ethyl 5-methyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate) (Fig. 1) is a 1,4-dihydropyridine-based long-acting calcium channel blocker extensively used for the treatment of hypertension, angina pectoris, and other cardiovascular diseases [1]. Like other calcium channel blockers, it acts by relaxing the smooth muscle cells of arterial wall by decreasing total peripheral resistance, thus reduces blood pressure; in angina, it increases blood flow to the heart muscle [2]. Essential hypertension results in an increased oxidative stress level, which requires the use of potent antiatherosclerotic drugs that not only directly affect the arterial wall, but also demonstrate antioxidant and free radical scavenging properties. The ability of dihydropyridine as calcium channel blockers to protect against oxidative endothelial

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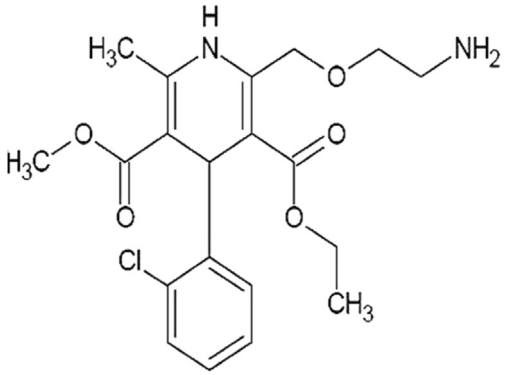

Fig. 1. Chemical structure of **A-1**.

cell injury in comparison with vitamin E (Trolox) is well established [3–7].

Herein, we report synthesis, crystal structure, thermal properties, in vitro antioxidant potential, metal chelating ability, and antiurease activity of 2-[2-(4-chloro-benzenesulfonylamino)-ethoxymethyl]-4-(2-chloro-phenyl)-5-hydroperoxycarbonyl-6-methyl-1,4-dihydro-pyridine-3-carboxylic acid 3-ethyl ester 5-methyl ester dehydrate (**A-2**), 2-[2-(4-chloro-benzoylamino)-ethoxymethyl]-4-(2-chloro-phenyl)-6-methyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid 3-ethyl ester 5-methyl ester (**A-3**), and 4-(2-chloro-phenyl)-2-[2-(2,5-dichloro-benzenesulfonylamino)-ethoxymethyl]-6-methyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid 3-ethyl ester 5-methyl ester (**A-4**) (Fig. 2). This work was a successful effort to enhance the therapeutic effect of amlodipine by preparing new more effective analogues. To achieve the task, sulfonamide and benzoyl ester groups were incorporated in **A-1**. These groups impart antimicrobial, anti-inflammatory, anticancer, antiprotozoal, antiviral, and carbonic anhydrase inhibitory activities [8–10]. All the synthesized compounds **A-2**–**A-4** were screened for their in vitro antioxidant, pro-oxidant chelation, and antiurease activities.

2. Experimental

2.1. Material and methods

All chemicals and materials used were of analytical grade. All melting points were obtained on an Electrothermal (Griffin 1090) melting point apparatus and reported without correction. The IR spectra of the compounds were scanned through Perkin Elmer 1600 FTIR (USA) and MIDAC-M 2000 (USA) by using KBr pellets over the range of 4000–400 cm^{-1}. Thermogravimetric analysis (TGA) (25–600 °C) profiles were recorded under an inert atmosphere (N_2) on an SDT Q600 (TA instruments, USA) at a ramp rate of 10 °C/min. Antioxidant capacity was evaluated using a UV-1700 Pharma Spec UV–Visible Spectrophotometer, Shimadzu, Japan, equipped with Peltier temperature-controlled device. Elemental analysis (CHNS) was performed using a Vario Micro Cube (Elementar, Germany). Mass spectra were recorded on a JEOL MS Route with ionization mode EI^+. ^1H NMR spectra were recorded on Bruker AVANCE AV 600 and DPXQ 400 spectrometers. The IUPAC name of each compound was derived using Chem sketch (freeware version) and atomic numbering scheme was assigned to interpret ^1H NMR spectra. The single-crystal data were collected using a Bruker Kappa APEX II CCD diffractometer (graphite monochromated Mo Kα radiation, $\lambda = 0.71073$ Å) at room temperature, and data reductions were performed using SAINT [11]. The structures were solved by direct methods with SHELXS, the resulting atomic models were developed and refined against $|F|^2$ using SHELXL [12]. The "observed data" threshold for calculating the $R(F)$ residuals was set as $I > 2\sigma(I)$. The C and N bound H atoms were placed at idealized locations (C–H = 0.93–0.97 Å and N–H = 0.86 Å) and refined as riding atoms. The O-bound H atoms were located in the difference Fourier maps and refined as riding on their relative atoms. All non-hydrogen atoms were refined with anisotropic parameters. The structural models were analyzed and validated with PLATON [13] and full refinement details using the crystal information file. Mercury program [14] software WinGX was used to prepare molecular graphics for publication [15]. Supramolecular analyses were performed, and the diagrams were prepared with the aid of PLATON and CrystalMaker [16].

2.2. Syntheses

Aqueous sodium carbonate solution (3–5%) containing **A-1** (286 mg, 0.7 mmol) was treated with equimolar ratio of 4-chlorobenzenesulfonyl chloride, 4-chlorobenzoyl chloride, and 2,5-dichlorobenzenesulfonyl chloride separately for 3–6 h. The execution and completion of reactions were indicated by thin-layer chromatography. White precipitates were formed by adding 3 N HCl dropwise up to 2.0 pH. The products were filtered and recrystallized in MeOH/EtOAc (50:50 v/v) to obtain colorless blocks.

2.2.1. 2-[2-(4-Chloro-benzenesulfonylamino)-ethoxymethyl]-4-(2-chloro-phenyl)-5-hydroperoxycarbonyl-6-methyl-1,4-dihydro-pyridine-3-carboxylic acid ethyl ester dehydrate (*A-2*)

Yield: 67%, mp 148–150 °C, ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.9 (d, $J = 8.1$ Hz, 2H, H-23, H-25), 7.5 (d, $J = 8.1$ Hz, 2H, H-22, H-26), 7.4–7.1 (m, 4H, H-2–H-6), 5.4 (s, 1H, H-7), 4.9 (s, 2H, H-18), 4.07 (m, 2H, H-16), 3.7 (m, 2H, H-19), 3.6 (s, 3H, H-13), 3.2 (m, 2H, H-20), 2.3 (s, 3H, H-14), 1.2 (t, 3H, H-17). IR (KBr) ν_{max} (cm^{-1}) 3377 (N–H stretch), 3267 (sec. sulfonamide), 1686, 1662 (C=O stretch), 1645, 1603 (C=C stretch), 1480, 1429 (aliphatic C–H, bending), 1281 (S=O, asymmetric stretch), 1202 (O=C–O ester, stretching), 1186 (O–C–C of ester, stretching), 1082 (S=O symmetric stretch), 1035 (aromatic C–Cl), 757, 737 (aromatic C–H, bending). MS m/z (%): 618 (2, M^+), 585 (45), 583 (100), 581 (94), 318 (6), 286 (8). Anal. Calcd for $C_{26}H_{32}Cl_2N_2O_9S$ (619.51): C, 50.41; H, 5.21; N, 4.52; S, 5.18. Found: C, 50.24; H, 5.33; N, 4.60; S, 5.43%.

2.2.2. 2-[2-(4-Chloro-benzoylamino)-ethoxymethyl]-4-(2-chloro-phenyl)-5-hydroperoxy carbonyl-6-methyl-1,4-dihydropyridine-3-carboxylic acid ethyl ester (*A-3*)

Colorless crystals. Yield: 71%, mp 79–82 °C. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.9 (d, $J = 8.1$ Hz, 2H, H-23, H-

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