Journal of Science and Technology – Engineering and Technology for Sustainable Development
Volume 36, Issue 3, July 2026, 008–015

Study on the Synthesis of Natural and Synthetic *β*-Amino Alcohols with Biological Activity

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Abstract

β-Amino alcohols are important bifunctional compounds characterized by the presence of both amine and hydroxyl groups within the molecule, which contributes to their diverse biological activities. Numerous experimental and clinical studies have demonstrated that β-amino alcohols play a central role in the pharmacophoric structures of various clinically used drugs This study focuses on the synthesis of a series of β-amino alcohols via epoxide ring-opening reactions using both natural and synthetic building blocks, followed by an evaluation of their novel biological activities. A total of 10 β-amino alcohols were successfully synthesized, including 05 novel compounds reported for the first time. These compounds were evaluated for cytotoxic activity against four cancer cell lines: rhabdomyosarcoma (RD), human hepatocellular carcinoma (Hep-G2), lung cancer (Lu), and uterine cancer (Fl), as well as for antimicrobial activity against 8 microbial strains representing 4 groups: gram-negative bacteria, gram-positive bacteria, filamentous fungi, and yeasts. The results showed that the cytotoxic activity of the synthesized compounds was generally low, with only two compounds exhibiting weak activity and the remainder showing no activity. Although these findings do not support the anticancer potential of the compounds, they do suggest a favourable safety profile for exploring other biological applications. In contrast, the antimicrobial screening yielded promising results: five compounds demonstrated inhibitory effects against 1–3 microbial strains, and notably, one compound exhibited activity against five strains.

Keywords: Anticancer, antimicrobial, *β*-Amino alcohol, epichlorohydrin ring opening, natural compounds, organic synthesis, semi-synthesis.

1. Introduction

β-Amino alcohol is a common scaffold, easily found not only in synthetic medicines but also in natural compounds. This moiety plays a crucial role in pharmacophore of medicines inhibiting *β*-adrenergic (*β*-blocker), applied in the treatment of hypertension (propranolol, atenolol, and nadolol, etc.) [1], inhibiting protease in anti-HIV (ritonavir, lopinavir, etc.) [2]. *β*-Amino alcohol bearing both hydroxyl group (-OH) and amino group (-NH_2, -NHR và -NR_2) on an aliphatic branch, where the hydroxyl group is at *β* position.

In natural compounds, most common *β*-amino alcohol moieties are found in hydroxy amino acid. For example, antibiotic vancomycin contains aryl serine and fungicide sphingofungin bearing a hydroxy amino acid residue at the polar site. Another group of natural compounds bearing cyclic amino alcohol has important bioactivities. Among those, quinine was used in anti-malaria medicines. Cyclic amino alcohols like polyhydroxylated alkaloid are called aza-sugar, i.e. castanospermine was reported as a strong antagonist of α- and *β*-glucosidase [3].

Studies have shown that amino alcohol derivatives from totarol have the ability to effectively inhibit *Plasmodium* parasites, opening up prospects in the treatment of malaria. [3]. Studies on bacteria, *N*-alkylated *β*-amino alcohols showed significant antibacterial activity, especially against Staphylococcus aureus, making them potential candidates for the treatment of bacterial infections. [4]. In cancer treatment, novel *β*-amino alcohols linked to the benzosuberone backbone have shown potent antiproliferative effects, suggesting potential as anticancer agents. [5]. Against *Mycobacterium tuberculosis*, *β*-amino alcohol has been identified as an inhibitor of the enzyme *N*-acetyltransferase – a promising target in the treatment of tuberculosis [6]. These compounds have also been studied in the treatment of Alzheimer's disease, where they demonstrate potential as multifunctional agents capable of acting on multiple aspects of this neurodegenerative disorder [7].

p-ISSN 3093-3242
e-ISSN 3093-3579
https://doi.org/10.51316/jst.191.etsd.2026.36.3.2
Received: Oct 21, 2025; Revised: Jan 21, 2026;
Accepted: Jan 28, 2026; Online: Jun 8, 2026

β-Amino alcohols can be synthesized through various methods. In 1942, Suter and Weston proposed the synthesis of α-alkyl ephedrine (*β*-amino alcohol) by Grignard reaction with the carbonyl group of racemic ephedrine hydrochloride [8]. A novel method for the synthesis of *β*-amino alcohols under mild reaction conditions was reported by Yang *et al.* via a two-step Smiles rearrangement reaction. [9] Furthermore, theoretical calculations were performed to confirm the plausibility of the mechanism. This method was shown to be particularly efficient for *N*-arylated amino alcohols, which are difficult to synthesize by conventional methods. The most practical and common method is the ring-opening reaction of epoxides [10], aziridine [11] or Mannich reaction [12]. Although Lewis acid-metal-catalysed reactions can proceed smoothly to produce *β*-amino alcohols in high yields. However, they involve toxic metal salts and the separation, recovery, and recycling of expensive or air-sensitive catalysts are also difficult [13].

Based on the references, the research team developed a method to synthesize *β*-amino alcohols based on the reaction of phenolic with epichlorohydrin, then conducted a ring-opening reaction with amine under mild reaction conditions, without using expensive or sensitive catalysts, with a yield of 30–65%.

2. Method and Experiment

2.1. Chemicals

Almost chemicals were purchased from trusted retailers, except natural compounds were collected from another research group with proved analysis.

- 4 phenolic compounds: 1-naphthol, 4-(hydroxymethyl) phenol, 2-(4-hydroxyphenyl) acetamide (Merck); 4-hydroxy coumarin (China).

- 4 amine compounds: isopropyl amine, 2-(1-Piperazinyl) ethanol (Merck); diethyl amine, morpholine (China); 5-Fluorouracil (Merck).

- Epichlorohydrin (Merck)

- K_2CO_3, NaOH, HCl, Na_2SO_4 anhydrous (China)

- Solvent: Ethyl acetate (EtOAc/EA), Dichloromethane (DCM), Methanol (MeOH), *n*-hexane (China) are distilled before using

- Silica gel 60 (0.063-0.200 mm) (Merck)

- Indirubin, Murrayafoline A are a natural compound, collected from Institute of Chemistry, Vietnam Academy of Science and Technology.

2.2. Synthesis Methods of β-Amino Alcohols

Phenolic compounds (1 equiv.) and K_2CO_3 were charged into a round bottom flask and dissolved in MeOH. Epichlorohydrin (5 equiv.) was added slowly into the flask. The reaction mixture was stirred at 50 to 60 °C for 4 hours. After the reaction, the solvent is evaporated. The crude product mixture was extracted with EtOAc twice, washed with water once, and washed with NaOH 1M once. The extract was dried with Na_2SO_4, filtered and evaporated to remove all the solvent. The resulting product was weighed to prepare for the next step without further purification.

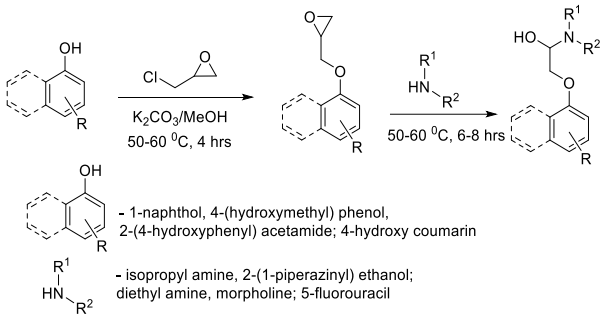

Fig. 1. Synthesis route of β-amino alcohols

Product of previous step was dissolved in a round bottom flask with MeOH. Corresponding amine was added to the mixture, stir well at 50 to 60 °C for 6–8 hours. After the reaction, solvent and amine were evaporated. Purification of individual product was conducted by silica gel column chromatography or crystallize in a suitable solvent.

2.3. Structure Analysis Equipment

Analysis were measured by modern methods, using following equipment:

- ^{1}H-NMR; ^{13}C-NMR spectra were measured on a Bruker AVANCE 500, in proper deuterated solvent.

- GC-MS spectra were measured on an Agilent: GC system 7890B, Detector MSD 5977B.

- High-Res MS spectra in the form of ESI/TOF-MS were measured on an Agilent 6230 TOF-MS. ESI-MS spectra were measured on a Thermo LCQ Fleet iontrap MS.

- Melting points were measured on an Electrothermal 1101D.

2.4. Bioactivity Determination Methods

- *Cytotoxicity activities*

Cancer cells were cultured *in vitro* according to Skehan *et al.* [14]. Cytotoxic activity against cancer cell lines was determined by the Sulforhodamine B (SRB) method of Likhitayawuid *et al.* [15] This method has been applied by the Laboratory of Experimental Biology, Institute of Chemistry since 1996 on a number of cancer cell lines including:

- RD: Human Rhabdomyosarcoma

- Hep-G2: Human Hepatocellular carcinoma

- Lu: Lung cancer

- Fl: Human Uterine

For samples preparation, the stock sample (1–10 mg/mL) was prepared in DMSO solvent, diluted with the medium at a concentration of less than 1% and then dropped into the wells of the experimental plate. Negative control series are DMSO 10%; Positive control series are the cytotoxic standard (ellipticine) diluted to a concentration of 0.01 mM in DMSO.; experimental series are test sample and cell suspension, plate incubated in CO_2 incubator at 37 °C for 3 days.

After 3 days of incubation, cells were fixed with cold trichloroacetic acid (TCA) solution. They were washed, dried, stained with 0.4% SRB in 1% acetic acid and washed again with 1% acetic acid to remove excess color; dried, resuspended with 10M Trisbase buffer solution on a horizontal shaker. Result was read on ELISA at 515–540 nm wavelength.

- *Antimicrobial activity determination*

Antimicrobial activity testing was conducted to evaluate the antibiotic activity of the extracts on 96-well microtiter plate according to the modern method of Vander Bergher and Vlietlinck (1991), [16] and McKane & Kandel (1996) [17].

Tested microorganisms strains were listed belowed:

- Gram (-) bacteria: *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 10145)

- Gram (+) bacteria: *Bacillus subtillis* subsp. *spizizenii* (ATCC 6633), *Staphylococcus aureus* subsp. *aureus* (ATCC 25923)

- Mold: *Aspergillus niger* (ATCC 6275), *Fusarium oxysporum* (ATCC 7601)

- Yeast: *Candida albicans* (ATCC 10231), *Saccharomyces cerevisiae* (VTCC–Y–62).

The test strains were activated and diluted according to McFarland standard 0.5 and then tested. Incubate plates at 37 ºC/24 hours for bacteria and 30 ºC/48 hours for filamentous fungi and yeasts.

Antimicrobial activity was calculated for minimum inhibitory concentration (MIC).

3. Result and Discussion

3.1. Synthesis and Structure Analysis of β-Amino Alcohol

Synthesis reactions were conducted according to the general procedure described in section 2.2 with different amines and phenolics, we obtained 10 *β*-amino alcohol compounds with the following structures. In which, compounds **5a** and **5b** are semi-synthetic compounds from natural compounds, indirubin isolated from *Strobilanthes cusia* and murrayafoline A isolated from *Glycosmis sternocapa* (Fig. 2):

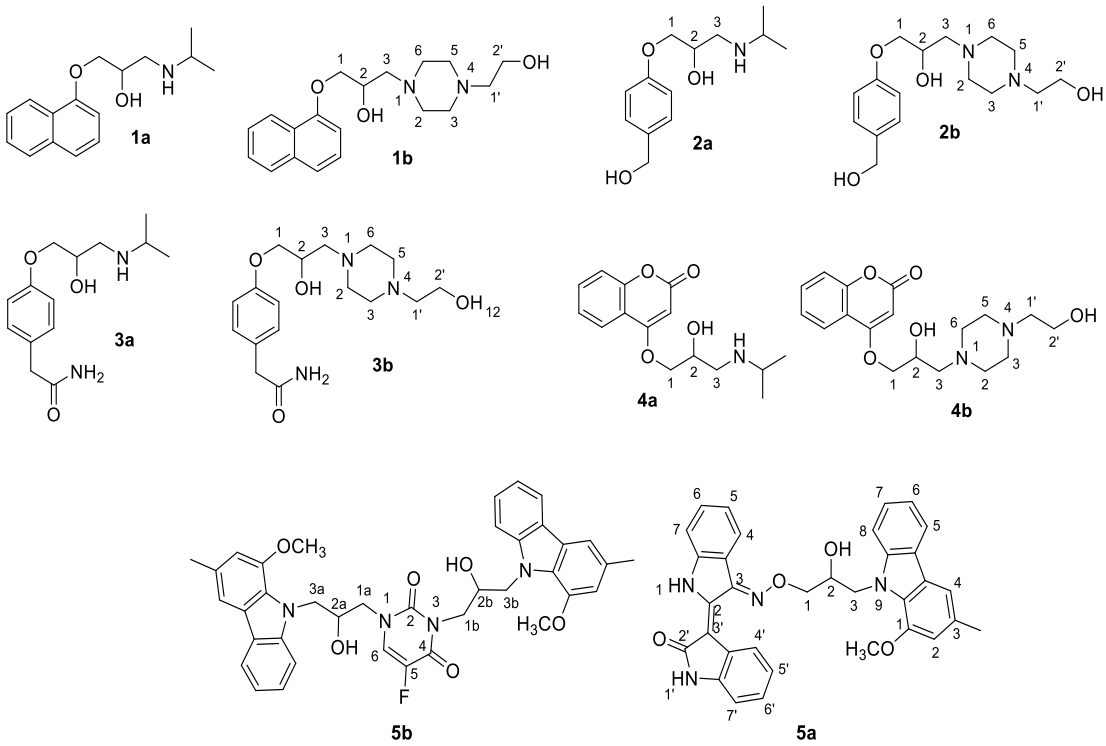

Fig 2. Scope of β-amino alcohols products

- Compound 1a (propranolol)

^{1}H-NMR (500 MHz, methanol-d_4) δ (ppm) 8.37 – 8.26 (m, 1H); 7.89 – 7.74 (m, 1H); 7.55 – 7.43 (m, 2H); 7.43 – 7.29 (m, 2H); 6.88 (dd. J = 7.6, 1.0 Hz, 1H); 4.22 (dtd, J = 8.9, 5.3, 3.7 Hz, 1H); 4.17 – 4.07 (m, 2H); 2.94 (dd, J = 12.0, 3.7 Hz, 1H); 2.84 (p, J = 6.3 Hz); 2.76 (dd, J = 12.0, 8.5 Hz, 1H); 1.10 (t, J = 6.0 Hz, 6H).

^{13}C-NMR (126 MHz, methanol-d_4) δ (ppm) 155.74, 135.99, 128.46, 127.36, 126.96, 126.93, 126.09, 122.93, 121.46, 105.98, 72.11, 69.89, 51.09, 49.81, 22.68, 22.52.

GC-MS spectra: Retention time of 7.88 min. MS, m/z: 114.2 (100%); 72.1 (58.82%); 43.1 (21.71%); 30.1 (32.54%).

- Compound 1b (3-(4-(2'-hydroxyethyl) piperazin-1-yl)-1-(naphthalen-1-yloxy) propan-2-ol)

^{1}H-NMR (500 MHz, chloroform-d_1) δ (ppm) 8.29 – 8.21 (m, 1H), 7.83 – 7.74 (m, 1H), 7.54 – 7.41 (m, 3H), 7.35 (dd, J = 7.9 Hz, 1H), 6.82 (d, J = 7.5 Hz, 1H), 4.31 – 4.08 (m, 3H), 3.62 (t, J = 5.4 Hz, 2H), 2.79 – 2.38 (m, 12H).

^{13}C-NMR (126 MHz, chloroform-d_1) δ (ppm) 154.43, 134.54, 127.52, 126.46, 125.82, 125.64, 125.26, 121.92, 120.64, 104.96, 70.59, 65.77, 60.85, 59.33, 57.78, 52.95.

GC-MS spectra: Retention time of 7.28 min. MS, m/z: 186 (38.59%), 127 (49.95%), 115 (100%).

- Compound 2a (1-(4-(hydroxymethyl)phenoxy)-3-(isopropylamino)propan-2-ol)

^{1}H-NMR (600 MHz, methanol-d_4) δ (ppm) 7.29 (d, J = 8.6 Hz, 2H), 6.94 (d, J = 8.6 Hz, 2H), 4.54 (s, 2H), 4.13 – 4.01 (m, 1H), 4.00 – 3.90 (m, 2H), 2.95 – 2.80 (m, 2H), 2.68 (dd, J = 12.0, 8.5 Hz, 1H), 1.12 (dd, J = 6.2 Hz, 6H).

^{13}C-NMR (151 MHz, methanol-d_4) δ (ppm) 158.28, 133.65, 128.62, 114.64, 70.55, 68.26, 64.89, 49.17, 49.12, 22.77, 22.66.

GC-MS spectra: Retention time of 13.45 min. MS, m/z: 72 (100%), 107 (4.16%), 239 (0.25%).

- Compound 2b (1-(4-(2-hydroxyethyl) piperazin-1-yl)-3-(4-(hydroxymethyl) phenoxy) propan-2-ol)

^{1}H-NMR (600 MHz, methanol-d_4) δ (ppm) 7.44 – 7.20 (m, 2H), 7.11 – 6.80 (m, 2H), 4.54 (s, 2H), 4.14 (ddt, J = 7.6, 5.9, 4.4 Hz, 1H), 4.01 (dd, J = 9.8, 4.3 Hz, 1H), 3.95 (dd, J = 9.8, 5.8 Hz, 1H), 3.72 (t, J = 5.9 Hz, 2H), 2.80 – 2.55 (m, 12H).

^{13}C-NMR (151 MHz, chloroform-d_1) δ (ppm) 159.68, 135.09, 129.62, 115.50, 71.92, 68.22, 64.85, 61.88, 60.95, 59.34, 54.03, 53.96.

GC-MS spectra: Retention time of 19.38 min. MS, m/z: 143 (100%), 169 (8.55%), 279 (6.90%)

HRMS (ESI) Calc for $C_{16}H_{27}O_4N_2$ $[M+H]^+$: 311.1926, found: 311.1959.

- Compound 3a (atenolol)

^{1}H-NMR (600 MHz, methanol-d_4) δ (ppm): 7.26–7.24 (d, 2H, Ar-H, J = 7.5 Hz), 6.95–6.93 (d, 2H, Ar-H, J = 7.5 Hz), 4.24–4.22 (ddt, 1H, J = 7.6, 5.9, 4.4 Hz), 4.08–3.99 (dd, 2H, J = 9.5, 4.4 Hz,), 3.49–3.43 (m, 3H), 3.30–3.27 (dd, J = 13.2, 4.3 Hz, 1H), 3.18–3.12 (t, J = 10.5 Hz, 1H), 1.39–1.38 (d, J = 3.5 Hz, 6H).

^{13}C-NMR (151 MHz, chloroform-d_1) δ(ppm): 159.90, 155.32, 129.55, 115.24, 73.27, 68.76, 55.85, 46.79, 42.31, 20.83.

Melting point: 154 °C

- Compound 3b (3-(4-(2'-hydroxyethyl)piperazin)-1-(4-(acetamide)phenoxy)propan-2-ol)

^{1}H-NMR (600 MHz, methanol-d_4) δ (ppm) 7.29 – 7.20 (m, 2H), 6.99 – 6.85 (m, 2H), 4.12 (ddt, J = 7.6, 5.9, 4.4 Hz, 1H), 4.00 (dd, J = 9.8, 4.2 Hz, 1H), 3.93 (dd, J = 9.8, 5.9 Hz, 1H), 3.70 (t, J = 6.0 Hz, 2H), 3.46 (s, 2H), 2.80 – 2.49 (m, 13H).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm) 167.82, 149.87, 121.71, 119.67, 106.23, 62.50, 58.82, 52.59, 51.71, 50.23, 44.84, 44.79, 33.03.

GC-MS spectra: Retention time of 24.23 min. MS, m/z: 143 (100%), 169 (8.00%), 306 (9.80%)

HRMS (ESI) Calc for $C_{17}H_{28}O_4N_3$ $[M+H]^+$: 338.2035, found: 338.2068

Melting point: 166 °C

- Compound 4a (3-(isopropylamino)-1-(4-oxy-2H-chromen-2-one)propan-2-ol)

^{1}H-NMR (500 MHz, methanol-d_4) δ (ppm) 7.97 (dd, J = 8.0, 1.6 Hz, 1H), 7.64 (ddd, J = 8.7, 7.4, 1.7 Hz, 1H), 7.43 – 7.32 (m, 2H), 5.85 (s, 1H), 4.34 – 4.15 (m, 3H), 3.00 – 2.86 (m, 2H), 2.81 (dd, J = 12.1, 7.6 Hz, 1H), 1.16 (dd, J = 6.3, 4.0 Hz, 6H).

^{13}C-NMR (151 MHz, methanol-d_4) δ (ppm) 167.62, 165.11, 154.54, 133.93, 125.42, 124.40, 117.57, 116.86, 91.29, 73.32, 69.01, 50.21, 50.09, 22.34, 22.25.

GC-MS spectra: Retention time of 16.03 min. MS, m/z: 72 (100%), 115 (23.92%), 222 (17.72%)

- Compound 4b (3-(4-(2'-hydroxyethyl)piperazin)-1-(4-oxy-2H-chromen-2-one)propan-2-ol)

^{1}H-NMR (600 MHz, methanol-d_4) δ (ppm) 7.97 (dd, J = 7.9, 1.6 Hz, 1H), 7.64 (ddd, J = 8.4, 7.3, 1.6 Hz, 1H), 7.40 – 7.32 (m, 2H), 5.85 (s, 1H), 4.32 – 4.23 (m, 2H), 4.19 (dd, J = 9.7, 5.6 Hz, 1H), 3.70 (t, J = 6.1 Hz, 2H), 2.72 – 2.48 (m, 12H).

^{13}C-NMR (151 MHz, methanol-d_4) δ (ppm) 167.71, 165.14, 154.52, 133.89, 125.40, 124.43, 117.56, 116.89, 91.21, 73.55, 67.69, 61.73, 61.25, 59.79, 54.42, 54.40.

GC-MS spectra: Retention time of 13.75 min. MS, m/z: 188 (4.09%), 243 (100%), 274 (6.65%)

HRMS (ESI) Calc for $C_{18}H_{25}O_5N_2$ $[M+H]^+$: 349.1719, found: 349.1752

Melting point: 127 °C

- Compound 5a ((2*Z*,3*E*)-3-((2-hydroxy-3-(1-methoxy-3-methyl-9*H*-carbazol-9-yl)propoxy)imino)-[2,3'-biindolinylidene]-2'-one)

^{1}H-NMR (600 MHz, DMSO-d_6) δ (ppm) 11.65 (s, 1H, N-H), 10.70 (s, 1H, N-H), 8.34 (d, J = 7.8 Hz, 1H), 8.11 (d, J = 7.8 Hz, 1H), 8.02 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.49 (s, 1H), 7.43 – 6.98 (m, 6H, Ar-H), 6.86 (d, J = 7.2 Hz, 1H), 6.82 (s, 1H), 6.54 (m, 1H, Ar-H), 4.87-4.84 (m, 1H), 4.66-4.61 (m, 2H), 4.52-4.49 (m, 2H), 3.87 (s, 3H, OCH_3), 2.43 (s, 3H, Ar-CH_3).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm) 170.80, 151.29 – 100.07 (27C), 79.24 (C-OH), 68.72, 55.55, 48.19 (OCH_3), 21.23.

GC-MS spectra: does not fly into the GC

- Compound 5b (5-fluoro-1,3-bis(2-hydroxy-3-(1-methoxy-3-methyl-9*H*-carbazol-9-yl) propyl) pyrimidine-2,4(1*H*,3*H*)-dione)

^{1}H-NMR (600 MHz, DMSO-d_6) δ (ppm) 8.04 – 8.01 (m, 2H), 7.99 (d, J = 7.8 Hz, 1H), 7.54 – 6.82 (m, 9H, Ar-H), 6.78 (s, 1H), 5.28 – 5.26 (m, 1H), 4.92 – 4.89 (m, 1H), 4.64 – 4.30 (m, 4H), 4.09 – 3.92 (m, 2H), 3.87 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.72 – 3.53 (m, 2H), 2.45 (s, 6H, Ar-CH_3).

^{13}C-NMR (151 MHz, DMSO-d_6) δ (ppm) 149.56, 146.07 (d, $^4J_{C\text{-}F}$ = 6.0 Hz, CO), 141.19 (d, $^2J_{C\text{-}F}$ = 39.3 Hz, CO), 128.57 (d, $^2J_{C\text{-}F}$ = 30.2 Hz, C6), 125.23, 125.09, 124.12, 122.07, 121.94, 119.87, 119.67, 118.51, 118.32, 112.34, 112.28, 110.18, 109.87, 109.07, 108.92, 68.41 (CH-OH), 67.81 (CH-OH), 55.56 (OCH_3), 55.42 (OCH_3), 52.95, 49.11, 45.06, 36.17, 21.25 (Ar-CH_3).

GC-MS spectra: does not fly into the GC

Among the obtained compounds, compounds **2b**, **3b**, **4b**, **5a** and **5b** are new compounds, all of which are *β*-amino alcohols obtained from phenolic corresponding to 2-(piperazin-1-yl)ethan-1-ol.

The HRMS spectrum of compound **2b** showed a signal $[M+H]^+$: 311.1926, suggested the molecular formula of $C_{16}H_{27}O_4N_2$.

On the ^{13}C-NMR spectrum of compound **2b,** 12 signals of C were found, in which the signal at 159.68 ppm suggests the presence of aromatic C attached to O. The signals at 115.50-135.09 ppm are aromatic C signals along with C-O signals in the signal region from 61.88 – 71.92 ppm.

On the ^{1}H-NMR spectrum, signals at 6.90 ppm, 7.32 ppm, containing 4 H suggested a symmetric *para*-substituted aromatic rings. Signals in the 2.55 – 2.77 ppm region with 12 protons suggested a piperazine ring with 2 substituents on N. Singlet signal at 4.54 ppm clearly represented CH_2OH on the aromatic ring. Signals at 4.01 and 3.95 ppm are doubled duplet with one of the coupling constants was 9.8 Hz suggested the split signals of CH_2 at C1 of the beta amino alcohol moiety. Two remaining coupling constants of those shared with ddt signal at 4.14 of CH-OH at C2 once again confirmed the beta amino alcohol structure in **2b**.

From the above data suggesting the skeleton of a *β*-amino alcohol containing a piperazine ring, compound **2b** was identified as **1-(4-(2-hydroxyethyl)piperazin-1-yl)-3-(4-(hydroxymethyl)phenoxy)propan-2-ol**.

Compounds **3b** and **4b** have similar spectral data to compound **2b**, especially the beta amino alcohol signature peak patterns. The differences between those are mainly in the signals of the phenolic part.

Compound **5a** was obtained as a pale-yellow solid, ^{13}C-NMR spectral data showed signals of 33 C atoms, in which the signal at 170.8 ppm was prominent, characteristic of the carbonyl group C=O, the signals of aromatic carbon in the region 151.29–100.07 ppm. Chemical shift value of 79.24 ppm suggested the presence of C-OH signal, and 48.19 ppm belonged to the methoxy group.

The ^{1}H-NMR spectrum showed the characteristic structure of the indirubin skeleton published in previous documents [18]. Notably, singlet signals at 11.65 and 10.7 ppm were NH group at 1, 1' position; proton signals including 1 doublet at 8.34 ppm and 1 doublet at 8.11 ppm of protons at H-4 and H-4' belonged to aromatic ring of indirubin skeleton.

In addition, signals of methylene group attached to -O and -N were detected in the region of 4.61–4.66 ppm and 4.49–4.52 ppm, suggesting the structure of *β*-amino alcohol bridge.

Murrayafoline A skeleton with aromatic ring protons was observed in the region of 6.54–7.43 ppm,

a singlet signal at 3.87 ppm suggested the presence of methoxy group attached to carbazone skeleton [19].

From the above data and compared with the reference documents, compound **5a** was identified as a new compound with the name **((2*Z*,3*E*)-3-((2-hydroxy-3-(1-methoxy-3-methyl-9*H*-carbazol-9-yl)propoxy)imino)-[2,3'-biindolinylidene]-2'-one)**.

Compound **5b** was obtained as a brown solid. The spectrum of this compound was similar to that of compound **5a** in the murrayafoline A skeleton and the *β*-amino alcohol bridge, the difference was that the indirubin skeleton was replaced by the murrayafoline A skeleton and the presence of the 5-fluorouracil skeleton. The characteristics of this skeleton are shown as follows:

The ^{13}C spectrum shows the signals of carbonyl groups at 146.07 and 141.2 ppm and of carbon attached to F atom at 141.9 ppm (C-5). The proton signal at H-6 was observed as a doublet at 7.99 ppm.

Based on the spectral data of the given compound and comparison with the reference literature, **5b** was identified as **(5-fluoro-1,3-bis(2-hydroxy-3-(1-methoxy-3-methyl-9*H*-carbazol-9-yl) propyl) pyrimidine-2,4(1*H*,3*H*)-dione)**.

3.2. Bioassay

3.2.1. Cytotoxicity Activity

The compounds were evaluated for cytotoxic activity and antimicrobial activity on the corresponding bacterial strains

The cytotoxic activity test results showed that 8 compounds from **1a**-**4b** did not show activity on all 6 tested cancer cell lines. On the other hand, semi-synthetic *β*-amino alcohols from natural compounds showed quite good activity and were higher than the original compounds. Notably, the IC_{50} on Hep-G2 of **5a** and **5b**, both containing the murrayafoline A component, was 3.1 and 2.2 times lower than that of the original compound, respectively. The activity on Hela also increased significantly, 3.1 times for **5a** and 4.7 times for **5b**. The inhibitory activity on LU, Jurkat, SW 480 and MCF-7 cell lines of **5b** was generally higher than that of **5a** and was remarkable when compared with the positive control ellipticine.

Table 1. Results of cytotoxic activity evaluation of several *β*-amino alcohols

ID	IC_{50} (µg/mL)					
	LU	**Hep-G2**	**Hela**	**Jurkat**	**SW 480**	**MCF-7**
5a	2.34	1.97	2.84	5.76	7.66	8.76
5b	2.03	2.86	1.90	1.75	2.96	2.43
Murrayafoline A [20]	-	6.18	8.91	-	-	-
Ellipticine	0.33	0.36	0.38	0.30	0.47	0.38

Table 2. Results of antimicrobial activity evaluation of several *β*-amino alcohols

ID	Starting conc. (µg/mL)	Minimum inhibitory concentration (MIC, µg/mL)								Comment
		Gram (-) bacteria		Gram (+) bacteria		Mold		Yeast		
		E. coli	*P. aeruginosa*	*B. subtillis*	*S. aureus*	*A. niger*	*F. oxysporum*	*S. cerevisiae*	*C. albicans*	
1b	100	**100**	**100**	(-)	**50**	(-)	(-)	(-)	(-)	3 strains
3b	100	(-)	(-)	(-)	**50**	(-)	(-)	(-)	(-)	1 strain
4a	100	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	Negative
4b	100	(-)	**100**	(-)	(-)	(-)	(-)	(-)	(-)	1 strain
5a	100	(-)	**100**	**50**	**50**	(-)	(-)	**100**	**25**	5 strain
5b	100	(-)	(-)	(-)	**50**	(-)	(-)	(-)	(-)	1 strain

Antimicrobial activity

The compounds were tested for antimicrobial activity (Table 3.2). Five out of ten tested compounds showed resistance to 1 to 3 pathogens. Compound **5a** alone had the best activity and was resistant to 5 pathogens including gram-negative (*P. aeruginosa*), gram-positive (*B. subtillis*, *S. aureus*) and yeast (*S. cerevisiae*, *C. albicans*).

1b is a derivative of piperazine and morpholine, both of which were resistant to 3 pathogens, including 2 gram-negative (*E. coli*, *P. aeruginosa*) and 1 gram-positive (*S. aureus*). **4b** is a derivative of coumarin and showed activity against *P. aeruginosa* (gram-negative). This result is also consistent with previous studies showing the special activity of coumarin derivatives against gram-negative bacteria in general [21-24].

4. Conclusion

- 10 *β*-amino alcohol compounds were synthesized using the oxirane ring-opening amine addition method of intermediate compounds which are products of substitution reactions between phenolic compounds and epichlohydrin. Among the synthesized compounds, there were 2 compounds containing the naphthol skeleton of propranolol (**1a-b**), 2 compounds containing the 2-(4-hydroxyphenyl)acetamide skeleton (**3a-b**) similar to atenolol, 2 compounds containing the 4-oxa-coumarin skeleton (**4a-b**).

- The anticancer activity of *β*-amino alcohol compounds was not as good as expected except for compounds **5a** and **5b** which contained active backbones. On the other hand, the antimicrobial activity of *β*-amino alcohol compounds was better, especially the derivatives of 4-hydroxy-2*H*-chromen-2-one. The best activity was on the gram-positive bacteria *S. aureus*. In addition, the group of compounds containing piperazine backbone in the amine moiety showed quite good activity against yeast strains.

Acknowledgement

This research is funded by Hanoi University of Science and Technology (HUST) under project number T2020-PC-213

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