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Synthesis, antioxidant activity, and HPLC enantioseparation of aryloxyaminopropanols derived from naphthalen-2-ol

Original Paper

Čižmáriková R.[1], Habala L.[1]✉, Valentová J.[1], Némethy A.[1], Bruchatá K[1], Hroboňová K.[2]

[1]*Department of Chemical Theory of Drugs, Faculty of Pharmacy, Comenius University, Bratislava*
[2]*Institute of Analytical Chemistry, Faculty of Chemical and Food Technology, Slovak University of Technology in Bratislava*

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Abstract The present work describes the synthesis, physico-chemical characteristics, antioxidative properties, and high-performance liquid chromatography (HPLC) enantioseparation of novel, potentially bioactive aryloxyaminopropanols – derivatives of naphthalen-2-ol modified in the basic part of their molecules. Reaction of naphthalene-2-ol with chloromethyloxirane leads to 2-[(naphthalen-2-yloxy)methyl]oxirane, which reacts in the next step with branched aliphatic amines (isopropylamine, *tert*-butylamine, and dimethylamine), aromatic amines (aniline, 3,4-dimethoxyphenylethylamine), and heterocyclic amines (pyrrolidine, imidazole, 2-methylimidazole, piperidine, morpholine, 4-methylpiperidine, or 2-methoxyphenylpiperidine). The target compounds were isolated in the form of free bases, as well as their salts with fumaric or hydrochloric acid. Their purity was established by thin-layer chromatography and their IR, UV, ^{1}H-NMR, and ^{13}C-NMR spectra were recorded. The antioxidant activities of prepared compounds were measured by the 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS) method and they were compared with the values for the corresponding salts. Enantioseparation was accomplished by means of enantioselective HPLC using amylose tris(3,5-dimethylphenyl)carbamate (Chiralpak AD), as well as Chirobiotic T (native teicoplanin) in some cases.

Keywords *β-sympatolytiká – aryloxyaminopropanoly – propranolol – nadolol – levobunolol – antiradikálová aktivita – HPLC-enantioseparácia*

INTRODUCTION

In order to investigate their structure–activity relationships, various derivatives of the aryloxyaminopropanol type have been prepared. They exhibit biological activity mainly as β-blockers and are employed because of their antianginal (Baker et al., 2011), antihypertensive (Tobe, 2014; Akbar et al., 2014), or antiarrhythmic (Zicha et al., 2006) effects. As competitive antagonists of β-adrenergic receptors, they are also active in the treatment of chronic heart failure (Cruickshank, 2010; Tsujimoto et al., 2018), since overactivation of adrenergic nervous system contributes to the pathophysiology of heart disease. Novel studies also indicate their anticancer activity (Fumagalli et al., 2020).

A large number of β-blockers have been prepared. The structural variations concern mainly the aromatic and basic part of the molecule, connected by an aminopropanol linker. Besides the benzene ring, another aromatic ring is present, which is, in most cases, a naphthalene core. Examples of β-blockers with a substituted benzene core are the cardioselective metoprolol with a methoxyethyl group (Brogden et al., 1977; Kukin et al., 2000; Fröhlich et al., 2015; Clemente-Moragón et al., 2021) and bisoprolol with a 2-propan-2-yloxyethoxymethyl group (De Groote et al., 2007; Yasui et al., 2020). β-blockers with vasodilatory properties include acebutolol (Li et al., 2018) and celiprolol (Baderkhan et al., 2021). The first β-blocker with a naphthalene core introduced into clinical practice was propranolol (Barton et al., 2015; Bolin et al., 2017; Čižmáriková et al., 2015; Čižmáriková et al., 2012).

Among the compounds with a hydrogenated naphthalene aromatic ring, nadolol, that is, (2*R*,3*S*)-5-[3-(*tert*-butylamino)-2-hydroxypropoxy]-1,2,3,4-tetrahydronaphthalen-2,3-diol (Čižmáriková et al., 2019; Lee et al., 2020), was studied from the point of view of stereochemistry. The (*S*)-(–) form of bunolol, a cyclic ketone with a modified naphthalene core, found application in clinical practice. The compound is 3,4-dihydronaphthalen-1-one substituted in position 5

* *E-mail: habala@fpharm.uniba.sk*

with a 3-(*tert*-butylamino)-2-hydroxypropoxyl group. This stereoisomer is used under the name levobunolol for the reduction of elevated intraocular pressure in patients with ocular hypertension or glaucoma (Ogasawara et al., 1999; Ishibashi et al., 2003).

Exchange of the propan-2-yl (isopropyl) group in the molecule of propranolol for a methoxyphenylpiperazine moiety leads to naftopidil, whose effect is shifted toward a selective blockade of α_1-receptors, while the affinity to α2- and β-adrenoreceptors is very low. Naftopidil also blocks the Ca^{2+} channels, thus inhibiting serotonin-induced aggregation of thrombocytes and lowering their serotonin uptake (Sponer et al., 1992; Kirsten et al., 1994).

Beside the blockage of β-adrenoreceptors, the beneficial effect of several β-blockers with aryloxyaminopropanol structure is also attributed to their antioxidant properties. The best-known antioxidant in this drug category is carvedilol, although antioxidative activity is also found in sotalol, atenolol, timolol, and nebivolol (De Groot et al., 2004; Gomes et al., 2006, Wendi et al., 2002).

The molecular structure of aryloxyaminopropanols entails a chiral center on the second carbon atom of the propan-2-ol linker, bringing about the existence of (*R*)- and (*S*)-enantiomeric forms. To obtain the enantiomerically pure drug, stereoselective synthesis and splitting of racemic mixtures are the options. Among the most common methods of enantioseparation is high-performance liquid chromatography (HPLC) on chiral stationary phases. Chiral separation of the synthesized compounds by HPLC was accomplished on chiral chromatography column, Chiralpak AD-H, and columns containing macrocyclic antibiotics (Kalíková et al., 2018; Li et al., 2020; Yang et al., 2020), Chirobiotic T, Chirobiotic TAG, and Chirobiotic V (Bruchatá et al., 2006; Pocrnić M., 2020; Nazareth et al., 2020).

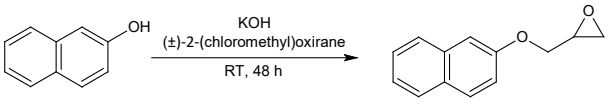
The aim of the present work was the preparation of novel derivatives of naphthalen-2-ol by a two-step synthesis, in the form of a racemic mixture (compounds I–XIII). The products were to be screened for their antioxidative activity. The study of separability of the prepared racemates into individual enantiomers *R* and *S* using two stationary phases and varying compositions of the mobile phase was another research objective.

EXPERIMENTAL PART

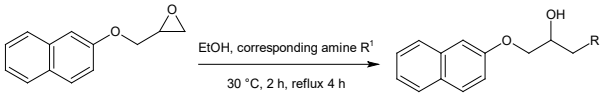
Synthesis of derivatives of 2-naphthol

Synthesis of 2-[(naphthalen-2-yloxy)methyl]oxirane (Bruchatá et al., 2006)

Potassium hydroxide (0.169 mol) was added to a mixture of (±)-2-(chloromethyl)oxirane (0.153 mol) and 2-naphthol (0.148 mol) in 50 ml of water. The reaction proceeded for 48 h at room temperature and under constant stirring. Thereafter, the product of the reaction was extracted into ethyl acetate and properly washed with a 5% NaOH solution as well as



Scheme 1. Synthesis of 2-[(naphthalen-2-yloxy)methyl]oxirane.



Scheme 2. Synthesis of (2RS)-1-(2-naphthyloxy)-3-(substituted amino)propan-2-ols.

with water. The solution of the resulting oxirane derivative was dried with magnesium sulfate. After evaporating of the solvent, the product was crystallized from hexane and used in the following synthetic step:

$C_{13}H_{12}O_2$, 200.23, yield 63%, 51 °C–53 °C (hexane), 55 °C (Srivastava et al., 2004) 50 °C–51 °C (Bruchatá et al., 2006) ^{1}**H NMR** (CD_3OD): δ 2.78–2.81 (m, 2H, CH(O)C**H**$_2$), 3.38–3.41 (m, 1H, C**H**), 3.94–4.00 (m, 2H, ArOC**H**$_2$), 7.13–7.18 (m, 2H, **H**^{1,3}naph), 7.24–7.33 (t, 1H, **H**^{7} naph), 7.34–7.42 (t, 1H, **H**^{6} naph), 7.73–7.77 (m, 3H, **H**^{4,5,8} naph)

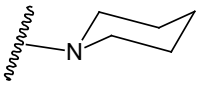
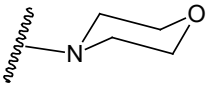
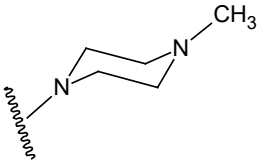
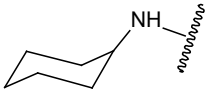
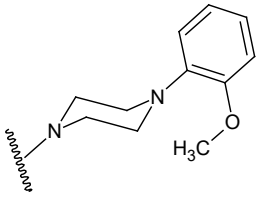
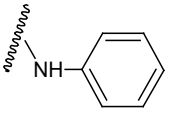
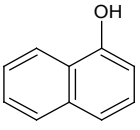
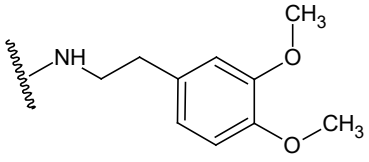
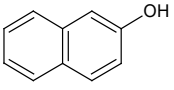
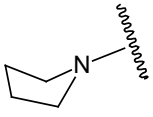
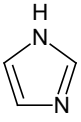
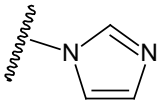
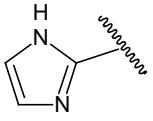
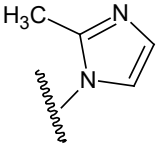
Synthesis of 2-naphthyloxyaminopropanols (Bruchatá et al., 2006)

Into a 250-ml round-bottom flask was subsequently added 0.08 mol oxirane derivative, 150 ml ethanol (EtOH), and 0.08 mol amine. The reaction mixture was kept at 30 °C for 4 h and then heated for 4 h under reflux. EtOH as well as the unreacted amine were removed under vacuum. The distillation residue was diluted with 50 ml of water and the base was extracted in an extraction funnel into diethyl ether. The extract was properly dried with K_2CO_3, and diethyl ether was removed in vacuum. The base can be crystallized from a suitable solvent. The final products can be isolated as free bases or as salts with acids. The salts were prepared by adding an ether solution of the anhydrous acid (e.g., fumaric acid) to a dry ether solution of the base until complete precipitation. The salts were finally purified by crystallization from ethyl acetate. The free bases can be released from their salts by alkalizing their aqueous solutions with ammonia and subsequent extraction into diethyl ether.

Melting points of the products were determined using a Kofler block (HMK; Franz Küstner, Germany) and were uncorrected. The purity of the prepared substances was checked by thin-layer chromatography (TLC) using silica plates Silufol® UV 254 (Merck) and ethyl acetate:diethylamine = 9:1 (v/v) as the mobile phase. Spectroline CM-10 (Sigma-Aldrich, St. Louis, MO, USA) was used for the detection under ultraviolet (UV)–visible (VIS) light.

Infrared spectra of the substances were recorded on Nicolet 6700 (Thermo Scientific, Waltham, MA, USA) spectrophotometer using an attenuated total reflexion (ATR) extension with ZnSe crystals. GENESYS 10S spectrophotometer

Table 1. List of the studied compounds.

Compound	*R*	Compound	*R*
I	-NHCH$(CH_3)_2$	X	
II	-NHC$(CH_3)_3$	XI	
III	-N$(CH_3)_2$	XII	
IV		XIII	
V		XIV	
VI		XV	
VII		XVI	
VIII		XVII	
IX			

Forms of the substances: Ia–XIIa salts with fumaric acid, Ib–XIIb salts with HCl

was used for the measurement of UV–VIS spectra in the wavelength range 200–400 nm. Solutions of the prepared aryloxyamino-propanols in MeOH (as free bases or as salts) had the concentration of approximately 0.2 mol/m^3.

^{1}H-NMR spectroscopy measurements were performed on a Varian Gemini 2000 spectrometer (Varian Inc., Palo Alto, CA, USA) with an operational frequency of 300 MHz for ^{1}H-NMR and 75 MHz for ^{13}C-NMR. Tetramethylsilane was employed as the internal standard. Deuterated solvents (chloroform, MeOH, DMSO, and water) were used for the preparation of sample solutions. Chemical shifts were given in ppm (d). The multiplicity of the signals was denoted as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet.

The elemental analysis was performed on a FLASH 2000 Organic Elemental Analyzer (Thermo Scientific).

(2*RS*)-1-(2-naphthyloxy)-3-(isopropylamino) propan-2-ol (I)

$C_{16}H_{13}O_2N$ base yield 59%, R_f: 0.62, m.p. 135 °C–6 °C (cyclohexane); 132.8–135.7 (Fagerstroem et al., 2006), ^{1}H-NMR ($CDCl_3$): δ 1.27 (d, 6H, CH(**CH**$_3$)$_2$), 2.97 (s, 1H, **CH**(CH$_3$)$_2$), 4.04–4.16 (m, 2H, C**H**$_2$O), 4.19–4.42 (m, 4H, Ar-O-C**H**$_2$-C**H**(O**H**)), 7.11–7.15 (d, 1H, **H**^{3}naph), 7.23 (s, 1H, **H**^{1}naph), 7.32 (t, 2H, **H**^{6,7}naph), 7.41–7.44 (m, 2H, **H**^{4,8}naph), 7.71–7.76 (m, 1H, **H**^{5}naph)
^{13}C-NMR (DMSO): δ 20.79 (CH(**C**H$_3$)$_2$), 48.93 (**C**H(CH$_3$)$_2$), 49.66 (**C**H$_2$NH), 66.43 (**C**HOH), 70.26 (O**C**H$_2$), 106.66 (**C**^{3}naph), 118.70 (**C**^{1}naph), 123.63 (**C**^{6}naph), 126.67 (**C**^{7,8}naph), 127.47 (**C**^{5}naph), 128.83, 129.23 (**C–C**$_{cond}$ naph), 134.30 (**C**^{4} naph), 156.39 (**C**^{2} naph)

(2*RS*)-1-(2-naphthyloxy)-3-(*tert*.butylamino) propan-2-ol (II)

$C_{17}H_{23}O_2N$ base yield 69%, R_f: 0.66, m.p. 112 °C–4 °C (cyclohexane); 113 °C–14 °C (Bruchatá et al., 2006) fumarate 213 °C–215 °C, 215 °C–216 °C (Bruchatá et al., 2006), ^{1}H-NMR ($CDCl_3$): δ 1.14 (s, 9H, C(CH$_3$)$_3$) 2.40 (dd, 1H, **CH**$_2$NH), 3.99–4.03 (m, 3H, OC**H**$_2$C**H**(OH)), 4.16 (m, 1H, OCH$_2$), 7.18 (d, 1H, **H**^{3} naph), 7.24 (s, 1H, **H**^{1} naph), 7.33 (t, 1H, **H**^{6} naph), 7.43 (t, 1H, **H**^{7} naph), 7.69–7.77 (m, 3H, **H**^{4,5,8} naph)
^{13}C-NMR (DMSO): δ 29.07 (C(**C**H$_3$)$_3$), 44.67 (**C**H$_2$NH), 50.56 (**C**(CH$_3$)$_3$), 68.53 (**C**HOH), 70.49 (O**C**H$_2$), 106.73 (**C**^{3} naph), 118.79 (**C**^{1} naph), 123.68 (**C**^{6} naph), 126.36, 126.36 (**C**^{7,8} naph), 127.60 (**C**^{5} naph), 129.02, 129.37 (**C–C**$_{cond}$ naph), 134.44 (**C**^{4} naph), 156.62 (**C**^{2} naph)

(2*RS*)-1-(dimethylamino)-3-(2-naphthyloxy) propan-2-ol (III)

$C_{15}H_{19}O_2N$ base yield 62%, R_f: 0.67, m.p. 77 °C–79 °C (hexane); fumarate 139 °C–141 °C hydrochloride 170 °C–2 °C, IR (cm^{-1}): base 3350 (νOH), 1629, 1600 (νC=C), 1258 (νArOalk); UV fumarate (CH_3OH, ε in m^2/mol): λ_1 261 log ε_1 3.99, λ_2 271 log ε_2 4.01, λ_3 313 log ε_3 3.45
^{1}H-NMR (CD_3OD): δ 2.85 (s, 6H, N(C**H**$_3$)$_2$), 3.24–3.35 (m, 2H, CHC**H**$_2$N), 4.05–4.17 (m, 2H, ArOC**H**$_2$), 4.35–4.40 (m, 1H, CH$_2$CHOH), 6.37 (s, 2H, C**H** fumar), 7.13 (d, 1H, **H**^{3} naph), 7.23 (s, 1H, **H**^{1} naph), 7.32 (t, 2H, **H**^{6,7} naph), 7.41–7.44 (m 2H, **H**^{4,8} naph), 7.71–7.76 (m, 1H, **H**^{5} naph)

(2*RS*)-1-(cyclohexylamino)-3-(2-naphthyloxy) propan-2-ol (IV)

$C_{19}H_{25}O_2N$ base yield 65%, R_f: 0.48, m.p. 62 °C–64 °C (cyclohexane), fumarate m.p. 161 °C–163 °C (ethyl acetate); IR (cm^{-1}): 3326 (νOH, νNH), 1629, 1600 (νC=C), 1216 (νArOalk); UV (CH_3OH, ε in m^2/mol): λ_1 229 log ε_1 4,02, λ_2 272 log ε_2 2,85
^{1}H-NMR ($CDCl_3$): 1.16–1.25 (m, 6H, **H**^{3,4,5} cyclohex), 1.60–1.75 (m, 4H, **H**^{2,6} cyclohex), 2.40–2.46 (m, 1H, **H**^{1}cyclohex), 2.79–2.95 (m, 2H, C**H**$_2$N), 3.60–3.88 (m, 4H, (C**H**$_2$)$_2$ cyclohex), 4.09–4.42 (m, 4H, Ar-O-C**H**$_2$-C**H**(O**H**)), 7.14 (d, 1H, **H**^{3} naph), 7.25 (s, 1H, **H**^{1} naph), 7.33 (t, 2H, **H** ^{6,7} naph), 7.42–7.45 (m, 2H, **H**^{4,8} naph), 7.70–7.75 (m, 1H, **H**^{5} naph)

(2*RS*)-1-anilino-3-(2-naphthyloxy)propan-2-ol (V)

$C_{19}H_{19}NO_2$ base yield 65%, R_f: 0.31, m.p. 89 °C–92°C (cyclohexane); IR (cm^{-1}): 3270 (νOH, NH), 3055 (νNH), 1628, 1600 (νC=C), 1219 (νArOalk); UV (CH_3OH, ε in m^2/mol): λ_1 225 log ε_1 3.81, λ_2 271 log ε_2 3.31
^{1}H-NMR ($CDCl_3$): δ 3.58–3.71 (m, 2H, C**H**$_2$N), 4.15–4.18 (m, 3H, 4H, Ar-O-C**H**$_2$-C**H**(O**H**)), 7.30–7.35 (m, 1H, **H**^{4} anil), 7.39–7.45 (m, 1H, **H**^{3} naph), 7.51–7.63 (m, 5H, **H**^{1,6,7} naph, **H**^{3,5} anil), 7.73–7.77 (m, 3H, **H**^{4,5,7} naph)
MW 293.36, calc. %C 77.79 %H 6.53 %N 4.77, found %C 77.58 %H 6.32 %N 4.49

(2*RS*)-1-(3,4-dimethoxyphenylethylamino)-3-(2-naphthyloxy)propan-2-ol (VI)

$C_{23}H_{27}O_4N$ base yield 75%, R_f: 0.57, m.p. 93.5 °C–95 °C (cyclohexane); 138 °C–142 °C (ethyl acetate), IR (cm^{-1}) (fumarate): 2760, 3155 (νOH, NH), 1625, 1597 (νC=C), 1256 (νArOalk); UV (CH_3OH, ε in m^2/mol): λ_1 203 log ε_1 3.52, λ_2 226 log ε_2 3.75, λ_3 272 log ε_2 3.67
^{1}H-NMR ($CDCl_3$): δ 2.62–2.68 (m, 4H, C**H**$_2$C**H**$_2$), 2.72–2.76 (m, 2H, CHC**H**$_2$N), 3.68 (s, 3H, OC**H**$_3$), 3.71 (s, 3H, OC**H**$_3$), 3.96–4.06 (m, 3H, ArOC**H**$_2$C**H**), 6.69–6.70 (m, 3H, **H**^{1} naph, **H**$^{2,6'}$arom), 6.79–6.82 (m, 1H, **H**^{3} naph), 7.13–7.17 (m, 1H, **H**^{5} benz), 7.29–7.36 (t, 2H, **H**^{6,7} naph), 7.45–7.46 (m, 2H, **H**^{4,8} naph), 7.78–7.82 (m, 1H, **H**^{5} naph)
MW 349.48, calc. %C 79.05 %H 7.79 %N 4.01, found %C 79.24 %H 7.53 %N 4.22

(2*RS*)-1-(2-naphthyloxy)-3-(pyrrolidin-1-yl)propan-2-ol (VII)

$C_{17}H_{21}O_2N$ base yield 73%, R_f: 0.67, m.p. 64 °C–65 °C (heptane); 65 °C–66 °C (Bruchatá et al., 2006), fumarate m.p. 98 °C–99 °C (cyclohexane); 93 °C–97 °C (Bruchatá et al., 2006)
^{1}H-NMR ($CDCl_3$): δ 1.79–1.83 (m, 4H, 2**H**^{3,4} pyrrol, 2.54–2.90 (m, 6H, C**H**$_2$N, 2**H**^{2,5} pyr) 4.09–4.15 (m, 4H, Ar-O-C**H**$_2$-C**H**(O**H**)), 7.15–7.77 (m, 7H, C**H** naph)
^{13}C-NMR (DMSO): δ 26.84 (**C**^{2,5} pyr), 56.08 (**C**^{3,4} pyr), 61.53 (**C**H$_2$N pyr), 65.22 (**C**HOH), 66.95 (**C**^{3,5} morph), 73.87 (O**C**H$_2$), 106.83 (**C**^{3} naph), 118.86 (**C**^{1} naph), 123.68 (**C**^{6} naph), 126.46, 126.32 (**C**^{7,8} naph), 127.61 (**C**^{5} naph), 129.05, 129.42 (**C–C**$_{cond}$ naph), 134.30 (**C**^{4} naph), 156.24 (**C**^{2} naph)

(2*RS*)-1-(2-naphthyloxy)-3-(imidazol-1-yl)propan-2-ol (VIII)

$C_{16}H_{16}O_2N_2$ base yield 62%, m.p. 122 °C–125 °C (cyclohexane), R_f: 0,31, IR (cm^{-1}) (fumarate): 3113 (νOH), 1628, 1601 (νC=C), 1217 (νArOalk); UV (CH_3OH, ε in m^2/mol): λ_1 226 log ε_1 4.02, λ_2 272 log ε_2 2.85, ^{1}H-NMR ($CDCl_3$): 3.94–3.97 (m, 2H, CH_2 **CH_2**CH), 4.09–4.00 (m, 3H, ArC**H_2**C**H**), 4.25–4.12 (m, 1H, **CH_2**CHOH), 6.97 (d, 2H, **H**^{4}**,** **H**^{5} imi), 7.61 (s, 1H, **H**^{2} imi), 7.85–7.17 (m, 7H, C**H** naph)
MW 268.32, calc. %C 71.62 %H 6.01 %N 10.44, found %C 71.45 %H 6.22 %N 10.23

(2*RS*)-1-(2-naphthyloxy)-3-(2-methylimidazol-1-yl) propan-2-ol (IX)

$C_{17}H_{18}O_2N_2$ base yield 64%, R_f: 0.49, m.p. 127 °C–130 °C (cyclohexane); fumarate m.p. 136 °C–138 °C, IR (cm^{-1}) (base): 3057 (νOH), 1629, 1600 (νC=C), 1258 (νArOalk); UV fumarate (CH_3OH, ε in m^2/mol): λ_1 261 log ε_1 3.96, λ_2 271 log ε_2 3.96, λ_3 321 log ε_3 3.40, ^{1}H-NMR ($CDCl_3$): δ 2.39 (s, 3H, C**H_3**), 4.29–4.39 (m, 2H, C**H_2**N), 4.42–4.85 (m, 3H, C**H_2**C**H**OH), 7.21 (d, 1H, **H**^{4} imi), 7.22 (d, 1H, **H**^{1} naph), 7.29–7.31 (m, 2H, **H**^{7,8} naph), 7.33–7.34 (m, 1H, **H**^{5} imi), 7.38 (d, 1H, H^3 naph), 7.73–7.74 (m, 2H, **H**^{4,6} naph), 7.76 (d, 1H, **H**^{5} naph)
MW 282.35, calc. %C 72.32 %H 6.45 %N 9.92, found %C 72.41 %H 6.65 %N 9.73

(2*RS*)-1-(2-naphthyloxy)-3-(piperidino)propan-2-ol (X)

$C_{18}H_{23}O_2N$ base yield 61%, R_f: 0.69, m.p. 82 °C–84 °C (hexane), 83 °C–84 °C (Bruchatá et al., 2006) fumarate 156 °C–159 °C (ethyl acetate), 157 °C–158 °C (Bruchatá et al., 2006)
^{1}H-NMR ($CDCl_3$): δ 1.48–1.59 (m, 6H, 2**H**^{3,4,5} piper), 2.41 (d, 2H, C**H_2**N), 2.53 (t, 4H, 2**H**^{2,6} piper), 4.09–4.15 (m, 5H, Ar-O-C**H_2**-C**H**(O**H**)), 7.25 (s, 1H, **H**^{1} naph), 7.29 (d, 1H, **H**^{3} naph), 7.34 (t, 1H, **H**^{6} naph), 7.42 (t, 1H, **H**^{7}naph), 7.70–7.76 (m, 3H, **H**^{4,5,8} naph)
^{13}C-NMR (DMSO) δ 24.05 (**C**^{4} piper), 25.85 (**C**^{3,5} piper), 54.75 (**C**^{2,6} piper), 61.26 (**C**H_2N piper), 65.17 (**C**HOH), 66.95 (**C**^{3,5} morph), 70.33 (O**C**H_2), 106.69 (**C**^{3} naph), 118.84 (**C**^{1} naph), 123.66 (**C**^{6} naph), 126.74, 126.33 (**C**^{7,8} naph), 127.59 (**C**^{5} naph), 129.01 (**C**^{4} naph), 129.35 (**C–C**$_{cond}$ naph), 134.30 (**C**^{4} naph), 156.65 (**C**^{2} naph)

(2*RS*)-1-(morpholino)-3-(2-naphthyloxy)-propan-2-ol (XI)

$C_{17}H_{21}O_3N$ base yield 58%, R_f: 0.40, m.p. 71 °C–73 °C (hexane); 70 °C–72 °C (Bruchatá et al., 2006), fumarate 132 °C–134 °C (ethyl acetate), 134 °C–136 °C (Bruchatá et al., 2006)
^{1}H-NMR ($CDCl_3$): δ 2.49–2.72 (m, 6H, **H**^{2,6} morph, C**H_2**-N), 3.73–3.76 (m, 6H, **H**^{3,5} morph, OC**H**(O**H**)), 4.10 (m, 2H, Ar-O-C**H_2**), 3.38 (m, 1H, C**H**-OH), 2.68 (m, 2H, C**H_2**-N morph), 7.16–7.21 (m, 2H, **H**^{1,3} naph), 7.33–7.36 (t, 2H, **H**^{6,7}naph), 7.43–7.45 (m, 2H, **H**^{4,8} naph), 7.71–7.77 (m, 1H, **H**^{5} naph)
^{13}C-NMR (DMSO): δ 53.75 (**C**^{2,6} morph), 61.08 (**C**H_2N morph), 65.33 (**C**HOH), 66.95 (**C**^{3,5} morph), 70.11 (O**C**H_2), 106.71 (**C**^{3} naph), 118.75 (**C**^{1} naph), 123.73 (**C**^{6} naph), 126.38, 126.75 (**C**^{7,8} naph), 127.61 (**C**^{5} naph), 129.05, 129.42 (**C–C**$_{cond}$ naph), 134.30 (**C**^{4} naph), 156.56 (**C**^{2} naph)

(2*RS*)-1-(4-methylpiperazin-1-yl)-3-(2-naphthyloxy)-propan-2-ol (XII)

$C_{18}H_{24}O_2N_2$ base yield 62 %, R_f: 0.37, m.p. 131 °C–133 °C (cyclohexane); 132 °C–134 °C (Bruchatá et al., 2006), fumarate 215 °C–217 °C (ethyl acetate), 215 °C–217 °C (Bruchatá et al., 2006)
^{1}H-NMR ($CDCl_3$): δ 2.30 (s, 3H, N-C**H_3**), 2.49–2.73 (m, 10H, C**H_2** piper, C**H_2**N), 4.09–4.17 (m, 4H, Ar-O-C**H_2**-C**H**(O**H**)), 7.14–7.77 (m, 7H, C**H** naph)
^{13}C-NMR (DMSO): δ 45.96 (N-**C**H_3), 53.14 (**C**^{3,5} *N*-methylpiper), 55.10 (**C**^{2,6} *N*-methylpiper), 60.39 (**C**H_2*N*-methylpiper), 65.07 (**C**HOH), 71.34 (O**C**H_2), 106.68 (**C**^{3} naph), 118.70 (**C**^{1} naph), 123.67 (**C**^{6} naph), 126.52, 126.33 (**C**^{7,8} naph), 127.59 (**C**^{5} naph), 129.01 (**C**^{4} naph), 129.35 (**C–C**$_{cond}$ naph), 134.30 (**C**^{4} naph), 156.65 (**C**^{2} naph)

(2*RS*)-1-(2-methoxyphenylpiperazin-1-yl)-3-(2-naphthyloxy)-propan-2-ol (XIII)

$C_{24}H_{28}O_2N_2$ base yield 64%, R_f: 0.84, m.p. 108 °C–109 °C (cyclohexane), fumarate 179 °C–180 °C (ethyl acetate), IR (cm^{-1}) fumarate 2915–3407 (νOH), 1629, 1600 (νC=C), 1261 (νArOalk); UV base (CH_3OH, ε in m^2/mol): λ_1 226 log ε_1 4.59, λ_2 272 log ε_2 4.40, λ_3 327 log ε_3 2.82
^{1}H-NMR ($CDCl_3$): base δ 2.65–2.69 (m, 4H, **H**^{2,6} piper), 2.89–2.91 (m, 2H, CHC**H_2**N), 3.10–3.14 (m, 4H, **H**^{3,5} piper), 3.87 (s, 3H, OC**H_3**), 4.13–4.18 (m, C**H_2**C**H**OH), 6.85–6.98 (m, 4H, **H**$^{3',4',5',6'}$ arom), 7.16–7.21 (m, 2H, **H**^{1,3} naph), 7.33–7.36 (t, 2H, **H**^{6,7} naph), 7.43–7.45 (m, 2H, **H**^{4,8} naph), 7.71–7.77 (m, 1H, **H**^{5} naph)
MW 376.50, calc. %C 76.56 %H 7.50 %N 7.44, found %C 76.35 %H 7.28 %N 7.23

ANTIOXIDATIVE ACTIVITY

2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid method

Aqueous solutions of 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS) with a concentration of 7.7 μg/ml (14 mM) and $K_2S_2O_8$ with a concentration of 1.32 mg/ml (4.9 mM) were prepared. These solutions were combined in 1:1 ratio and left for 24 h in a refrigerator in the dark. The wells were filled with 60 μl of sample solution at a concentration of 10^{-2} or 10^{-3} mol/dm^3, respectively, and then 240 μl of ABTS solution was added. Thereafter, the absorbance was determined

spectrophotometrically at a wavelength of 734 nm for 30 min at 1-min interval. The measurement was carried out on a 96-well plate. Three parallel measurements were performed for each sample. During measurement, the colorless ABTS undergoes oxidation by potassium peroxodisulfate, yielding the stable blue-green $ABTS^{\cdot+}$ radical. Addition of antioxidants causes reduction of the $ABTS^{\cdot+}$ radical and discoloration of the solution. The antioxidant activity relates to the activity of the standard substance trolox, whose activity was determined simultaneously with the samples measured. The method is dependent on pH, hence buffers containing disodium hydrogen phosphate and potassium dihydrogen phosphate were used for the measurement (Re et al., 1999; Malík et al., 2017).

High-performance liquid chromatography

I. The compounds were separated on a column with a polysaccharide chiral stationary phase. HPLC instrument AGILENT 1200 (Agilent Technologies, Santa Clara, CA, USA) was used, which comprised an automatic dosing system, quaternary high-pressure pump, degasser of the mobile phase, and a diode array detector. The collection and processing of chromatographic data was carried out by the software program Agilent ChemStation for LC system (Agilent Technologies). The separation of enantiomers was achieved on a chiral stationary phase Chiralpak AD (0.46 × 25cm; 5 µm ID) with tris(3,5-dimethylphenylcarbamate)amylose as the chiral selector. The mobile phase was an 80:10:10:0.1 (v/v/v/v) mixture of hexane, EtOH, MeOH, and *N*-ethylenamine, respectively. HPLC solvents were acquired from Merck (Darmstadt, Germany). The mobile phase flow rate was 0.8 ml/min, injection volume was 20 µl, and the column temperature was set to 25 °C. Chromatograms were recorded at a wavelength of 265 ± 8 nm.

II. The compounds were separated on a column with a macrocyclic chiral stationary phase using an HPLC instrument (Series 1100), containing a binary high-pressure pump, automatic dosing system, column thermostat, and diode array detector. Separation of enantiomers was carried out on a chiral stationary phase with the chiral selector teicoplanin (Chirobiotic T [0.45 × 25 cm, 5 µm ID]). The mobile phase consisted of a mixture of MeOH, acetonitrile, acetic acid, and triethylamine in a 45:55:0.3:0.2 (v/v/v/v) ratio. HPLC-quality solvents were purchased from Merck. Dead time was estimated as the elution time of MeOH. Sample solutions with 0.1 mg/ml concentration were prepared by dissolution of an exact amount of substance in MeOH.

The enantioseparation was evaluated setting the following chromatographic criteria:

$$\text{retention factor (k): } k_1 = (t_{1-} t_0)/t_0 \text{ , } k_2 = (t_{2-} t_0)/t_0$$
$$\text{selectivity factor (α): } \alpha = k_2/k_1$$
$$\text{resolution factor } (R_s)\text{: } R_s = 2\,(t_{2-} t_1)/(w_1 + w_2)$$

Table 2. Screening of antioxidant activities of salts and free bases of the prepared compounds.

Compound	Working label	Inhibition of ABTS (%) ± SD
I	B2N IZP	90.90 ±1.90
Ib	H2NIZP	31.66 ±2.73
II	B2N4t	81.97 ±1.94
IIa	F2N4t	9.33 ±3.77
IIIa	F2NDMA	8.12 ±3.20
IVa	F2N-CH	33.51 ±3.30
VIIa	F2N pyrr	11.71 ±0.64
VIIb	H2N pyrr	21.99 ± 0.81
VIII	B2N-IMI	52.18 ±1.5
IX	B2N-2IMI	57.10 ±6.60
Xa	F2Npiper	6.01 ±1.09
XIa	F2Nmorph	17.76 ±0.94
XII	B2NCH_3piper	92.92 ±1.16
XIIIa	F2NMFP	41.71 ±9.50
XVI	Imidazole	Inactive
XVII	2-methylimidazole	5.42 ±1.30
XIV	Naphthalen-1-ol	99.64 ±0.16
XV	Naphthalen-2-ol	99.63 ±0.30
Propranolol[a]	Standard	97.48 ± 2.34

[a]*Čižmáriková et al., 2020*

where t_1 and t_2 are the retention times (min) and w_1, w_2 are the peak widths at the bases of the peaks (min) for the respective enantiomers.

Mobile phase: hexane/EtOH/MeOH/ethylethanamine with the following composition:

A 85:7.5:7.5:0.1 (v/v/v/v),
B 80:10:10:0.1 (v/v/v/v),
C 75:12.5:12.5:0.1 (v/v/v/v),
D 70:15:15:0.1 (v/v/v/v)

DISCUSSION

The aim of the present work was to synthesize a series of compounds of the aryloxyaminopropanol type, derived from naphthalen-2-ol (compounds I–XIII) with modifications in the basic part and to investigate their antioxidant activities and possibilities of HPLC enantioseparation. The reaction of naphthalen-2-ol with (±)-2-(chloromethyl)oxirane yielded 2-[(naphthalen-2-yloxy)methyl]oxirane as a white substance with 63% yield. This compound reacted in the next step with individual branched aliphatic amines (isopropylamine, *tert*-butylamine, or dimethylamine), aromatic amines (aniline or

Table 3. Chromatographic parameters of the derivatives of 2-naphthol on the chiral column Chiralpak AD-H.

Compound	Mobile phase	t_1	t_2	k_1	k_2	α	Rs
I	B	7.88	13.83	1.11	2.71	2.44	14.88
III	B	10.41	12.90	1.70	2.35	1.38	4.15
IVa	A	12.26	21.14	1.97	4.13	2.09	12.96
IVa	B	10.44	17.77	1.69	3.58	2.12	12.01
V	A	49.08	84.03	11.37	20.17	1.77	12.83
V	B	37.82	64.31	8.49	15.13	1.78	12.32
VIa	**B**	29.48	65.29	6.59	15.82	2.40	14.32
VII	B	11.20	12.91	1.33	1.69	3.85	1.27
VIIIa	**D**	17.72	20.87	4.54	5.52	0.82	3.50
VIIIa	B	27.97	33.75	6.32	7.83	1.24	4.21
IX	B	56.58	--	-	-	-	-
IX	**D**	41.44	-	-	-	-	-
XII	B	13.45	18.05	2.60	3.80	6.35	1.46
XIIIa	B	8.55	-	-	-	-	-
XIIIa	C	7.75	-	-	-	-	-
XIIIa	A	9.75	-	-	-	-	-

Table 4. Chromatographic parameters of the derivatives of 2-naphthol on the chiral column Chirobiotic T.

Compound	Mobile phase	t_1	t_2	k_1	k_2	α	Rs
III	E	15.20	15.60	3.93	4.06	1.03	0.77
IV	E	15.98	17.04	3.32	3.61	1.09	1.18
V	E	3.18	-	-	-	-	-
VI	E	17.53	19.80	3.74	4.36	1.17	2.67

E: MeOH:acetonitrile:acetic acid:diethylethanamine = 45:55:0.3:0.2 (v/v/v/v)

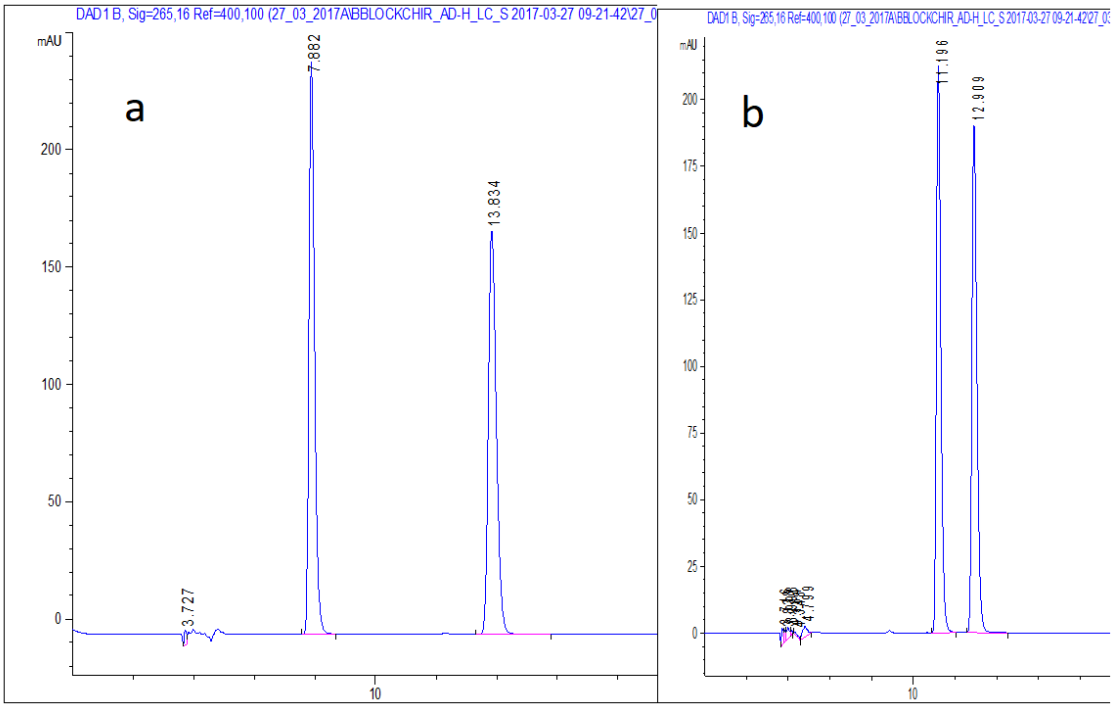


Figure 1. HPLC chromatograms for enantioseparation of the compounds I (a) and VII (b) on Chiralpak AD-H column with the mobile phase B.

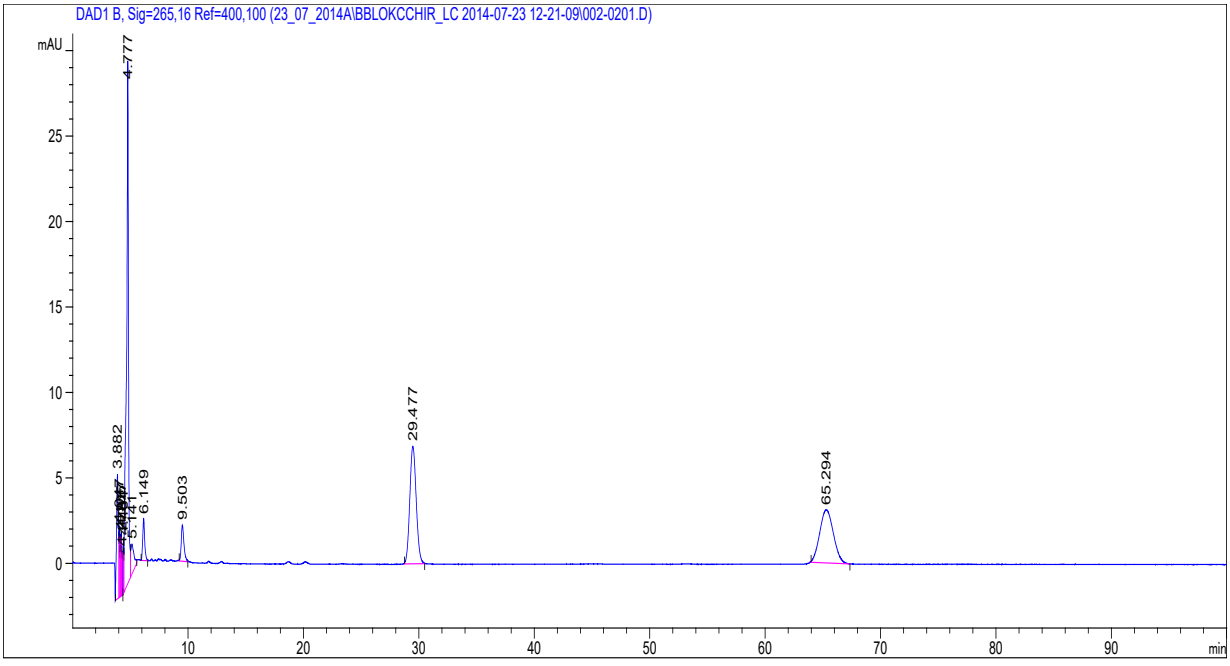


Figure 2. HPLC chromatogram for enantioseparation of the compound VIa on Chiralpak AD-H column with the mobile phase B.

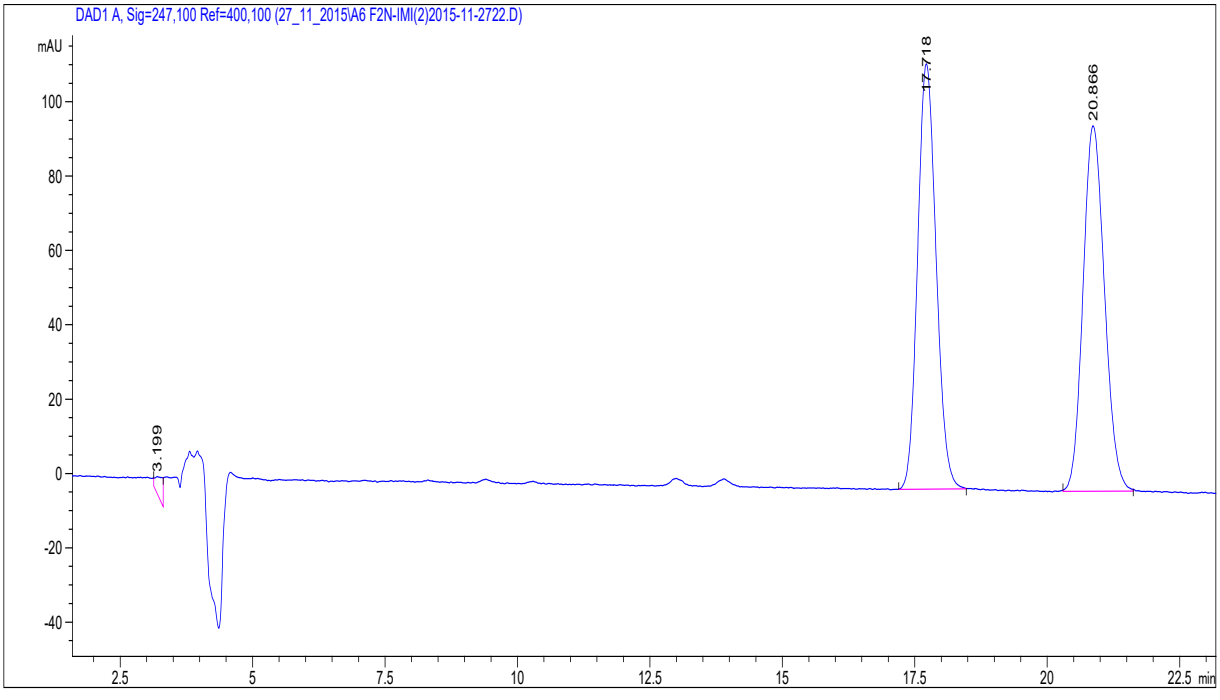


Figure 3. HPLC chromatogram for enantioseparation of the compound VIIIa on Chiralpak AD-H column with the mobile phase D.

3,4-dimethoxyphenylethylamine), and heterocyclic amines (pyrrolidine, imidazole, 2-methylimidazole, piperidine, morpholine, 4-methylpiperidine, or 1-(2-methoxyphenyl) piperidine).

The products were isolated in the form of free bases with 59%–75% yield. The free bases were converted to white solid salts by reactions with fumaric and hydrochloric acid, respectively.

The purity of the products was evaluated using TLC, and the melting points of the prepared compounds were determined (Scheme 1, Table 1).

Apart from comparing experimentally measured melting points with the data in literature, the identity of the synthesized compounds was established also by analysis of their recorded IR, UV (except the compounds described in Bruchatá et al., 2006), ^{1}H- and ^{13}C-NMR spectra.

In the IR spectra, signals of (νOH) and (νOH νNH) in the range of 2915–3407 cm^{-1}, (νC=C) between 1597 and 1629 cm^{-1}, and (νArOalk) between 1217 and 1261 cm^{-1} were detected. Two or three absorption bands could be identified in the UV spectra (ε in m^2/mol): λ_1 225–226 nm, λ_2 261–272 nm, and λ_3 313–321 nm, corresponding to π–π* transitions with ε in the range: ε_1 3.75–5.15, ε_2 2.82–3.96, and ε_3 3.14–3.45.

Hydrogens of the methyl groups of isopropyl in compound I appeared in ^{1}H-NMR as doublet at 1.27 ppm, in compounds II and III in the *tert*-butyl group as singlets at 1.14 ppm, and in dimethylamine at 2.85 ppm. Hydrogens of the cyclohexane ring in compound IV were observable as multiplets in the range of 1.60–2.46 ppm, of the pyrrolidine ring in compound VII in the range of 1.70–2.90, and of piperidine ring in compound X in the range of 1.48–2.53 ppm. Hydrogens of the morpholine ring in compound XI and of piperazine in compounds XII and XIII showed multiplets in the range of 2.49–3.76.

Methoxy groups connected to the aromatic ring in compound VI could be found as singlets at 3.68 and 3.71 ppm. Hydrogens of the propanol moiety appeared at approximately 4 ppm and the dianion of fumaric acid in compound III as a singlet signal at 6.37 ppm. Signals of aromatic protons in naphthalene, imidazole, and benzene rings arose at 6.71–7.99 ppm.

To evaluate potential biological effects of the synthesized compounds, preliminary *in vitro* screening of antioxidant activity of selected intermediates and products was carried out. The ABTS method was used to determine the antioxidative activities, being more sensitive for this type of compounds than the DPPH technique. The ABTS method was based on discoloration of the blue-green solution of the active radical ABTS^{+} upon its reaction with an antioxidant. The absorbance was measured at 734 nm wavelength.

The results of the screening showed that the free bases of the products I, II, and XII exerted much higher activities (in the range of 81.97%–92.92%), while the bases containing imidazole (VIII) and 2-methylimidazole (IX) were less active (52.18% and 57.10%, respectively). Their salts (Ib, IIa, IIIa, IVa,VIIa, VIIb, Xa, XIa, XIIIa) exerted comparatively lower activities in the range of 6.01%–41.71%. The starting compounds naphthalen-2-ol and naphthalen-1-ol showed 99.6% activity (Table 2). High antioxidative activities of the salts of β-blockers were reported in Čižmáriková et al. (2020). Comparison between the salts and their free bases indicated lower activity of the free bases in the case of bevantolol and toliprolol, similar to previous observations (Čižmáriková et al., 2021).

The prepared compounds contain a stereogenic carbon atom in the connecting chain, which is the reason for their optical activity. Hence, they appeared as two enantiomers which differed (in achiral environment) only in their ability to rotate the plane of polarized light either to the right (+) or to the left (–). Absolute configuration of derivatives with only one stereogenic center (according to the Cahn–Ingold–Prelog system) can be either (*R*) or (*S*). In clinical practice, they are mostly used in the racemic form, even though many reports indicate different pharmacodynamic, pharmacokinetic, and toxicologic behaviors of the respective enantiomers. In the group of aryloxyaminopropanols, higher activity was found in the (–)-enantiomers with the absolute configuration (*S*).

In regard to HPLC enantioseparation, the present work builds on a previous study by Bruchatá et al. (2006), which dealt with the enantioseparation of the compounds I, IIa, VIIa, Xa, XI, and XIIa on chiral columns based on macrocyclic antibiotics vancomycin, teicoplanin, and teicoplanin aglycone. Successful separation on all columns was possible only with the compounds I and IIa with a branched alkyl substituent. Vancomycin-containing column was unable to split the compound with piperidine (Xa), and the enantioseparation of the compound XII containing 4-methylpiperazin-1-yl failed on all employed chromatographic columns, probably due to sterical shielding of the stereoselective center.

Chiral stationary phase of the chromatographic column Chiralpak AD used in our study contains tris-(3,5-dimethylphenylcarbamate)amylose as the chiral selector. Carbamate groups form hydrogen bonds with amino and oxo groups of the analyte, and the efficacy of the separation was also facilitated by formation of inclusion complexes, dipole–dipole and π–π* interactions of aromatic moieties of the analyte and phenylamide. The mobile phases used consisted of 70%–90% of hexane, supplemented with a mixture of MeOH and EtOH in various ratios and with a small amount of ethylethanamine responsible for better separation and symmetrical shapes of the peaks (mobile phases A–D). The presence of alcohols in the mobile phase facilitated better enantioseparation and affected the formation of hydrogen bonds, hence affecting the interactions with the stationary phase.

Baseline separation was achieved with enantiomers of the compounds I, III, IV, VII, VIIIa, and XII, with selectivity factor α in the range 0.82–6.35 and resolution factor R_s 1.46–14.88. Enantioseparations of the compound with aniline (V) and with 3,4-dimethoxyphenyl (VI) were successful, albeit with long elution times.

Enantiomers of the compound VIIIa with imidazole in the basic part were separated using the mobile phase B (α = 1.24, Rs = 4.21), even though longer analysis time was needed. Increase in alcohol content of the mobile phase using the conditions D (70% hexane) led to shortening of the elution time while maintaining the efficacy of enantioseparation (α = 1.22, Rs = 3.70). The compound IXa containing a 2-methylimidazole moiety could not be split into enantiomers using the conditions B or D, which was possibly caused by steric hindrance at the nitrogen atom by a methyl group, preventing the access to this atom. The enantioseparation of compounds

with a 4-(2-methoxyphenyl)piperazin-1-yl substituent (XIIIa) was not successful using either mobile phase (A, B, C, and D) (Table 3, Figures 1–3). When using the Chirobiotic T column, the enantioseparation of compounds III, IV, and VII was feasible, with α = 1.03–1.17 and R_s = 0.77–2.67. Compound V containing an aniline moiety could not be separated on this column (Table 4).

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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