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Research Article

Synthesis and Cytotoxic Evaluation of Homoveratrylamine-Based Derivatives Derived from Carboxylic Acids

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ABSTRACT

Condensation reactions between homoveratrilamine and various carboxylic acids provide an efficient route to structurally diverse amide and isoquinoline derivatives with potential biological activity. In this study, a series of amides and 1-substituted dihydro- and tetrahydroisoquinolines were synthesized from homoveratrilamine and itaconic acid, mandelic acid, cinnamic acid, m-iodobenzoic acid, 2,4-dinitrobenzoic acid, and 2,4-dichlorobenzoic acid. Amides (**4**, **5**, and **12**) and 1-substituted dihydro- (**6**, **13**-**16**) and tetrahydroisoquinolines (**17**) were successfully obtained. The cytotoxic activity of the synthesized compounds was evaluated in vitro using the MTT assay against four human cancer cell lines cervical carcinoma (HeLa), mammary adenocarcinoma (HBL-100), laryngeal adenocarcinoma (HEp-2), and T-lymphoblastic leukemia (CCRF-CEM) as well as three non-malignant cell lines, including African green monkey kidney (Vero B) cells, rat embryonic fibroblasts, and rat hepatocytes. The antitumor drug cisplatin was used as a positive control. Proliferative activity was identified for dihydroisoquinolines differing in substituents in the aromatic moiety. This effect emerged and increased in the following order: iodophenyl < dichloro < dinitro < dimethoxy. The transition from dihydroisoquinoline **15** to tetrahydroisoquinoline **17**, while retaining the iodophenyl fragment in the structure, also led to the appearance of proliferative properties in cervical carcinoma cells, resulting in an 18% increase in proliferation. Among all tested derivatives, the itaconic acid-based dihydroisoquinolines **6** exhibited the most pronounced cytotoxic activity against HeLa, HBL-100, and HEp-2 cells, with IC_{50} values of 24.9, 13.1, and 27.1 μM, respectively. Notably, it exhibited considerably lower cytotoxicity toward Vero B cells and hepatocytes, with IC_{50} values of 95.9 and 100 μM, respectively; however, it proved to be highly toxic to skin fibroblasts (IC_{50} = 12.6 μM). These results indicate that the itaconic acid dihydroisoquinoline derivative demonstrates pronounced selective cytotoxicity toward cancer cells while largely sparing normal cells, highlighting its potential as a promising lead compound for further optimization.

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1. INTRODUCTION

One of the most pressing challenges in modern medicine and pharmacology is the discovery of new anticancer agents. It is well established that many biologically active compounds have been developed from natural products and their synthetic derivatives, which exhibit activity against various types of cancer (Darji et al., 2024; Kadir et al., 2022; Shakri et al., 2020; Niyazmetov et al., 2020; Malikova et al., 2020; Dusmatova et al., 2019; Tseomashko et al., 2013). However, despite the availability of a wide range of cytotoxic and anticancer drugs in contemporary experimental and clinical oncology, most of them, including targeted therapeutics, suffer from significant limitations, such as high toxicity toward healthy tissues and organs, as well as the development of drug resistance over time (Stubbs et al., 2025; Basak et al., 2021; Dy et al., 2013). The identification of novel compounds that exhibit selective cytotoxic activity against cancer cells while maintaining low toxicity toward normal cells would substantially expand the arsenal of effective anticancer agents. Synthetic and naturally occurring amide- and isoquinoline-containing compounds are widely used in medicinal chemistry. Drugs based on amide and isoquinoline scaffolds display a broad spectrum of biological activities, including anticancer effects and form key components of many therapeutic agents used in clinical practice (Qing et al., 2018; Diaz et al., 2015; Larghi et al., 2009). In addition, amides play an important role in organic synthesis as key intermediates in the construction of heterocyclic systems, such as isoquinolines (Reddy et al., 2013). These compounds often exhibit favourable bioavailability and metabolic stability and therefore represent promising scaffolds for the development of targeted anticancer agents.

The classical method for the synthesis of isoquinolines is the Bischler-Napieralski reaction, which involves the cyclodehydration of acyl derivatives of β-phenethylamines to form 3,4-dihydroisoquinolines upon heating in an inert solvent in the presence of dehydrating agents such as polyphosphoric acid, P_2O_5, $POCl_3$, or $ZnCl_2$. Since its development, this method has been repeatedly refined, leading to a significant expansion in both the range of acyl derivatives employed and the variety of condensing agents used (Tukhtaev et al., 2021; Aghekyan et al., 2009; Gurjar et al., 2007; Shukla et al., 2006). Previous investigations have shown that the reaction of homoveratrilamine with dibasic fatty acids ranging from C_5 to C_{10} predominantly yields the corresponding amides (Saidov et al., 2015). In contrast, reaction with succinic acid (C_4) produces a mixture of two compounds, namely the amide and the imide (Saidov et al., 2013). Similarly, the use of malic and fumaric acids results in a mixture of three products: α-lactam, amide, and imide (Saidov et al., 2016). Building upon these findings, the present study extends this approach by employing itaconic acid, mandelic acid, and substituted benzoic acids (*m*-iodo-, 2,4-dinitro-, and 2,4-dichlorobenzoic acids) as starting materials in combination with homoveratrilamine. Itaconic (methylenesuccinic) acid is an unsaturated dibasic acid that can be synthesized chemically from citric or aconitic acid and is also known as a metabolic product of certain *Aspergillus* species. Previous reports have described the preparation of itaconic acid imides from itaconic anhydride, demonstrating its suitability as a versatile precursor for nitrogen-containing compounds (Kolotova et al., 2016).

From a medicinal chemistry perspective, the incorporation of different dicarboxylic, aromatic, and unsaturated acid residues into the homoveratrilamine framework provides an opportunity to modulate both the electronic and steric properties of the resulting molecules. Such structural variations may significantly influence membrane permeability, target affinity, and metabolic stability, ultimately affecting cytotoxic potency and selectivity (Mao et al., 2020). In this context, the formation of amide, imide, or lactam functionalities may play a critical role in determining biological activity. Despite the extensive body of research on isoquinoline derivatives (Kim et al., 2023; Azamatov et al., 2022), systematic studies addressing the cytotoxic potential and selectivity of amide- and isoquinoline-based compounds derived from homoveratrilamine and structurally diverse organic acids remain limited (Zhurakulov et al., 2025). In particular, the biological properties of compounds obtained from itaconic, mandelic, and substituted benzoic acids have not been sufficiently explored (Nehra et al., 2022).

In this study, we synthesized and evaluated a series of amide- and isoquinoline-based compounds to examine their cytotoxic activity against cancer cell lines and their selectivity toward normal cells. This approach, based on established reactions of homoveratrilamine with various dibasic acids, aims to identify promising candidates for the development of effective and safe anticancer agents.

2. METHODOLOGY

2.1. Instrumentation

Infrared (IR) spectra were recorded using an FT-IR/NIR Spectrum 3 spectrometer (PerkinElmer) equipped with an attenuated total reflectance (ATR) system. NMR spectra were obtained on JNM-ECZ400R and JNM-ECZ600R spectrometers (JEOL, Japan) operating at 400 and 600 MHz for ^1H

measurements, respectively, using $CDCl_3$ as the solvent. Tetramethylsilane (TMS, 0.00 ppm) was used as the internal standard for ^1H NMR spectra, while the residual solvent signal of $CDCl_3$ (δ_C 77.16 ppm relative to TMS) was used as the internal reference for ^{13}C NMR spectra (Salleh et al., 2015; Salleh et al., 2019). High-resolution electrospray ionization mass spectra (HR-ESI-MS) were recorded on an Agilent Technologies 6420 mass spectrometer equipped with a triple quadrupole LC/MS system operating in ESI mode (TIC scan), and supplemented by CAMAG TLC-MS analysis using an ACQUITY QDa detector. The progress of reactions and the purity of the synthesized compounds were monitored by thin-layer chromatography (TLC) on silica gel plates (Silufol L/W, 10 cm × 20 cm, Sigma-Aldrich) with a fluorescent indicator (F_{254}, Germany), using various solvent systems. Spots were visualized under UV light at 254 nm. Melting points were determined using a BOETIUS micro melting point apparatus and are uncorrected. Itaconic acid dichloride was prepared according to the reported method by Freidlina et al. (1973).

2.2. Preparation of Amides

Equimolar amounts (1:1 molar ratio) of homoveratrilamine and the corresponding carboxylic acid were dissolved in methanol (5 mL) and stirred until the formation of the corresponding salt was complete. The reaction mixture was then heated in an oil bath at 180°C for 2 h. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion, the reaction mixture was dissolved in chloroform (100 mL). The organic phase was successively washed with 3% hydrochloric acid solution, followed by distilled water, then with 2% sodium hydroxide solution, and finally with distilled water until neutral pH was achieved. The chloroform layer was dried over anhydrous sodium sulfate (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by crystallization from an acetone–hexane mixture to afford the desired product.

***N*,1-Bis-(3,4-dimethoxyphenylethyl)-2-oxopyrrolidine-3-carboxyamide** (**4**). $C_{25}H_{32}N_2O_6$. Prepared from homoveratrilamine (3.62 g, 0.02 mol) and itaconic acid (1.30 g, 0.01 mol). Yield: 87% (4.0 g). m.p. 87-88°C. R_f = 0.73 ($CHCl_3$:MeOH = 8:1). ^1H NMR (400 MHz, $CDCl_3$, δ ppm, J in Hz): 2.58 (2H, m, H-2″), 2.68 (4H, q, J = 7.8, H-α, α′), 2.96 (1H, m, J = 7.7, H-3″), 3.33 (1H, t, J = 9.4, H-4″), 3.42 (4H, q, J = 7.7, H-β, β′), 3.56 (1H, dd, J = 6.8, 9.6, H-4″), 3.75, 3.76, 3.77/3.78 (3H, s, OCH_3-3,4,3′,4′), 6.25 (1H, br. s, NH), 6.64–6.70 (4H, m, H-2,2′,6,6′), 6.72 (2H, d, J = 8.5, H-5,5′). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 33.0 (C-3′), 35.1 (C-α, α′), 37.4 (C-2′), 41.0 (C-4′), 44.6 (C-β), 50.5 (C-β′), 55.9-56.9 (4×OCH_3), 111.4 (C-5,5′), 111.8 (C-2), 111.9 (C-2′), 120.6 (C-6), 120.7 (C-6′), 130.6 (C-1), 131.1 (C-1′), 149.0 (Ar-CO), 171.7 (C=O), 173.5 (C=O). MS (*m/z*): 456 $[M]^+$, 346, 219, 165, 113, 60.

***N*¹,*N*⁴-Bis(3,4-dimethoxyphenylethyl)-2-methylenesuccinamide** (**5**). $C_{25}H_{32}N_2O_6$. Itaconic acid dichloride (3.0 g, 0.018 mol) in benzene (20 mL) was treated with homoveratrilamine (6.5 g, 0.036 mol) in benzene (10 mL) added dropwise over 2 h at room temperature. Yield: 76% (4.5 g). m.p. 113-114°C. R_f = 0.71 ($CHCl_3$:MeOH = 8:1). ^1H NMR (400 MHz, $CDCl_3$, δ ppm, J in Hz): 2.73 (2H, t, J = 7.2, H-α), 2.77 (2H, t, J = 7.1, H-α′), 3.12 (2H, s, H-2″), 3.43 (2H, q, J = 7.2, H-β), 3.51 (2H, q, J = 7.1, H-β′), 3.84 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.86 (6H, s, OCH_3), 5.46 (1H, s, H-a-1‴), 5.64 (1H, s, H-b-1‴), 6.49 (1H, br s, NH), 6.56 (1H, br.s, NH), 6.74 (6H, m, Ar-H).

1-(1-(3,4-Dimethoxyphenylethyl)pyrrolidin-3-yl)-6,7-dimethoxy-3,4-dihydroisoquinoline(**6**). $C_{25}H_{30}N_2O_5$. Prepared from amide 5 (0.398 g, 0.87 mmol) in dry benzene (30 mL) and $POCl_3$ (4.6 g, 0.03 mol, 2.8 mL) under reflux for 3 h (method A). Yield: 60% (0.23 g). m.p. 193-197°C. R_f = 0.75 ($CHCl_3$:MeOH = 8:1). ^1H NMR (600 MHz, $CDCl_3$, δ ppm, J in Hz): 2.99 (2H, t, J = 7.0, H-4′), 3.05 (2H, t, J = 6.6, H-4), 3.87 (2H, m, H-3′), 3.90 (3H, s, OCH_3), 3.91 (6H, s, OCH_3), 4.01 (3H, s, OCH_3), 4.22 (2H, t, J = 6.6, H-3), 6.72 (1H, s, H-5′), 6.87 (1H, s, H-8′), 6.97 (1H, s, H-5), 7.03 (1H, s, H-8), 7.45 (1H, s, H-9), 8.12 (1H, s, H-11).

***N*-(3,4-Dimethoxyphenylethyl)-3-iodobenzamide** (**12**). $C_{17}H_{18}INO_3$. Prepared from homoveratril-amine (0.38 g, 2.1 mmol) and 3-iodobenzoic acid (0.52 g, 2.1 mmol) according to method A. Yield: 56% (0.48 g). m.p. 90-92°C. R_f = 0.80 ($CHCl_3$:MeOH = 6:1). ^1H NMR (600 MHz, $CDCl_3$, δ ppm, J in Hz): 2.86 (2H, t, J = 6.9, H-β), 3.67 (2H, q, J = 6.9, H-α), 3.85 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.06 (1H, br s, NH), 6.73 (1H, d, J = 1.9, H-2), 6.76 (1H, dd, J = 8.1, 2.0, H-6), 6.83 (1H, d, J = 8.1, H-5), 7.14 (1H, d, J = 7.8, H-5′), 7.62 (1H, dd, J = 7.8, 1.7, H-4′), 7.80 (1H, dd, J = 7.8, 1.8, H-6′), 8.02 (1H, s, H-2′).

2.3. Preparation of 3,4-Dihydroisoquinolines

Method B: A mixture of homoveratrilamine (1 mmol), the corresponding aromatic acid (1 mmol), and $POCl_3$ (4 mmol) in xylene (10 mL) was refluxed for 6-8 h. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion, the solvent was removed under reduced

pressure, and the resulting residue was suspended in cold water (3 mL). The mixture was then basified with 2 M aqueous NaOH to pH 8 and extracted with chloroform. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the corresponding 3,4-dihydroisoquinoline derivatives.

Method C: Homoveratrilamine (1 mmol) and the appropriate aromatic acid (1 mmol) were dissolved in toluene (2 mL), followed by the addition of $POCl_3$ (4 mmol). The reaction mixture was transferred to a sealed microwave reaction tube and irradiated in a microwave oven at 140°C for 30 min. After cooling, the solvent was removed under reduced pressure and the residue was suspended in water (3 mL). The mixture was alkalized with 2 M aqueous NaOH to pH 8 and extracted with chloroform. The combined chloroform extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by crystallization from acetone to give the desired compounds.

1-(2,4-Dinitrophenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (**13**). $C_{17}H_{15}N_3O_6$. Method B: Prepared from homoveratrilamine (0.15 g, 0.83 mmol), 2,4-dinitrobenzoic acid (0.176 g, 0.83 mmol), and $POCl_3$ (0.003 mol) in m-xylene (10 mL). Yield: 68% (0.21 g). Oily product. R_f = 0.50 ($CHCl_3$:MeOH = 6:1). Method C: Prepared from homoveratrilamine (0.15 g, 0.83 mmol), 2,4-dinitrobenzoic acid (0.21 g, 0.83 mmol), $POCl_3$ (0.003 mol), and toluene (2 mL, ρ = 0.864 g mL^{-1}). Yield: 60% (0.18 g). Oily product. R_f = 0.60 ($CHCl_3$:MeOH = 8:1). ^{1}H NMR (600 MHz, $CDCl_3$, δ ppm, J in Hz): 3.25 (2H, t, J = 7.1, H-3), 3.96 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 4.68 (2H, t, J = 7.1, H-4), 6.87 (1H, s, H-8), 7.43 (1H, s, H-5), 7.96 (1H, dd, J = 2.0, 9.1, H-5′), 8.04 (1H, d, J = 9.2, H-6′), 8.70 (1H, d, J = 2.0, H-3′).

1-(2,4-Dichlorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (**14**). $C_{17}H_{15}Cl_2NO_2$. Method B: Prepared from homoveratrilamine (0.096 g, 0.53 mmol), 2,4-dichlorobenzoic acid (0.102 g, 0.53 mmol), and $POCl_3$ (0.002 mol) in m-xylene (10 mL). Yield: 65% (0.104 g). Oily product. R_f = 0.60 ($CHCl_3$:MeOH = 8:1). Method C: Prepared from homoveratrilamine (0.17 g, 0.94 mmol), 2,4-dichlorobenzoic acid (0.18 g, 0.94 mmol), $POCl_3$ (0.004 mol), and toluene (2 mL, ρ = 0.864 g/mL). Yield: 60% (0.198 g). m.p. 170-172°C. R_f = 0.60 ($CHCl_3$:MeOH = 8:1). ^{1}H NMR (600 MHz, $CDCl_3$, δ ppm, J in Hz): 3.22 (2H, t, J = 6.8, H-4), 3.69 (3H, s, OCH_3), 3.80 (1H, q, J = 6.8, H-3), 3.95 (3H, s, OCH_3), 6.72 (1H, s, H-8), 6.90 (1H, s, H-5), 7.03 (1H, s, NH^+), 7.26 (1H, dd, J = 8.3, 2.0, H-5′), 7.34 (2H, m, Ar-H, residual acid salt), 7.38 (1H, d, J = 2.0, H-3′), 7.45 (1H, s, H-3″), 7.51 (1H, d, J = 8.3, H-6′).

1-(3-Iodophenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (**15**). $C_{17}H_{16}INO_2$. Method B: Prepared from homoveratrilamine (0.162 g, 0.90 mmol), 3-iodobenzoic acid (0.224 g, 0.90 mmol), and $POCl_3$ (0.004 mol) in m-xylene (10 mL). Yield: 63% (0.23 g). Oily product. R_f = 0.50 ($CHCl_3$:MeOH = 8:1). Method C: Prepared from homoveratrilamine (0.107 g, 0.60 mmol), 3-iodobenzoic acid (0.147 g, 0.60 mmol), $POCl_3$ (0.002 mol), and toluene (2 mL, ρ = 0.864 g/mL). Yield: 39% (0.10 g). m.p. 180-184°C. R_f = 0.76 ($CHCl_3$:MeOH = 8:1). ^{1}H NMR (600 MHz, $CDCl_3$, δ ppm, J in Hz): 2.65 (2H, t, J = 6.8, H-4), 3.63 (2H, t, J = 6.8, H-3), 3.75 and 3.85 (each 3H, s, 2 × OCH_3), 6.76 (1H, s, H-8), 7.00 (1H, s, H-5), 7.50 (2H, m, Ar-H), 8.05 (1H, dd, J = 8.0, 2.0, H-4′), 8.25 (1H, d, J = 2.0, H-2′).

(6,7-Dimethoxy-3,4-dihydroisoquinolin-1-yl)(phenyl)methanol (**16**). $C_{18}H_{19}NO_3$. Method B: Prepared from homoveratrilamine (0.78 g, 4.3 mmol), mandelic acid (0.65 g, 4.3 mmol), and $POCl_3$ (0.002 mol) in m-xylene (10 mL). Yield: 70% (0.96 g). m.p. 180-182°C. R_f = 0.70 ($CHCl_3$:MeOH = 4:1). Method C: Prepared from homoveratrilamine (0.403 g, 2.22 mmol), mandelic acid (0.40 g, 2.22 mmol), $POCl_3$ (0.009 mol), and toluene (2 mL, ρ = 0.864 g/mL). Yield: 57% (0.40 g). Oily product. Rf = 0.82 ($CHCl_3$:MeOH = 8:1). ^{1}H NMR (600 MHz, $CDCl_3$, δ ppm, J in Hz): 3.25 (2H, t, J = 7.5, H-3), 3.62 (3H, s, OCH_3), 4.02 (3H, s, OCH_3), 4.09 (2H, t, J = 8.0, H-4), 6.85 (1H, s, H-5), 7.23 (1H, s, H-8), 7.76 (2H, t, J = 8.3, Ar-H-3′,5′), 7.83 (1H, dt, J = 8.1, Ar-H-4′), 8.04 (2H, dd, J = 1.3, 8.5, Ar-H-2′,6′).

1-(3-Iodophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**17**). $C_{17}H_{18}INO_2$. Method B: Prepared from homoveratrilamine (0.107 g, 0.60 mmol), 3-iodobenzoic acid (0.147 g, 0.60 mmol), and $POCl_3$ (0.002 mol) in xylene (10 mL). Yield: 52% (0.127 g). m.p. 238-240°C (acetone). R_f = 0.78 ($CHCl_3$:MeOH = 8:1). ^{1}H NMR (600 MHz, $CDCl_3$, δ ppm, J in Hz): 3.07 (2H, m, H-4), 3.22 (2H, m, H-3), 3.67 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 5.36 (1H, s, H-1), 6.19 (1H, s, H-8), 6.64 (1H, s, H-5), 7.14 (1H, t, J = 7.8, H-5′), 7.40 (1H, d, J = 7.8, H-4′), 7.70 (1H, dd, J = 1.6, 1.0, H-2′), 7.72 (1H, dd, J = 7.9, 0.9, H-6′), 9.87 (0.5H, br.s, NH), 10.75 (0.5H, br.s, NH).

2.4. Cytotoxicity

Epithelial carcinoma of the cervix (HeLa), mammary gland adenocarcinoma (HBL-100, ATCC NTV-124), and laryngeal adenocarcinoma (HEp-2, ATCC CCL-23) cell lines were obtained from the Central Bank of Cell Culture Collections at the Institute of Cancer Research, Russian Academy of Sciences. T-lymphoblastic leukemia cells (CCRF-CEM, ATCC CCL-19) were provided by the University of Heidelberg, Germany, and African green monkey kidney cells (Vero B, ATCC CRL-1587) were obtained from the American Type Culture Collection (ATCC). Primary normal fibroblasts were isolated

from 2-3 day-old rat pups according to the method reported by Khamidova et al. (2021), and hepatocytes were isolated from 30-35 day-old rats using a modified protocol described by Cabral et al. (2018). Cancer cell lines were maintained in RPMI-1640 medium (Capricorn Scientific, Germany), whereas normal cell lines were cultured in DMEM/F-12 medium (Capricorn Scientific, Germany) supplemented with 10% fetal bovine serum (Gibco, USA), 1% L-glutamine, and 1×antibiotic-antimycotic solution (Lonza, Belgium). For cytotoxicity assays, monolayer cultures were gently detached using Versene solution prior to seeding or treatment. Passaged cancer cell lines were seeded into 96-well plates at a density of 2×10^4 cells/mL, while primary cells were seeded at 5×10^4 cells/mL to compensate for their lower proliferation rates. Cells were allowed to attach and grow for 24 h under standard culture conditions (5% CO_2, 80% humidity) before treatment. Test compounds were dissolved in DMSO, with the final DMSO concentration not exceeding 0.8% (v/v). The initial screening of compounds as cytotoxic candidates was performed at a concentration of 100 μM. Cells were incubated with the compounds for 24 h under the same conditions. After treatment, 20 μL of MTT solution (5 mg/mL; Acros Organics, Belgium) was added to each well, followed by incubation for 3-4 h. The culture medium was then removed, and 50 μL of DMSO was added to dissolve the resulting formazan crystals. Absorbance was measured at 630 nm using a microplate reader. Cell viability was expressed as a percentage relative to untreated control cells. For compounds that induced more than 50% cell death at 100 μM, cytotoxicity was further evaluated at concentrations of 10, 30, and 70 μM, and IC_{50} values were calculated.

All experiments were performed in triplicate and repeated in three independent experiments. Statistical analysis and data processing were carried out using Origin 8.6 software. The data were statistically analyzed using Student's t-test, with significance defined at $p < 0.05$.

3. RESULTS AND DISCUSSION

The reaction of homoveratrilamine (**1**) with itaconic acid (**2**) and its corresponding acid chloride (**3**) was investigated. It was found that the interaction between the amine and itaconic acid (**2**) afforded a higher yield of the amide when the corresponding ammonium salt was first formed, followed by heating at 180°C for 1-2 h to give the target product. Under these conditions, a mixture of two products was obtained. The first compound corresponded to product 5 and was formed in low yield (6%), whereas the second compound, product 4, was obtained as the major product in 87% yield (Figure 1). The reaction mixture was purified by crystallization from an acetone-hexane (1:1) solvent system. These results suggest that, in addition to the formation of amide **5**, a competing intramolecular cyclocondensation reaction occurs, involving two carboxyl groups and one amino group, leading predominantly to the formation of compound **4**.

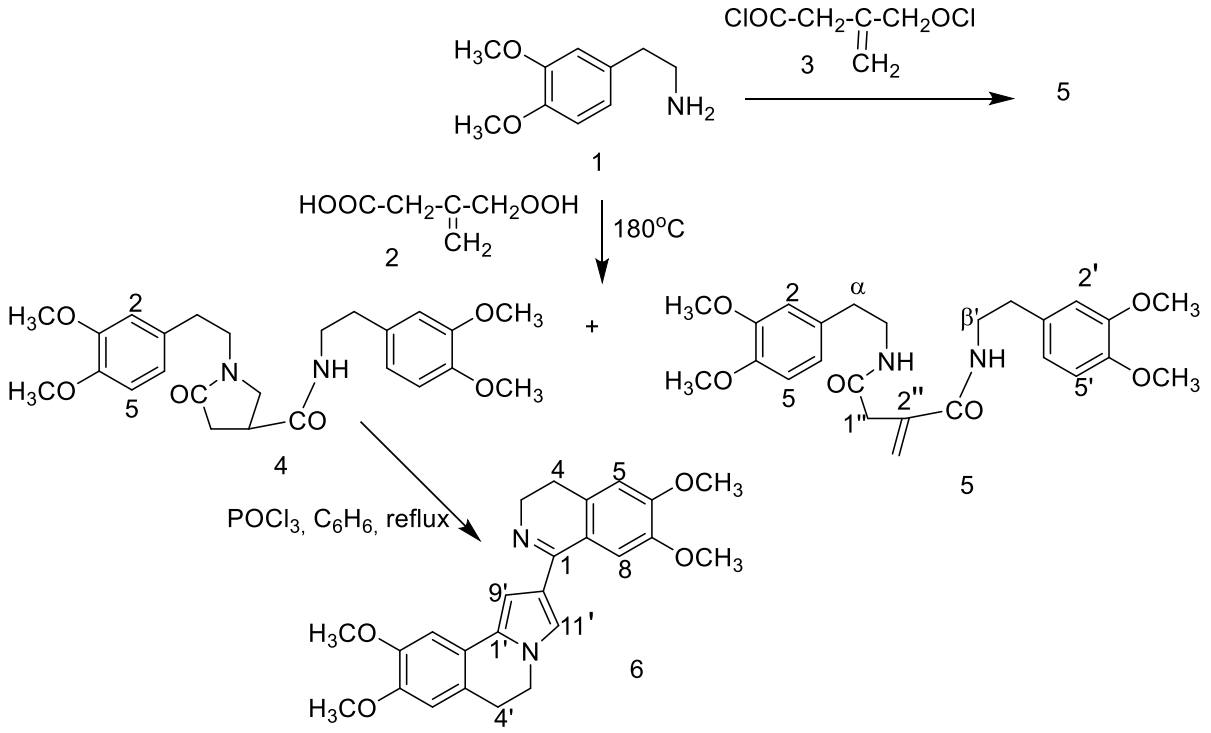
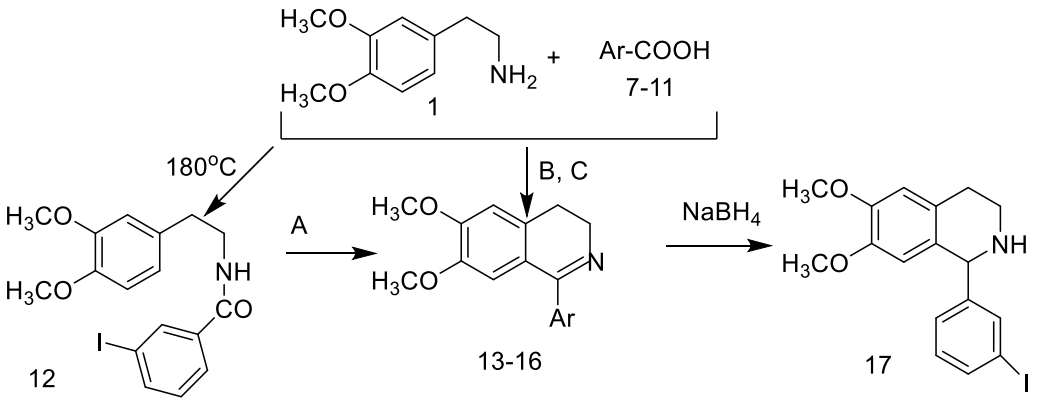


Figure 1. Synthesis of amides 4 and 5 from homoveratrilamine, itaconic acid dichloride 2, and chloroanhydride 3, followed by cyclization of 4 via the Mannich reaction

Due to the position of the double bond in the itaconic acid molecule **2**, it is considered more reactive than its isomers, citraconic and mesaconic acids. This enhanced reactivity increases the likelihood of forming the cyclic product **4** when the reaction mixture is heated to 180°C, presumably as a result of double-bond activation followed by intramolecular cyclization. In contrast, at room temperature in the presence of itaconic acid dichloride, compound **5** is predominantly formed.

The structures of compounds **4**-**6** were established based on a combination of ^{1}H and ^{13}C NMR spectroscopy and high-resolution mass spectrometry (HR-MS). In the mass spectra of all amides, a characteristic molecular ion peak [M]^+ was observed. For compound **4**, the molecular ion peak appeared at *m/z* 456, corresponding to the molecular formula $C_{25}H_{32}O_6N_2$, along with fragment ions at *m/z* 346, 219, 165, 113, and 60. In the ^{1}H NMR spectrum of compound **4**, signals corresponding to the homoveratrilamine fragments were clearly identified. The α,α′-methylene protons appeared at δ 2.68 (4H, t, J = 7.8 Hz), while the β,β′-methylene protons were observed as a quartet at δ 3.42 (4H, J = 7.7 Hz). The NH proton resonated at δ 6.25 as a broadened singlet. The aromatic H-5 and H-5′ protons appeared at δ 6.71 ppm as a doublet with a coupling constant of 8.5 Hz. Notably, the absence of signals corresponding to an exocyclic $=CH_2$ group confirmed that cyclization had occurred. The methylene protons of the 2″ position of the oxopyrrolidine ring appeared as a multiplet at δ 2.58, the 3″ methine proton resonated at δ 2.96, and the diastereotopic 4″ protons were observed at δ 3.33 (H-ax) and 3.56 ppm (H-eq). On the basis of these spectroscopic features, compound 4 was identified as N,1-bis(3,4-dimethoxyphenylethyl)-2-oxopyrrolidine-3-carboxamide.

The structure of amide **5**, synthesized using acid chloride **3**, was also fully consistent with its spectroscopic data. Subsequent cyclodehydration of amide **5** using $POCl_3$ as a condensing agent in the Bischler-Napieralski reaction afforded dihydroisoquinoline **6**. In the ^1H NMR spectrum of compound 6, the H-β′ signal was shifted downfield to δ 4.22 (t, J = 6.6 Hz, H-3′), and the NH proton signal was absent, indicating successful cyclization. Furthermore, the aromatic protons H-5, H-5′, H-8, and H-8′, as well as H-9 and H-11, appeared as singlets, which is characteristic of the isoquinoline framework. These data confirm the formation of 1-(1-(3,4-dimethoxyphenylethyl)pyrrolidin-3-yl)-6,7-dimethoxy-3,4-dihydroisoquinoline. In addition to the classical synthesis of dihydroisoquinolines (**6** and **12**) via the intermediate amide formation (method A), alternative one-pot approaches were explored. The preparation of dihydroisoquinolines **13**-**16** was achieved directly by treating homoveratrilamine (**1**) with acids **8**-**11** (the reaction with cinnamic acid (**7**) afforded a mixture of products) in the presence of $POCl_3$ either by refluxing in xylene (method B) or under microwave irradiation (method C), as shown in Figure 2. These methods provide efficient and practical routes to structurally diverse dihydroisoquinoline derivatives.



Ar= 2,4-(NO2)2C6H3-(8, 13); 2,4-Cl2C6H3-(9, 14); m-IC6H4-(10, 15); C6H5CH(OH)-(11, 16)

Method A: $POCl_3$, C_6H_6, reflux; Method B: MW, $POCl_3$, toluene; Method C: $POCl_3$,xylene, reflux

Figure 2. Synthesis of amides (12) and dihydro- and tetrahydroisoquinolines (**13-17**) by A,B,C methods

The data obtained showed that dihydroisoquinolines can be efficiently synthesized using the developed method B, bypassing the stage of preparation, isolation and purification of amides. The cytotoxic potential of the synthesized derivatives was assessed against four cancer cell lines using the MTT assay (Niks et al.,1990). A concentration of 100 μM allows for the initial selection of compounds exhibiting both cytotoxic and proliferative activity, while also saving time and consumables by avoiding testing at additional concentrations. Cisplatin, a well-established anticancer drug, was employed as the reference standard (Tables 1 and 2).

Based on the results presented in Table 1, dihydro- and tetrahydroisoquinoline derivatives of iodobenzoic acid (compounds **12** and **17**), prepared via different methods, as well as compound **16**, a dihydroisoquinoline derivative of mandelic acid, stimulated proliferation of HeLa cervical carcinoma cells by approximately 15-20% relative to the control under the same conditions. In addition, the mandelic acid derivative also enhanced proliferation of HBL-100 breast adenocarcinoma cells. An investigation of the structure-function relationships of dihydroisoquinolines differing in substituents in the aromatic moiety demonstrated that the proliferative activity of the compounds decreases in the following order: **16** (dimethoxy) > **13** (dinitro) > **14** (dichloro) > **15** (iodophenyl). Compound **16** induced proliferation of cervical carcinoma and breast adenocarcinoma cells by 19.5% and 22%, respectively, whereas compound **15** had no effect on cell growth. At the same time, the transition from dihydroisoquinoline 15 to tetrahydroisoquinoline **17**, while retaining the iodophenyl fragment, resulted in the emergence of a proliferative effect, manifested as an 18% increase in the proliferation of cervical carcinoma cells.

Table 1. Cytotoxicity of the compounds against cancer cell lines (100 μM)

Compound, 100 μM	Alive cells (%), Mean ± SEM, * p < 0.05			
	CCRF-CEM	**HeLa**	**HBL-100**	**HEp-2**
5	81.5 ± 9.0	87.3 ± 9.0	95.0 ± 8.8	96.8 ± 8.3
6	**48.4 ± 5.5***	**5.1 ± 0.6***	**1.1± 0.3***	**2.7 ± 0.4***
12	77.6 ± 8.3	115,0 ± 4,9*	100.0 ± 0.0	107.0 ± 5,0
13	82.0 ± 3.1	109,0 ± 8,4*	111,0 ± 6,0*	108.0 ± 7,8
14	107,0 ± 4,6	62.8 ± 6.2	92.6 ± 5.3	82.1 ± 6.5
15	97.3 ± 7.1	98.0 ± 10.0	93.2 ± 10.0	89.1 ± 7.4
16	95.6 ± 8.0	119,5 ± 5,7*	122.0 ± 5,7*	92.7 ± 5.5
17	87.4 ± 9.5	118,0 ± 2,9*	100.0 ± 5.0	88.3 ± 6.2
Cisplatin	48.4 ± 5.0	7.6 ± 1.1	0.0 ± 0.0	54.3 ± 3.6
control	100.0	100.0	100.0	100.0

***** $p < 0.05$ indicate statistically significant differences between control and experimental groups

There are no reports in the literature on the effects of dihydro- and tetrahydroisoquinoline derivatives based on mandelic and iodobenzoic acids. However, previous studies have shown that derivatives of iodobenzoic and mandelic acids with another molecular skeleton generally exhibit anticancer activity, demonstrating cytotoxic effects and cell cycle arrest in various tumor cell lines, including lung and colorectal cancers (Demir-Yazici et al., 2022; Girek et al., 2019). Despite similar three-dimensional arrangements, the biological activity of isoquinolines in general, and racemic tetrahydroisoquinolines in particular that are chemically related to compound 17, critically depends on the nature and position of the substituent in the C ring (Terenteva et al, 2017). Accordingly, even closely related compounds may differ markedly in their biological effects. In contrast, our results indicate that the dihydroisoquinoline derivatives investigated in this study unexpectedly promoted the proliferation of breast cancer cells, suggesting that incorporation of the dihydroisoquinoline scaffold may alter the biological profile of these acid-based fragments. This highlights the importance of scaffold context in modulating the activity of structurally related molecules. Thus, these compounds were deprioritized due to inactivity or proliferative effects. Of the compounds tested, only compound **6**, a dihydroisoquinoline derivative of itaconic acid, exhibited significant cytotoxic activity. At 100 μM, the extent of cell growth inhibition ranged from 51.6% to 98.9%, depending on the specific cancer cell line. For the dihydroisoquinoline derivative of itaconic acid, which exhibited cytotoxicity, the IC_{50} values were determined for both cancerous and non-transformed cells. For HBL-100 breast adenocarcinoma cells, the IC_{50} was 13.1 μM; for HeLa cervical carcinoma cells, 24.9 μM; and for laryngeal adenocarcinoma cells, 27.1 μM. The T-lymphoblastic leukemia CCRF-CEM cell line was less sensitive to this compound, with IC_{50} value of 95.9 μM.

Table 2. Cytotoxicity of the itaconic acid–derived dihydroisoquinoline (**6**) in comparison with cisplatin in cancerous and non-malignant cell lines

Cells / Substance	IC_{50} value (μM), Mean ± SEM	
	(6)	**Cisplatin**
CCRF-CEM	95.9 ± 6,8	96.7 ± 6,8
HeLa	24.9 ± 2,0	38,3 ± 3,9
HBL-100	13.1 ± 2,1	12.3 ± 1,5
HEp-2	27.1 ± 3,0	68,6 ± 3,5
Vero B	95.9 ± 7.6	29,9 ± 3,0
primary fibroblasts	12.6 ± 2.1	>100 μM
primary hepatocytes	100.0 ± 3.9	>100 μM

The marked cytotoxicity of dihydroisoquinoline **6**, compared to derivatives **12–17**, which are either proliferative or inactive, is likely due to its dimeric structure. One fragment corresponds to a dihydroisoquinoline moiety (as in **12–16**), while the other is a pyrrolidine ring, a combination that

fundamentally modifies the molecule's biological activity. Compound **6** was further assessed for cytotoxicity in non-transformed cells, including African green monkey kidney cells (Vero B), rat epithelial fibroblasts, and rat hepatocytes. The data indicate that the compound displayed minimal activity toward kidney and liver cells, while measurable cytotoxicity was observed only in skin fibroblasts, with an IC_{50} value of 12.6 μM. The differential sensitivity of skin and liver cells to compound **6** may be attributed to the high detoxification capacity of hepatocytes, which efficiently metabolize and inactivate this compound. In contrast, skin fibroblasts possess a more limited enzymatic repertoire, leading to intracellular accumulation of compound **6** and the manifestation of pronounced cytotoxicity (Sevior et al, 2012, Eijl et al, 2012). Itaconic acid is an endogenous metabolite produced in activated macrophages and participates in the regulation of cellular metabolism and immune responses (Ma et al., 2025). Recent research suggests that itaconate and its derivatives can modulate various signaling and metabolic pathways implicated in carcinogenesis, potentially leading to perturbations in tumor cell energy metabolism and attenuation of proliferative capacity. This positions itaconic acid as a promising scaffold for the rational design of anticancer agents (Ma et al., 2025).

Derivatives of itaconic acid, including esters, amides, α,β-unsaturated carbonyl systems and hybrid molecules incorporating additional pharmacophoric moieties, have been investigated for their cytotoxic effects in vitro. Such compounds are capable of inducing oxidative stress, causing perturbations in the cell cycle and activating apoptotic pathways in cancer cells. In a representative study by Perković et al., a series of itaconic acid-based hybrids bearing fluoroaniline, pyridine, indole, quinoline and related aromatic scaffolds demonstrated antiproliferative activity against a panel of human cancer cell lines, with GI_{50} values predominantly in the low micromolar range (e.g., quinoline-containing hybrid **12** exhibited GI_{50} as low as 0.7-1.3 μM across multiple solid tumor lines, and homodimer 15 showed GI_{50} values of 0.7-2.4 μM against MCF-7 and other models) (Perković et al., 2020). These observations support the relevance of the itaconate core in imparting measurable cytotoxicity. In our study, the cytotoxic profile of the itaconic acid-derived dihydroisoquinoline **6**, as reflected by its IC_{50} values in the low micromolar range across tested cancer cell lines, is consistent with previously reported itaconic hybrid scaffolds. Although the molecular targets and mechanisms remain to be fully elucidated, the observed activity aligns with literature precedent and underscores the feasibility of leveraging an itaconate backbone in the design of novel anticancer agents. The comparative potency of compound 6, when considered alongside the literature values, lends further support to our chosen molecular design strategy.

4. CONCLUSION

For the first time, condensation reactions of homoveratrilamine with itaconic, mandelic, and substituted benzoic acids (meta-iodo, 2,4-dinitro, and 2,4-dichlorobenzoic acids) afforded amides **4**, **5**, **12**, 1-substituted dihydro (**6**, **13**-**16**) and tetrahydroisoquinoline (**17**) derivatives. Thus, we have demonstrated that, in addition to the two-stage Bischler–Napieralski reaction, refluxing in xylene and microwave irradiation can be successfully applied to the one-step synthesis of dihydroisoquinolines. It was shown that, depending on the reaction conditions, itaconic acid can yield either a conventional amide or oxopyrrolidinone (**4**) and pyrrolidino-isoquinoline (**6**) derivatives. The cytotoxic effects of the synthesized compounds were evaluated in vitro using four human cancer cell lines and three non-malignant cell lines, employing the MTT assay. It was established that the proliferative activity of dihydroisoquinolines, differing in substituents in the aromatic moiety, emerges and increases in the following order: iodophenyl < dichloro < dinitro < dimethoxy. The transition from dihydroisoquinoline **15** to tetrahydroisoquinoline **17**, while retaining the iodophenyl fragment in the structure, results in the appearance of a proliferative effect in cervical carcinoma cells, with an 18% increase in proliferation. Among the tested compounds, the itaconic acid dihydroisoquinoline derivative exhibited pronounced cytotoxicity against HeLa, HBL 100, and HEp-2 cancer cells, while displaying relatively low toxicity toward Vero B cells and hepatocytes. Nevertheless, its pronounced cytotoxicity toward fibroblasts underscores the critical need for further structural refinement to obtain a promising anticancer candidate with improved efficacy and reduced off-target toxicity. In conclusion, the biological effects of dihydro- and tetrahydroisoquinolines on cellular growth and metabolism are governed not by the isoquinoline scaffold itself but by the nature and topology of the substituents within the molecule. Consequently, a systematic and comprehensive evaluation of the biological activity of all newly synthesized derivatives is critically important for the rational development and selection of promising anticancer agents.

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CONFLICT OF INTEREST
The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTION
Ziroat Urunbaeva, Abdusalom Saidov: Conceptualization, Methodology, Software. Elvira Yusupova, Valentina Vinogradova: Data collection, Writing original draft. Umida Khamidova: Visualization, Investigation. Shakhnoz Azimova: Supervision. Mukaddas Umarova: Software, Validation. Ekaterina Terenteva: Writing, Reviewing and Editing.

DATA AVAILABILITY
Data will be made available upon reasonable request.

DECLARATION OF GENERATIVE AI
Not applicable.

ETHICS
Not applicable.

REFERENCES

Aghekyan AA, Arakelyan EA, Panosyan GA, Khachatryan AG, Markaryan EA. (2009). Synthesis of novel 1,2-functionally-substituted 6,7-dimethoxy-4-spirocyclo-pentanetetrahydroisoquinolines. *Chemistry of Heterocyclic Compounds*, 45(9), 1069-1074. doi:10.1007/s10593-009-0385-5

Azamatov AA, Zhurakulov ShN, Vinogradova VI, Tursunkhodzhaeva FM, Khinkar RM, Malatani RT, Aldurdunji MM, Tiezzi A, Mamadalieva NZ. (2023). Evaluation of the local anesthetic activity, acute toxicity, and structure-toxicity relationship in series of synthesized 1-aryltetrahydroisoquinoline alkaloid derivatives in vivo and in silico. *Molecules*, 28, 477-494. doi:10.3390/molecules28020477

Basak D, Arrighi S, Darwiche Ya, Deb S. (2021). Comparison of anticancer drug toxicities: Paradigm shift in adverse effect profile. *Life*, 12(1), 48. doi:10.3390/life12010048

Cabral F, Miller CM, Kudrna KM, Hass BE, Daubendiek JG, Kellar BM, Harris EN. (2018). Purification of hepatocytes and sinusoidal endothelial cells from mouse liver perfusion. *Journal of Visualized Experiments*, 132, e56993. doi:10.3791/56993

Darji P, Patel J,.Patel B, Chudasama A, Fnu PI, Nalla S. (2024). A comprehensive review on anticancer natural drugs. *World Journal of Pharmacy and Pharmaceutical Sciences*, 13(4), 717-734. doi:10.20959/wjpps20244-27049

Demir-Yazici K, Guzel-Akdemir O. (2022). Synthesis and potential antitumor activities of mandelic acid linked 2-aryl-1,3-thiazolidin-4-ones. *Journal of Research in Pharmacy*, 26(4), 931-940. https://doi.org/10.29228/jrp.191

Diaz G, Miranda IL, Diaz MA. (2015). Quinolines, isoquinolines, angustureine, and congeneric alkaloids-occurrence, chemistry, and biological activity. Phytochemicals - Isolation, Characterisation and Role in Human Health, IntechOpen, p. 141-162. doi:10.5772/59819

Dusmatova DE, Terent'eva EO, Bobakulov KhM, Mukhamatkhanova RF, Tsai EA, Tashkhodzhaev B, Sham'yanov ID, Azimova ShS, Abdullaev ND. (2019). Nonpolar constituents of *Inula grandis* roots cytotoxic activity of Igalan. *Chemistry of Natural Compounds*, 55(3), 571-574. doi:10.1007/s10600-019-02747-y

Dy GK, Adjei AA. (2013). Understanding, recognizing, and managing toxicities of targeted anticancer therapies. *CA: A Cancer Journal for Clinicians*, 63(4), 249-79. doi:10.3322/caac.21184

Eijl S, Zhu Zh, Cupitt J, Gierula M, Götz Ch, Fritsche E, Edwards RJ. (2012). Elucidation of xenobiotic metabolism pathways in human skin and human skin models by proteomic profiling. *PLoS One*, 7, e41721. doi: 10.1371/journal.pone.0041721

Freidlina RK, Velichko FK, Chukovskaya ET, Khorlina MY, Krentsel BA., Il'ina DE, Gasanov RG. (1973). Methods of Heteroorganic Chemistry, Chlorine, Aliphatic Compounds, Moscow, Russia.

Girek M, Kłosiński K, Grobelski B, Pizzimenti S, Cucci MA, Daga M, Barrera G, Pasieka Z, Czarnecka K, Szymański P. (2019). Novel tetrahydroacridine derivatives with iodobenzoic moieties induce G0/G1 cell cycle arrest and apoptosis in A549 non-small lung cancer and HT-29 colorectal cancer cells. *Molecular and Cellular Biochemistry,* 460(1), 123-150. doi:10.1007/s11010-019-03576-x

Gurjar MK, Pramanik C, Bhattasali D, Ramana CV, Mohapatra DK. (2007). Total syntheses of schulzeines B and C. *The Journal of Organic Chemistry*, 72(17), 6591-6594. doi:10.1021/jo070560h

Kadir NHA, Salleh WMNHW, Ghani NA. (2022). A systematic review on essential oils and biological activities of the genus *Syzygium* (Myrtaceae). Rivista Italiana Delle Sostanze Grasse, 99(2), 165-178.

Khamidova UB., Terenteva EO, Azimova ShS. (2021). Isolation of skin fibroblasts by new modified method. *Uzbek Biological Journal*, 5, 7-10.

Kim AN, Ngamnithiporn A, Du E, Stoltz BM. (2023). Recent advances in the total synthesis of the tetrahydroisoquinoline alkaloids (2002–2020). *Chemical Reviews*, 123, 9447-9496. doi:10.1021/acs.chemrev.3c00054

Kolotova NV, Starkova AV, Gashina SV. (2016). Synthesis and biological activity of monosubstituted hydrazides of itaconic and dimethylmaleic acids. *Issues of Ensuring the Quality of Medicines*, 3(13), 15-23.

Larghi EL, Bohn ML, Kaufman TS. (2009). Aaptamine and related products: Their isolation, chemical syntheses, and biological activity. *Tetrahedron*, 65(22), 4257-4282. doi:10.1016/j.tet.2009.03.027

Ma K, Zhou P, Zhang W, Zeng L, Tao K, Zhang P. (2025). Itaconic acid: a regulator of immune responses and inflammatory metabolism. *Current Issues in Molecular Biology*, 47(7), 534. doi:10.3390/cimb47070534

Malikova RN, Sakhautdinov IM, Terenteva EO, Khashimova ZS, Yunusov MS, Azimova ShS. (2020). Synthesis and cytotoxic activity of a series of functionalized maleopimarimides. *Chemistry of Natural Compounds*, 56, 101-104 doi:10.1007/s10600-020-02953-z

Mao Ya, Soni K, Sangani Ch, Yao Y. (2020). An overview of privileged scaffold: Quinolines and isoquinolines in medicinal chemistry as anticancer agents. *Current Topics in Medicinal Chemistry*, 20(28), 2599-2633. doi:10.2174/1568026620999200917154225

Nehra B, Mathew B, Chawla PA. (2022). A medicinal chemist's perspective towards structure activity relationship of heterocycle based anticancer agents. *Current Topics in Medicinal Chemistry*, 22(6), 493-528. doi:10.2174/1568026622666220111142617

Niks M, Otto M. (1990). Towards an optimized MTT assay. *Journal of Immunological Methods*, 130, 149-151. doi: 10.1016/0022-1759(90)90309-j

Niyazmetov AR, Terent'eva EO, Khamidova UB, Khashimova ZS, Azimova ShS, Vinogradova VI. (2020). Synthesis of derivatives of the 2-arylquinoline alkaloid dubamine and their cytotoxicity. *Chemistry of Natural Compounds,* 56, 511-517. doi:10.1007/s10600-020-03074-3

Perkovic I, Beus M, Schols D, Persoons L, Zorc B. (2020). Itaconic acid hybrids as potential anticancer agents. *Molecular Diversity,* 26(1), 1-14. doi:10.1007/s11030-020-10147-6

Qing ZX, Huang JL, Yang XY, Liu JH, Cao HL, Xian F, Zeng JG. (2018). Anticancer and reversing multidrug resistance activities of natural isoquinoline alkaloids and their structure-activity relationship. *Current Medicinal Chemistry*, 25(38), 5088-5114. doi:10.2174/0929867324666170920125135

Reddy YD, Kumari YB, Dubey PK. (2013). Synthesis of a novel water soluble phthalimide derivative of acetaminophen as potential analgesic and antipyretic agent. *Indian Journal of Chemistry*, 52(39), 691-693. doi:10.1002/chin.201337061

Saidov AS, Turgunov KK, Levkovich MG, Vinogradova VI. (2015). Synthesis of bis-tetrahydroisoquinolines based on homoveratrylamine and several dibasic acids. 4. Reaction with malonic and succinic acids. *Chemistry of Natural Compounds*, 51, 316-319. doi:10.1007/s10600-015-1268-x

Saidov AS, Alimova M, Levkovich MG, Vinogradova VI. (2013). Synthesis of bis-tetrahydroisoquinolines based on homoveratrylamine and a series of dibasic acids. *Chemistry of Natural Compounds*, 49, 302-304. doi:10.1007/s10600-013-0586-0

Saidov ASh, Levkovich MG, Vinogradova VI. (2016). Interaction of homoveratrilamine with malic and fumaric acids. *Chemistry for Sustainable Development*, 24(6), 823-826.

Salleh WMNHW, Ahmad F, Khong HY. (2015). Chemical constituents from *Piper caninum* and antibacterial activity. *Journal of Applied Pharmaceutical Science*, 5(6), 20-25. doi:10.7324/JAPS.2015.50604

Salleh WMNHW, Hashim NA, Khamis S. (2019). Chemical constituents and lipoxygenase inhibitory activity of *Piper stylosum* MiQ. *Bulletin of the Chemical Society of Ethiopia*, 33(3), 587-592. doi:10.4314/bcse.v33i3.19

Sevior DK, Pelkonen O, Ahokas JT. (2012). Hepatocytes: the powerhouse of biotransformation. *The International Journal of Biochemistry & Cell Biology,* 44(2), 257-261. doi: 10.1016/j.biocel.2011.11.011

Shakri NM, Salleh WMNHW, Khamis S, Ali NAM, Shaharudin SM. (2020). Chemical composition of the essential oils of four *Polyalthia* species from Malaysia. *Zeitschrift für Naturforschung C A Journal of Biosciences*, 75(11-12), 473-478. doi:10.1515/znc-2020-0097

Shukla KH, Boehmler DJ, Bogacyzk S, Duvall BR, Peterson WA, McElroy WT, DeShong P. (2006). Application of palladium-catalyzed allylic arylation to the synthesis of a (±)-7-deoxypancratistatin analogue. *Organic Letters*, 8, 4183-4186. doi:10.1021/ol061070z

Stubbs NM, Roady TJ, Schwermann MP, Eteshola EO, MacDonald WJ, Purcell C, Ryspayeva D, Verovkina N, Tajiknia V, Ghandali M, Voong V, Lannigan AJ, Raufi AG, Lawler S, Holder SL, Carneiro BA, Cheng L, Safran HP, Graff SL, Dizon DS, Mani SA, Seyhan AA, Sobol RW, Wong ET, Chen CC, Gokaslan Z, Taylor MS, Rivers BM, El-Deiry WS. (2025). Acquired resistance to molecularly targeted therapies for cancer. *Cancer Drug Resistance*, 8, 27. doi:10.20517/cdr.2024.189

Terenteva EO, Khashimova ZS, Tsay EA, Jurakulov ShN, Saidov ASh, Vinogradova VI, Azimova ShS. (2017). Chemical modification of tetrahydroisoquinolines and their cytotoxic activity. *Asian Journal of Pharmacy and Pharmacology*, 3(3), 66-78.

Tseomashko NE, Terent'eva EO, Kodirova DB, Okhunov II, Aripova SF, Khashimova ZS, Azimova ShS. (2013) Synthesis of convolinine and cytotoxic activity of alkaloids of the genus *Convolvulus* and their derivatives. *Chemistry of Natural Compounds*, 48, 1039-1041. doi:10.1007/s10600-013-0459-6

Tukhtaev DB, Yusupov AB, Vinogradova VI. (2021). Synthesis of new amides based on N-phthaloyl-α-amino acids. *Egyptian Journal of Chemistry,* 64, 3049-3058 doi:10.21608/ejchem.2021.48494.2990

Zhurakulov SN, Mamadalieva NZ, Vinogradova VI, Mollica A, Procino E, Turgunov KK, Umarova MR, Terenteva EO, Azimova ShS. (2025). Design and synthesis of cryptostyline I derivatives: Cytotoxic activity and molecular docking insights. *ChemistrySelect*, 10, e01526, 1-15. doi.org/10.1002/slct.202501526