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Synthesis and assessment of the cytotoxic effect of some of 1,4-dihydropyridine derivatives which contain azole moiety

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Abstract: A number of 1,4-dihydropyridine derivatives (**9a**–**d**, **10a**–**d** and **11a**–**d**) were designed and synthesized by the reaction of 1,3,4-oxadiazole-5-thiones and 1,2,4-triazole-5-thiones to 2,6-dibromomethyl-3,5-diethoxycarbonyl-4-(3--nitrophenyl)-1,4-dihydropyridine. The synthesized compounds were characterized using FT-IR, ^{1}H-NMR, ^{13}C-NMR spectral data, ESI-MS and elemental analysis. The cytotoxicity of the synthesized compounds was evaluated in human breast cancer (MCF-7) cells based on the results of MTT assay. The results indicated that compound diethyl 4-(3-nitrophenyl)-2,6-bis[((5-(3-nitrophenyl)-1,3,4-oxadiazol-2-yl)thio)methyl]-1,4-dihydro pyridine-3,5-dicarboxylate (**9b**) with (IC_{50} = 23±2.32 μM) was the most potent derivative against MCF-7 cells. Based on the results, the use of oxadiazole moiety in the C2 and C6 positions of 1,4-dihydropyridine ring system enhanced the cytotoxic potential of these derivatives. Therefore, some of the oxadiazole-substituted 1,4-DHPs may facilitate further modifications which result in the discovery of potent cytotoxic agents.

Keywords: dimethylformamide; 3-nitrobenzaldehyde; 1,3,4-oxadiazole; 1,2,4-triazole.

INTRODUCTION

1,4-Dihydropyridines (DHPs) have assumed considerable importance in the field of organic and medicinal chemistry due to their interesting pharmacological activities. The results of different studies have highlighted the fact that the DHPs are highly effective calcium antagonists and are used for treating various cardiovascular system (CVS) activities.[1–3] In addition to the CVS activities of DHPs, they possess a variety of biological activities including, cytotoxic activities,[4–6] anti-proliferative activities,[7] multidrug resistance activities[8,9] and anti-tumour activities.[10–13] However, synthesizing DHPs derivatives is an active and ongoing

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research area. Chemotherapy is still one of the most effective methods for treating cancer. The potential uses of the DHPs scaffolds in the chemotherapy are well-documented and stem from their suitability for reversing the drug resistance in the treatment of cancer.[14,15] Calcium channel blockers like verapamil[16] and nicardipine,[17] among others have been reported to successfully overcome drug resistance.

Notwithstanding, the introduction of calcium channel blockers to clinical use might pose a therapeutic problem which results from their strong vasodilator function.[18] Consequently, a substance which has a strong capability to overcome anticancer drug resistance and does not lead to calcium antagonistic activity can be of great value in chemotherapy. Research has shown that, generally, DHPs display more cytotoxicity towards cancer cells in comparison with the non-cancer cells.[19] The discovery of new DHP derivatives can encourage the development of novel and effective therapies for diverse pathologies, including cancer.

The efficiency of oxadiazole and triazole derivatives has been assessed and proved for a wide range of pharmacological uses. The connection of 1,3,4-oxadiazoles or 1,2,4-triazoles to the 1,4-DHPs core has produced a combination scaffold. The DHPs can be selectively functionalized in several positions. The synthesis and anticancer activities of bis(1,3,4-oxadiazole-2-thiol) and bis(4-amino-1,2,4-triazole-3-thiole) derivatives of DHPs in the C3 and C5 have been reported.[20] Moreover, research has shown the synthesis and biological activities of 1,3,4-oxadiazole derivatives which are linked to N1 of DHP ring system.[21] In spite of the highly developed chemistry of the DHPs, there is not adequate information about the synthesis of 1,4-DHPs bearing-substituents other than hydrogen atoms or alkyl groups in the C2 and C6. In our previous study, we reported the synthesis and antimicrobial assessment of 1,4-dihydropyridines with azole derivatives in the C2 and C6 positions of DHP ring.[22] Based on the above-mentioned gap in the related literature, the present study focuses on synthesizing the novel 1,4-dihydropyridine derivative, which are linked to triazole and oxadiazole moieties, and evaluating their cytotoxic activities.

EXPERIMENTAL

The chemicals of Sigma–Aldrich and Merck were used to produce the chemicals of this study. The solvents were purified based on the standard procedures before their use in the study. The thin-layer chromatography (TLC) analysis was performed in the case of the recoated silica gel (E-Merck kieselgel 60 F_{254} Aluminium sheets) plates. *N*-bromosuccinimide (NBS) and tetramethylsilane (TMS) were purchased from Merck. The melting points were determined on open capillaries using a digital melting point apparatus. The FT-IR spectra were recorded as KBr pellets on a thermo Nicolet Nexus 670 FT-IR. The ^{1}H- and ^{13}C-NMR spectra were recorded on the Bruker Avance AQS 300 MHz spectrometer at 300 and 100 MHz, respectively. The chemical shifts were measured in dimethyl sulfoxide (DMSO-d_6) as solvent relative to TMS as the internal standard. These abbreviations were used to describe the multiplicities of signals in NMR spectra (s = singlet, d = doublet, t = triplet, q = quartet, dd =

doublet of doublets and br = broad signal). The mass spectra were recorded on a JEOL-JMS 600 (FAB MS) instrument and the ESI-MS spectra were recorded on an Agilent Technologies 5975C VL MSD mass spectrometer which operated at an ionization potential of 70 eV. The CHNS analysis was performed using CHNS-932 Leco analyser. The **3a**–**d**[23,24], **4a**–**d**[25], **5a**–**d**[26] and **6a**–**d**[27] compounds were produced according to the reviewed literature.

Analytical and spectral data of the synthesized compound are given in Supplementary material to this paper.

Procedure for preparing diethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (7)

A mixture of ethylacetoacetate (0.02 mol, 2.60 g), ammonium acetate (0.015 mol, 1.16 g) and 3-nitrobenzaldehyde (0.01 mol, 1.51 g) in 50 % ethanol (50 mL) was mixed well under reflux for 12 h. The contests were cooled after the reaction (which was monitored by TLC *via* *n*-hexane/EtOAc (4:1) as eluent. The precipitate was filtered, washed with water and crystallized from ethanol.[28,29]

*Procedure for synthesizing diethyl 2,6-bis(bromomethyl)-4-(3-itrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**8**)*

NBS (0.02 mol, 3.56 g) was added to a solution of the diethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**7**, 0.01 mol, 3.74 g) in methanol (100 mL) portion-wise at ambient temperature. The reaction mixture was stirred at room temperature for 24 h. The pale yellow precipitate was filtered and washed with water. The precipitate was crystallized from ethanol.[29]

*General procedure for synthesizing the **9a**–**d**, **10a**–**d** and **11a**–**d** compounds*

A mixture of **3a**–**d, 4a**–**d** or **6a**–**d** (0.02 mol), NaOH (0.02 mol, 0.8 g) and DMF/H_2O (50/50, 50 mL) was stirred at room temperature for 1 h. Moreover, diethyl 2,6-bis(bromomethyl)-4-(3-nitrophenyl)-1,4-dihydropyridine-3, and 5-dicarboxylate (**8**, 0.01 mol, 5.32 g) were added to it and it was stirred at room temperature for 8–12 h. The reaction mixture was poured into water (100 mL) and the residue was extracted with CH_2Cl_2. The organic layer was washed with water, dried over Na_2SO_4 and evaporated and recrystallized from ethanol.

Biological assessment

Reagent and chemical. (RPMI-1640) and fetal bovine serum (FBS) were purchased from (Gibco, USA). 3-(4,5-Dimethylthiazole-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was obtained from Sigma. Penicillin/streptomycin was purchased from Invitrogen (San Diego, CA, USA). Dimethyl sulphoxide (DMSO) were obtained from Merck.

Cell culture. The human breast cancer cells (MCF-7) were purchased from National Cell Bank of Iran (Pasteur, Tehran, Iran). These cells were cultured in Roswell Park Memorial Institute 1640 (RPMI-1640) (Gibco, USA) medium which was enriched with 10 % fetal bovine serum (FBS, Gibco, USA), 100 unit/mL penicillin and 100 mg/mL streptomycin and was maintained under 37 °C and 5 % CO_2 conditions. The cells, which reached the 70 % confluence, were sub cultured and were used for conducting the experiments.

Cell viability assay (MTT). In order to determine the cytotoxic effect of various compounds on the viability of MCF-7 cells, the MTT reduction assay was performed as described previously.[30-32] First MCF-7 cells were plated in 96-well microplates at a density of 1×10^4 cells per well and were maintained overnight at 37 °C to allow them to attach to the bottom of the wells. After cell attachment, the medium was removed and cells were treated with various compounds (**9a**–**d**, **10a**–**d** and **11a**–**d**) at the concentrations which ranged from 10 to 100 μM.

All of the compounds were dissolved in DMSO and were diluted in medium in a way that the maximum concentration of DMSO in the wells did not exceed 0.5 %. Cells were further incubated for 48 h. Thirdly, the fresh medium, which contained 500 µg/mL MTT powder, was added to each well and plates were incubated for another 4 h time at 37 °C. Then MTT and media mixtures were removed and formazan crystals which formed by the mitochondrial dehydrogenase activity of vital cell were solubilized in 200 µl DMSO and was put on an orbital shaker for 20 min. Finally, the absorbance of each plate was measured at 570 nm with the background correction at 620 nm using an Elisa plate reader (Statefax, USA). Effects of the drug cell viability were calculated using cells treated with DMSO as control. Cell survival was calculated using the formula: Survival, % = [(absorbance of treated cells – absorbance of culture medium)/(absorbance of untreated cells – absorbance of culture medium)]×100. The experiment was done in triplicate and the inhibitory concentration (*IC*) values were calculated from a dose-response curve. Graph Pad Prism software 6.01 was used to calculate IC_{50} values. IC_{50} is the concentration in µM required for 50 % inhibition of cell growth as compared to that of the untreated control. IC_{50} values were determined from the linear portion of the curve by calculating the concentration of agent that reduced absorbance in treated cells, compared to control cells, by 50 %. Evaluation is based on mean values from three independent experiments, each comprising at least six micro cultures per concentration level. IC_{50} Values represent the mean of triplicate determination (n = 3) ± *SD* with (95 %) confidence interval. The cytotoxicity of the synthesized derivatives was not compared to standard drugs.[33]

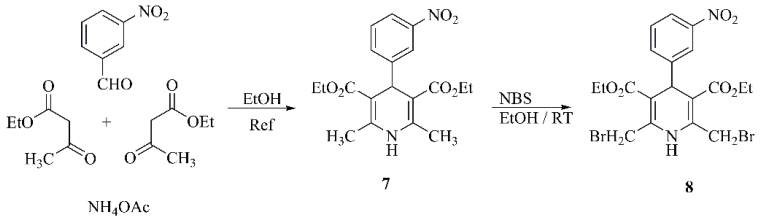
RESULTS AND DISCUSSION

The **3a**–**d**, **4a**–**d**, **5a**–**d** and **6a**–**d** derivatives were prepared according to the method which was described in the relevant literature.[23–27] It is well-known that the thiol–thione tautomeric equilibrium exists in **3a**–**d**, **4a**–**d** and **6a**–**d** compounds. On the basis of ^{1}H-NMR and FT-IR experimental findings, it is argued that the thione tautomer is more stable than thiol in the solution. ^{1}H-NMR spectra of these compounds exhibited the NH signal as a broad peak in the δ 12–14 ppm range which supports the proposed thione structure. The appearance of a C=S absorption peak in the 1248–1278 cm^{-1} region indicated that the oxadiazoles and triazoles were in their thione form.[34]

Diethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**7**) was synthesized using the classical Hantzsch three-component reaction method. This method includes the cyclocondensation of 3-nitrobenzaldehyde with two equivalents of ethyl acetoacetate in the presence of a nitrogen donor such as ammonia or ammonium acetate (based on the procedure reported in the literature).[33] We needed a quick entry into 1,4-dihydropyridine-3,5-dicarboxylic acid diesters in which the 2,6-methyl groups were altered by a range of different groups. Allylic bromination is the replacement of a hydrogen on a carbon adjacent to a double bond. Allylic bromination in dihydropyridines was performed by NBS.

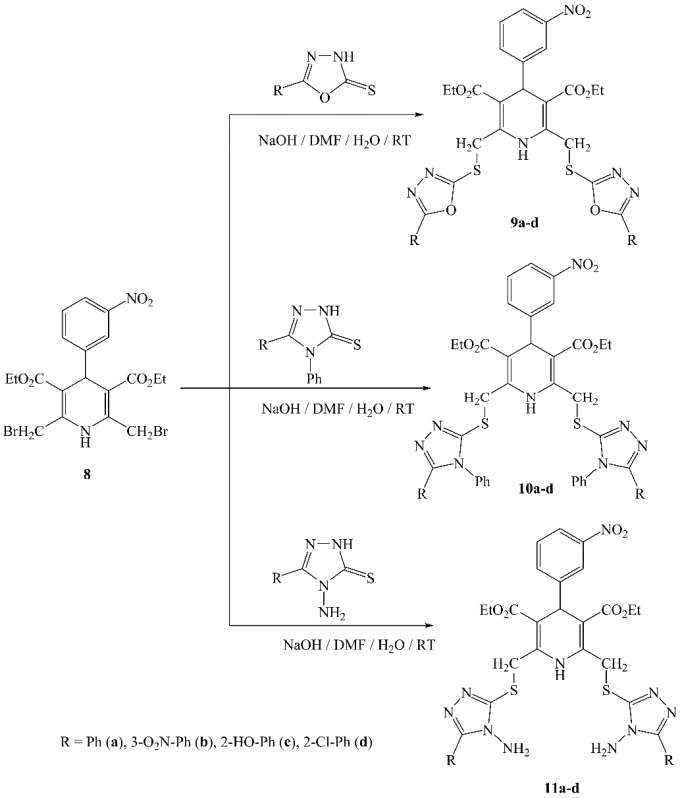
The synthesis of 2,6-dibromomethyl-3,5-diethoxycarbonyl-1,4-dihydropyridine (**8**) was achieved as a result of the bromination of the corresponding 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**7**) by NBS in methanol according to the procedure which was described in the literature.[29] The

bromine atoms in compound **8** can be replaced with the other substituents (Scheme 1).



Scheme 1. Synthesis of compound **8**.

The replacement of the bromines of compound **8** with 1,2,4-triazole-5-thiones **3a**–**d**, 1,3,4-oxadiazole-5-thiones **4a**–**d** and 4-amino-3-mercapto-1,2,4-triazoles **6a**–**d** was carried out in the presence of sodium hydroxide as a base in DMF in order to afford the corresponding coupled 1,4- DHP_S (**9a**–**d**, **10a**–**d** and **11a**–**d**) (Scheme 2).



Scheme 2. The synthesis of compounds **9a**–**d**, **10a**–**d** and **11a**–**d**.

The structures of **9a**–**d**, 10**a**–**d** and **11a**–**d** compounds were identified using spectroscopic methods. In the IR spectra the disappearance of the C=S absorption peak in the 1248–1278 cm^{-1} region and the absence of NH peak at δ 12–14 ppm supported the connection of oxadiazole and triazoles to 1,4-DHP ring. The CH_2X protons in the C2 and C6 positions of symmetrically substituted 1,4-dihydropyridine ring became diastereotopic and provided an AB system in the corresponding ^{1}H-NMR spectra. The extent of the observed anisotropy of the methylene protons must have been influenced by the spatial conformation between the ester groups and the formation of a CH···O=C intramolecular hydrogen bonding.[35]

The increase in concentration resulted in a decrease in the viability of cells for all of the compounds and indicated that the cytotoxicity of all of the compounds depended on the concentration. Some of the compounds including **10a** and **c** did not display a high level of cytotoxicity towards MCF-7 cells. Nonetheless, a number of the other compounds including **9b** and **d** displayed a high level of cytotoxicity towards these cells at a concentration which was confirmed by their IC_{50} values. According to the in vitro MTT assay, the IC_{50} represents the concentration of the newly synthesized compounds that is required for 50 % inhibition of the human breast cancer cell (MCF-7) viability. The IC_{50} value for each compound was calculated and summarized in Table I. As shown in Table I, based on the IC_{50} value, the most cytotoxic compound was **9b**. Therefore, it can be suggested that, this compound is a potent cytotoxic agent.

TABLE I. Cytotoxic activity of the synthesized 1,4-DHP derivatives assessed by the MTT assay

Compound	R	Molecular weight	IC_{50} / μM MCF-7	IC_{50} / μg mL^{-1} MCF-7
9a	C_6H_5–	726	45±2.72	32.67
9b	3-NO_2–C_6H_4–	816	23±2.32	18.76
9c	2-HO–C_6H_4–	758	40±4.65	30.32
9d	2-Cl–C_6H_4–	794	33±1.55	26.20
10a	C_6H_5–	876	63±3.10	55.12
10b	3-NO_2–C_6H_4–	966	57±4.27	55.06
10c	2-OH–C_6H_4–	908	>100	
10d	2-Cl–C_6H_4–	944	49±3.10	46.25
11a	C_6H_5–	754	54±3.10	40.71
11b	3-NO_2–C_6H_4–	844	44±1.8	36.16
11c	2-HO–C_6H_4–	786	51±4.6	39.16
11d	2-Cl–C_6H_4–	822	47±4.65	38.63

CONCLUSION

In the present study, diethyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3 and 5-dicarboxylate derivatives were coupled with 1,3,4-oxadiazole-5-thiones and 1,2,4-triazole-5-thiones in the C2, C6 positions of 1,4-dihydropyridine ring system in order to produce compounds with greater cytotoxicity. The synthesized compounds were characterized using FT-IR, ^{1}H-NMR, ^{13}C-NMR spec-

tral data, ESI mass and elemental analysis. The cytotoxic effects of the new compounds on human breast cancer (MCF-7) cells were investigated using MTT assay. The results of the MTT assay showed that a number of compounds including **9b** and **d** displayed good cytotoxicity at a certain concentration. This finding was confirmed by their IC_{50} values. The highest potency was observed in the case of MCF-7 cells (**9b**: IC_{50} = 23±2.32 μM). Based on the results, the **10c** compound did not have a cytotoxic effect on the tested cancer cell line due to its bulky scaffold and the steric hindrance in its site of action. These preliminary encouraging results of the biological screening of the tested compounds may offer an excellent framework for the discovery of potent cytotoxic agents in this field.

SUPPLEMENTARY MATERIAL

Additional data and information are available electronically at the pages of journal website: https://www.shd-pub.org.rs/index.php/JSCS/article/view/9811, or from the corresponding author on request.

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ИЗВОД

СИНТЕЗА И ОДРЕЂИВАЊЕ ЦИТОТОКСИЧНОГ ЕФЕКТА ДЕРИВАТА 1,4-ДИХИДРОПИРИДИНА КОЈИ САДРЖЕ АЗОЛСКУ СТРУКТУРУ

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Синтетисана је серија деривата 1,4-дихидропиридина (**9a**–**d**, **10a**–**d** и **11a**–**d**) реакцијом 1,3,4-оксадиазол-5-тиона или 1,2,4-триазол-5-тиона са 2,6-дибромметил-3,5-диетоксикарбонил-4-(3-нитрофенил)-1,4-дихидропиридином. Синтетисана једињења су окарактерисана помоћу FT-IR, ^{1}H-NMR, ^{13}C-NMR и ESI-MS спектара и елементалном анализом. Испитана је цитотоксичност добијених деривата према ћелијама хуманог канцера дојке (MCF-7) MTT есејом. Резултати указују да једињење диетил 4-(3-нитрофенил)-2,6-бис[((5-(3-нитрофенил)-1,3,4-оксадиазол-2-ил)тио)метил]-1,4-дихидропиридин-3,5-дикарбоксилат (**9b**) са (IC_{50} = 23 ± 2,32 μM) има највећу активност према MCF-7 ћелијама. На основу добијених резултата оксадиазолски део структуре на C2 и C6 положајима 1,4-дихидропиридинског система повећава цитотоксични потенцијал ових деривата. Из тога произилази да би неки 1,4-DHP деривати који садрже оксадиазолске супституенте омогућили припрему нових активнијих једињења.

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