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Antioxidant activity of novel phenolic compounds bearing basic substituents—synthesis and insights from molecular modeling

Original Paper

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Abstract Free radicals are important reactive species that perform both positive and negative functions within living organisms. Antioxidants play a significant part in preventing or managing diseases linked to oxidative stress, including cancer, cardiovascular disease, and neurodegenerative disorders. In the presented work, a two-step synthesis was used to prepare 15 phenolic compounds substituted with various *N*-heterocyclic moieties as potential antioxidants. The starting materials were 4-hydroxyphenylalkyl ketones, which were converted into 4-hydroxy-3-chloromethylphenylalkyl ketones via chloromethylation. These then reacted with various aliphatic amines (dimethylamine, diethylamine, isopropylamine, isobutylamine, and tert-butylamine) and heterocyclic amines (pyrrolidine, piperidine, morpholine, azepane, and 4-methylpiperazine). The purity of the products was confirmed by thin-layer chromatography, and their infrared (IR), ultraviolet (UV), and proton nuclear magnetic resonance (^{1}H NMR) spectra were measured. Their antioxidant activity was determined using the DPPA and ABTS methods. The ABTS results show antioxidant activity values ranging from 85% to 95%, which are higher than the values for oxygen derivatives. Conformational analysis revealed a stronger hydrogen bond between OH and N than between OH and O. In the case of the compound containing isobutyl, the formation of an intramolecular hydrogen bond (NH···O) is considered more likely.

Keywords *substituted phenols – 4-hydroxyphenylalkanones – antioxidants – antiradical activity – molecular modeling*

INTRODUCTION

Compounds containing phenolic groups are found in many different areas of life. The inclusion of phenolic groups within pharmaceutical compounds endows them with reactive functionality of an acidic nature. One such group of bioactive compounds are drugs in which the phenolic group forms part of the structure of beta-2-agonists, which are used in the acute treatment of obstructive airway diseases (Čižmáriková et al., 2020; Yang et al., 2021). Furthermore, it is found in the structure of the main opium alkaloid morphine (Lugo et al., 2002; Mercadante, 2010) used as an analgesic, mainly in palliative care, as well as in the tetrahydroisoquinoline alkaloid ecteinascidin used to treat patients with advanced soft tissue sarcoma where previous drugs have been unsuccessful (Zewail-Foote & Hurley, 1999; Held-Warmkessel, 2003; Lau et al., 2005). The phenol group is also present in the structure of the anthelmintic niclosamide (Barini et al., 2018), as well as in tetracycline (Agwuh & MacGowan, 2006; Nelson et al., 2011) and ansamycin (Wrona et al., 2008; Skrzypczak et al., 2022) antibiotics. Propofol, a non-barbiturate intravenous anesthetic of phenolic nature, is extensively utilized in surgical settings for the induction and maintenance of sedation (Condello et al., 2021; Ferrier et al., 2022; Čižmáriková et al., 2023). The phenol group is found in the structure of the hormonal contraceptive estrogen (Stuenkel et al., 2015), the thyroid hormone thyroxine (Mondal et al., 2016; Dutta et al., 2021) and its synthetic form levothyroxine (Sue & Leung, 2020; Jonklaas, 2022), the stress hormone adrenaline (Gough & Nolan, 2018; Gil-Jardine et al., 2022), and the neurotransmitters dopamine (Lerner at al., 2021; Mirabella et al., 2023) and serotonin (Fuller, 1992; David & Gardier, 2016; Liu et al., 2020). A large and important group of natural polyphenolic compounds are the flavonoids (Panche at al., 2016). They exhibit a broad spectrum of biological effects and are candidate compounds in the development of various medical agents in therapy as well as prevention of disease (Hasnat et al., 2024; Stachelska et al., 2025; Ullah et al., 2020). In particular, they are powerful antioxidants (Pietta, 2000; Zahra et al., 2024). Other fields of interest include infectious diseases (Liu et al., 2025; Cushnie & Lamb, 2005), cancer (Kopustinskiene et al., 2020;

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Mir et al., 2024), inflammation (Al-Khayri et al., 2022), and neurodegenerative diseases (Cheng et al., 2025).

The antiradical (Bendary et al., 2013; Čižmáriková et al., 2020), antimicrobial (Taguri et al., 2006; Cueva et al., 2010), antituberculosis (Mazlunat et al., 2019; Islam et al., 2021), and chelating activity of various substituted phenols were investigated (Olennikov et al., 2014; Rahim et al., 2016). Depending on the substituents present, phenols exist in so-called open and cyclic forms. Typically, this is a cyclic form that is associated with the presence of a hydrogen bond. The strength of a hydrogen bond can be studied by conformational analysis, and one of the parameters for determining its strength is the distance between the atoms forming the hydrogen bond (Rademacher et al., 2005; Lithoxoidou & Bakalbassis, 2005).

A significant number of phenolic compounds have been shown to possess substantial antiradical activity, which has been associated with their function as powerful antioxidants and anti-inflammatory agents important in the prevention of chronic diseases such as cancer, cardiovascular disease, diabetes, and neurodegenerative disorders. Both the bioactivity and toxicity of phenols are affected by the number and arrangement of their phenolic groups (Calliste et al., 2001; Amouar et al., 2009; Kadoma et al., 2010). Furthermore, phenols have the ability to form complexes with metal ions (Hider et al., 2001; Fernandez et al., 2002).

The amine moiety is also considered a potent pharmacophore, for example, in mitochondria targeting agents with anticancer activity (Gao et al., 2025; Skrzypczak et al., 2021).

The aim of this study was to prepare novel phenolic derivatives bearing substituted amino moieties (compounds I–XV, Table 1) via a two-step synthesis. The antioxidant capacity of the products was then evaluated using two different methods.

EXPERIMENTAL

The melting point of the synthesized substances was determined using a Kofler block (HMK, Franz Küstner, Germany) and is uncorrected. The purity of the prepared compounds was verified by thin-layer chromatography (TLC) using Silufol® UV 254 silica gel plates (Merck) and a mixture of propan-1-ol:diethylamine solvents in a ratio of 9:1 v/v. A UV lamp was used for detection. Elemental analysis was performed using a FLASH 2000 Organic Elemental Analyzer (Thermo Scientific, Waltham, Massachusetts, USA).

Infrared spectra were measured using a reflective technique with an ATR adapter with ZnSe crystals and a Nicolet 6700 spectrophotometer (Thermo Scientific, Waltham, Massachusetts, USA). Ultraviolet spectra were measured using a GENESYS 10S spectrophotometer in the wavelength range of 200–400 nm. The concentrations of the measured base and salt solutions of the prepared aryloxyaminopropanols in methanol were approximately 0.2 $mol.m^{-3}$. ^{1}H-NMR spectra were measured on a Varian Gemini 2000 Spectrometer (Varian Inc., Palo Alto, USA) with an operating frequency of 300 MHz for ^{1}H NMR. Tetramethylsilane was used as an internal standard. Deuterated solvents were used to dissolve the samples, namely, deuterated chloroform, methanol, DMSO, and water. Chemical shifts (δ) are expressed in ppm. Signal multiplicity is expressed as follows: s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet.

Synthesis

Preparation of [3-(chloromethyl)-4-(hydroxy)phenyl] alkylketones (Čižmáriková et al., 2002)

A sulfonation flask was set up with a mechanical stirrer, a contact thermometer, and a powder funnel. Then, 0.15 mol of 4-hydroxyphenylpropan-1-one and 90 mL of concentrated hydrochloric acid were added. The temperature was kept constant, and 7.5 g of paraformaldehyde was gradually added. The mixture was stirred, and the reaction was left to continue for 4.5 hours. After precipitation, the solid product was collected by means of suction filtration, washed with water, and then crystallized from benzene or ethyl acetate. The product was used without further purification.

[3-(chloromethyl)-4-(hydroxy)phenyl]methylketone Yield 62%, mp 159–161 °C (Čižmárikova et al., 2002: yield 57%, mp 160–162 °C).

[3-(chloromethyl) -4-(hydroxy)phenyl]ethylketone Yield 55%, mp 132–135 °C (Da Re & Verlichi, 1956: yield 59%, mp 133–136 °C).

Preparation of [3-(aminomethyl)-4-(hydroxy)phenyl] methylketone

To a solution of 0.02 mol of 4-hydroxy-3-(chloromethyl) phenylethanone in 100 mL of anhydrous benzene or toluene, 0.04 mol of the appropriate amine is added at laboratory temperature and under constant stirring, and the reaction mixture is allowed to react further for 5 hours under constant stirring. The precipitated salt of the basic amine is then removed by suction and washed with benzene or toluene, and the solvent is distilled off. The residue after distillation is acidified with 5% HCl and washed with ethyl acetate. The acidic fraction is neutralized with $NaHCO_3$ to a pH value of 7.0 and extracted with benzene. The organic layer is washed with water and dried with Na_2SO_4, and the solvent is distilled off. The residue after distillation is crystallized from hexane, heptane, or cyclohexane. The crystalline product is obtained after cooling.

Preparation of [4-hydroxy-3-(piperidinomethyl)phenyl] methylketone (Mannich synthesis)

0.04 mol of piperidine and 0.05 mol of paraformaldehyde are heated with a sufficient amount of ethanol (5 to 7 mL) until a clear solution is formed. After clarification, the solution is cooled and 0.05 mol of 4-hydroxyphenylmethylketone in 10 mL of ethanol is gradually added. The resulting mixture is left to react for 1 hour at laboratory temperature and then

refluxed for 2 hours. The reaction mixture is left to cool to room temperature for 24 hours at laboratory temperature, ethanol is distilled off, and the final product is recrystallized from hexane. Yield 58%, MS: m/z (I/%) M^+ 233(100%), 218 (30%), 149 (34), 98 (62%), 84 (20%).

[3-(dimethylaminomethyl)-4-(hydroxy)phenyl] ethylketone (I)

Yield 30%, mp 39–41°C (hexane); R_f 0.84

IR (cm^{-1}): 2800–3000 (νOH), 1680 (νC=O), 1597 (νC=C), 1251 (νC-N); **UV** (CH_3OH, ε in $m^2.mol^{-1}$): λ_1 220 log ε_1 2.52, λ_2 270 log ε_2 2.54;

^{1}**H-NMR** (HMDSO, δ in ppm): 1.14 (s, 6H N(CH_3)$_2$, 1.26 (J = 7.10 Hz, t, 3H, $COCH_2CH_3$), 2.91 (J = 7.20 Hz, q, 2H, -$COCH_2CH_3$), 3.61 (s, 2H, CH_2N), 6.62 (J = 8.20 Hz, d, 1H, Ar**H**^{5}), 7.70 (J = 2.10 Hz, d, 1H, Ar**H**^{2}), 7.75 (J = 8.10 Hz, d, 1H, Ar**H**^{6}), 11.12 (s, 1H, O**H**)

$C_{12}H_{17}O_2N$, M_r 207.27; **Elem. analysis**: calc. %C 69.56 %H 8.27 %N 6.76, found %C 69.53 %H 8.02 %N 6.62.

[3-(diethylaminomethyl)-4-(hydroxy)phenyl] methylketone (II)

Yield 35%, mp 40–42 °C (hexane); R_f 0.85

IR (cm^{-1}): 2800–3276 (νOH), 1681 (νC=O), 1594 (νC=C), 1282 (νC-N); **UV** (CH_3OH, ε in $m^2.mol^{-1}$): λ_1 224 log ε_1 2.62, λ_2 288 log ε_2 2.67

^{1}**H-NMR** (HMDSO, δ in ppm): 1.09 (J = 7.30 Hz, t, 6H, N(CH_2CH_3)$_2$), 2. 49 (s, 3H, $COCH_3$), 2.60 (J = 7.20 Hz, q, 4H, N(CH_2CH_3)$_2$), 3.75 (s, 2H, CH_2N), 6.71 (J = 8.25 Hz, d, 1H, Ar**H**^{5}), 7.60 (J = 2.15 Hz, d, 1H, Ar**H**^{2}), 7.80 (J = 8.15 Hz, d, 1H, Ar**H**^{6}), 11.22 (s, 1H, O**H**)

$C_{13}H_{19}O_2N$, M_r 221.30; **Elem. analysis**: calc. %C 70.56 %H 8.65 %N 6.33, found %C 70.44%H 8.86 %N 6.50.

[4-(hydroxy)-3-(isopropylaminomethyl)phenyl] methylketone (III)

Yield 37%, mp 60–62 °C (hexane); R_f 0.42

IR (cm^{-1}): 2800–3274 (νOH), 1683 (νC=O),1595 (νC=C), 1283 (νC-N); UV (CH_3OH, ε in $m^2.mol^{-1}$): λ_1 224 log ε_1 2.62, λ_2 288 log ε_2 2.67

^{1}**H-NMR** (HMDSO, δ in ppm): 1.08 (J = 6.30 Hz, d, 6H, HC(CH_3)$_2$), 2.32 (s, 3H, $COCH_3$), 2.60–3.00 (m, 1H, C**H**), 3.95 (s, 2H, CH_2N), 6.62 (J = 8.25 Hz, d, 1H, Ar**H**^{5}), 7.50 (J = 2.30 Hz, d, 1H, Ar**H**^{2}), 7.81 (J = 8.35 Hz, d, 1H, Ar**H**^{6}), 11.32 (s, 1H, O**H**)

$C_{12}H_{17}O_2N$, M_r 207.27; **Elem. analysis**: calc. %C 69.51 %H 8.27 %N 6.76, found %C 69.63 %H 8.40 %N 7.05.

[4-(hydroxy(isopropylaminomethyl)phenyl]ethylketone (IV)

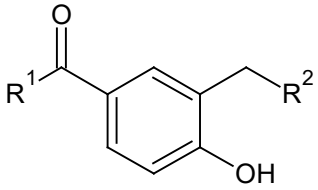
Yield 31%, mp 63–65 °C (hexane); R_f 0,40

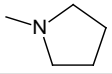
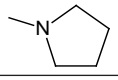
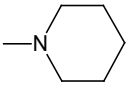
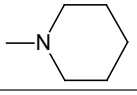
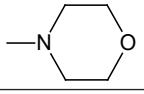
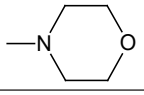
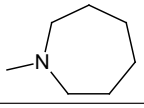
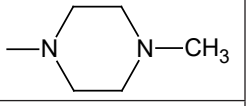
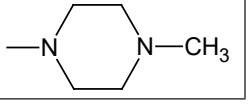
IR (cm^{-1}): 2900–3300 (νOH), 1684 (νC=O), 1596 (νC=C), 1285 (νC-N); **UV** (CH_3OH, ε in $m^2.mol^{-1}$): λ_1 225 log ε_1 2.63, λ_2 289 log ε_2 2.68

^{1}**H-NMR** (HMDSO, δ in ppm): 1.05 (J = 7.30 Hz, d, 6H, 2 CH_3), 1.25 (J = 7.20 Hz, t, 3H, $COCH_2CH_3$), 2.42–3.00 (m, 1H, C**H**), 2.89 (J = 7.20 Hz, q, 2H, $COCH_2CH_3$), 4.00 (s, 2H, CH_2N), 6.75 (J = 8.30 Hz, d, 1H, Ar**H**^{5}), 7.50 (J = 2.16 Hz, d, 1H, Ar**H**^{2}), 7.75 (J = 8.40 Hz, d, 1H, Ar**H**^{6}), 11.02 (s, 1H, O**H**)

$C_{13}H_{19}O_2N$, M_r 221.8; **Elem. analysis**: calc. %C 72.84 %H 8.56 %N 5.66, found %C 73.00 %H 8.71 %N 5.90.

Table 1. Overview of the substances studied



Substance	R^1	R^2
I	CH_2CH_3	$N(CH_3)_2$
II	CH_3	$N(CH_2CH_3)_2$
III	CH_3	$NHCH(CH_3)_2$
IV	CH_2CH_3	$NHCH(CH_3)_2$
V	CH_3	$NHCH_2CH(CH_3)_2$
VI	CH_3	$NHC(CH_3)_3$
VII	CH_3	
VIII	CH_2CH_3	
IX	CH_3	
X	CH_2CH_3	
XI	CH_3	
XII	CH_2CH_3	
XIII	CH_3	
XIV	CH_3	
XV	CH_2CH_3	

[4-(hydroxy)-3-(isobutylaminomethyl)phenyl] methylketone (V)

Yield 36%, mp 83–85 °C (hexane); R_f 0.30

IR (cm^{-1}): 2800–3000 (νOH), 1685 (νC=O), 1607 (νC=C), 1286 (νC-N); **UV** (CH_3OH, ε in $m^2.mol^{-1}$): λ_1 218 log ε_1 2.01, λ_2 268 log ε_2 1.97

^{1}**H-NMR** (HMDSO, δ in ppm): 0.94 (J = 6.70 Hz, d, 6H, CH(C**H**$_3$)$_2$), 1.97 (m, 1H, C**H**), 2.50 (s, 3H, COC**H**$_3$), 2.72 (J = 6.80Hz, d, 2H C**H**$_2$-CH), 4.11 (s, 2H, C**H**$_2$N), 7.88 (J = 8.35 Hz, d, 1H, Ar**H**^{5}), 7.90 (J = 2.20 Hz, d, 1H, Ar**H**^{2}), 8.01 (J = 8.22 Hz, d, 1H, Ar**H**^{6}), 11.12 (s, 1H, O**H**)
$C_{13}H_{19}O_2N$, Mr 221.8; **Elem. analysis**: calc. %C 72.84 %H 8.56 %N 5.66, found %C 72.77% H 8.42 %N 5.42.

[4-(hydroxy)-3-(tert-butylaminomethyl)phenyl] methylketone (VI)
Yield 40%, mp 89–91 °C (hexane); R_f 0.57
IR (cm^{-1}): 2900–3000 (νOH), 1675 (νC=O), 1596 (νC=C), 1235 (νC-N); **UV** (CH_3OH, ε in m^2.mol^{-1}): λ_1 230 log ε_1 2.87, λ_2 318 log ε_2 3.22
^{1}**H-NMR** (HMDSO, δ in ppm): 1.15 (s, 9H, C(C**H**$_3$)$_3$), 2.51 (s, 3H, COC**H**$_3$), 4.01 (s, 2H, C**H**$_2$N), 6.80 (J = 8.30 Hz, d, 1H, Ar**H**^{5}), 7.25 (J = 2.30, d, 1H, Ar**H**^{2}), 7.78 (J = 8.20 Hz, d, 1H, Ar**H**^{6}), 10.12 (s, 1H, O**H**)
$C_{13}H_{19}O_2N$, M_r 221.8; **Elem. analysis**: calc. %C 72.84 %H 8.56 %N 5.66, found %C 72.67 %H 8.50 %N 5.63.

[4-(hydroxy)-3-(pyrrolidin-1-ylmethyl)phenyl] methylketone (VII)
Yield 42%, mp 86–89 °C (hexane); R_f 0.52
IR (cm^{-1}): 2800–3000 (νOH), 1667 (νC=O), 1597 (νC=C), 1251 (νC-N); **UV** (CH_3OH, ε in m^2.mol^{-1}): λ_1 220 log ε_1 2.52, λ_2 270 log ε_2 2.54
^{1}**H-NMR** ($CDCl_3$, δ in ppm): 1.60–2.05 (m, 4H, C**H**$_2$ pyrrolidine 3,4), 2.50–2.80 (m, 4H, C**H**$_2$ pyrrolidine 2,5), 2.67 (s, 3H, COC**H**$_3$), 3.87 (s, 2H, NC**H**$_2$), 6.87 (J = 8.45 Hz, d, 1H, Ar**H**^{5}), 7.56 (J = 2.10 Hz, d, 1H, Ar**H**^{2}), 7.71 (J = 7.82 Hz, d, 1H, Ar**H**^{6}), 11.51 (s, 1H, O**H**)
$C_{13}H_{17}O_2N$, M_r 219.29; **Elem. analysis**: calc. %C 71.21 %H 7.81 %N 6.39, found %C 71.32 %H 8.10 %N 6.40.

[4-(hydroxy)-3-(pyrrolidin-1-ylmethyl)phenyl] ethylketone (VIII)
Yield 45%, mp 91–94 °C (hexane); R_f 0.39
IR (cm^{-1}): 2800–3100 (νOH), 1665 (νC=O), 1598 (νC=C), 1252 (νC-N); **UV** (CH_3OH, ε in m^2.mol^{-1}): λ_1 222 log ε_1 2.54, λ_2 272 log ε_2 2.56
^{1}**H-NMR** ($CDCl_3$, δ in ppm): 1.15 (t, 3H, $COCH_2C$**H**$_3$), 1.70–1.90 (m, 4H, C**H**$_2$ pyrrolidine 3,4), 2.49–2.84 (m, 4H C**H**$_2$ pyrrolidine 2,5), 2.90 (J = 7.20 Hz, q, 2H, COC**H**$_2$CH$_3$), 3.80 (s, 2H, NC**H**$_2$), 6.75 (J = 8.45 Hz, d, Ar**H**^{5}), 7.13 (J = 2.10 Hz, d, 1H, Ar**H**^{2}), 7.26 (J = 8.40 Hz, d, 1H, Ar**H**^{6}), 11.31 (s, 1H, O**H**)
$C_{14}H_{19}O_2N$, M_r 233.31; **Elem. analysis**: calc. %C 72.07 %H 8.21 %N 6.00, found %C 72.40 %H 8.52 %N 5.61.

[4-(hydroxy)-3-(piperidinomethyl)phenyl]methylketone (IX)
Yield 60%, mp 57–59 °C, (hexane); R_f 0.61
IR (cm^{-1}): 2800–3000 (νOH), 1679 (νC=O), 1598 (νC=C), 1250 (νC-N); **UV** (CH_3OH, ε in m^2.mol^{-1}): λ_1 219 log ε_1 2.53, λ_2 270 log ε_2 2.55
^{1}**H-NMR** ($CDCl_3$, δ in ppm): 1.45–1.67 (m, 4H, C**H**$_2$ piperidine 2,6), 2.40–2.60 (m, 6H, C**H**$_2$ piperidine 3,4), 2.50 (s, 3H, C**H**$_3$), 3.63 (s, 2H, NC**H**$_2$), 6.73 (J = 8.40 Hz, d, 1H, Ar**H**^{5}), 7.51 (J = 2.15 Hz, d, 1H, Ar**H**^{2}), 7.67 (J = 8.45 Hz, d, 1H, Ar**H**^{6}), 11.93 (s, 1H, O**H**)
$C_{14}H_{19}O_2N$, M_r 233.12; **Elem. analysis**: calc. %C 72.07 %H 8.21 %N 6.00, found %C 72.26 %H 8.05 %N 5.87.

[4-(hydroxy)-3-(piperidinomethyl)phenyl]ethylketone (X)
Yield 62%, mp 67–69 °C (hexane); R_f 0.79
IR (cm^{-1}): 2800–3000 (νOH), 1680 (νC=O), 1599 (νC=C), 1255 (νC-N); **UV** (CH_3OH, ε in m^2.mol^{-1}): λ_1 220 log ε_1 2.55, λ_2 272 log ε_2 2.65
^{1}**H-NMR** ($CDCl_3$, δ in ppm): 1.55–1.60 (m, 4H, C**H**$_2$ piperidine 2,6), 2.50 (J = 7.20 Hz, t, 3H, $COCH_2C$**H**$_3$), 2.55–2.68 (m, 6H, C**H**$_2$ piperidine 3,4,5), 2.96 (J = 7.15 Hz, q, 2H, COC**H**$_2$CH$_3$), 3.66 (s, 2H, NC**H**$_2$), 6.75 (J = 8.50 Hz, d, 1H, Ar**H**^{5}), 7.54 (J = 2.20 Hz, d, 1H, Ar**H**^{2}), 7.69 (J = 8.30 Hz, d, 1H, Ar**H**^{6}), 11.90 (s, 1H, O**H**)
$C_{15}H_{21}O_2N$, M_r 247.34; **Elem. analysis**: calc. %C 72.84 %H 8.56 %N 5.66, found %C 72.66 %H 8.45 %N 5.57.

[4-(hydroxy)-3-(morpholinomethyl)phenyl] methylketone (XI)
Yield 54%, mp 58–60 °C (hexane); R_f 0.48
IR (cm^{-1}): 2500–3400 (νOH), 1672 (νC=O), 1597 (νC=C), 1251 (νC-N); **UV** (CH_3OH, ε in m^2.mol^{-1}): λ_1 220 log ε_1 2.52, λ_2 270 log ε_2 2.54
^{1}**H-NMR** ($CDCl_3$, δ in ppm): 2.53 (s, 3H, C**H**$_3$CO), 2.56-2.60 (m, C**H**$_2$ morpholine 3,5), 3.72-3.76 (m, C**H**$_2$ morpholine 2,6**),** 3.77 (s, 2H, NC**H**$_2$), 6.84 (J = 8.30 Hz, d, 1H, Ar**H**^{5}), 7.67 (J = 2.10 Hz, d, 1H, Ar**H**^{2}), 7.82 (J = 8.20 Hz, d, 1H, Ar**H**^{6}) 10.57 (s, 1H, O**H**)
$C_{13}H_{17}O_3N$, M_r 235.1; **Elem. analysis**: calc. %C 66.36 %H 7.28 %N 5.95, found %C 66.52 %H 7.37 %N 5.65.

[4-(hydroxy)-3-(morpholinomethyl)phenyl]ethylketone (XII)
Yield 56%, mp 67–69 °C (hexane); R_f 0.58
IR (cm^{-1}): 2600–3200 (νOH), 1675 (νC=O), 1598 (νC=C), 1257 (νC-N); **UV** (CH_3OH, ε in m^2.mol^{-1}): λ_1 221 log ε_1 2.54, λ_2 272 log ε_2 2.56
^{1}**H-NMR** ($CDCl_3$, δ in ppm): 1.25 (t, 3H, $COCH_2C$**H**$_3$), 2.49 (m, 4H, CH_2N morph 2,6), 2.93 (J = 7.20 Hz, q, 2H, COC**H**$_2$CH$_3$), 3.77 (s, 2H, NC**H**$_2$), 6.80 (J = 8.25 Hz, d, 1H, Ar**H**^{5}), 7.62 (J = 2.15 Hz, d, 1H, Ar**H**^{2}), 7.80 (J = 8.30 Hz, d, 1H, Ar**H**^{6}), 10.50 (s, 1H, OH)
$C_{14}H_{19}O_3N$, M_r 249.31; **Elem. analysis**: calc. %C 67.45 %H 7.68 %N 5.62, found %C 67.52 %H 7.47 %N 5.75.

[3-(azepan-1-ylmethyl)-4-(hydroxy)phenyl]methylketone (XIII)
Yield 35%, mp 69–71 °C (hexane); R_f 0.80
IR (cm^{-1}): 2800–3275 (νOH), 1673 (νC=O), 1584 (νC=C), 1265 (νC-N); **UV** (CH_3OH, ε in m^2.mol^{-1}): λ_1 226 log ε_1 2.97, λ_2 294 log ε_2 3.07
^{1}**H-NMR** ($CDCl_3$, δ in ppm): 1.69-1.75 (m, 8H, C**H**$_2$ azepan 3,4,5,6), 2.50 (s, 3H, COC**H**$_3$), 2.63-2.85 (m, 4H, C**H**$_2$ azepane

2,7), 3.84 (s, 2H, NC**H**$_2$), 6.82 (J = 8.10 Hz, d, 1H, **H**^{5} arom), 7.64 (J = 2.12 Hz, d, 1H, **H**^{2} arom), 7.80 (J = 8.25 Hz, d, 1H, **H**^{6} arom), 10.57 (s, 1H, O**H**)
$C_{15}H_{21}O_2N$, M_r 247.34; **Elem. analysis**: calc. %C 72.84 %H 8.56 %N 5.66, found %C 72.62 %H 8.35 %N 5.42.

[3-(*N*-methylpiperazin-1-ylmethyl)-4-(hydroxy)phenyl] methylketone (XIV)
Yield 33%, mp 83–85 °C (hexane); R_f 0.22
IR (cm^{-1}): 2900–3280 (νOH), 1685 (νC=O), 1583 (νC=C), 1265 (νC-N); **UV** (CH_3OH, ε in $m^2.mol^{-1}$): λ_1 222 log ε_1 3.09, λ_2 278 log ε_2 3.12
^{1}**H-NMR** (DMSO-d_6, δ in ppm): 2.55 (s, 3H, COC**H**$_3$), 2.31 (s, 3H, NC**H**$_3$), 2.64–2.78 (m, 8H,C**H**$_2$ piperazine 2,3,5,6), 3.74 (s, 2H, C**H**$_2$N), 6.82 (J = 8.10 Hz, d, 2H, Ar**H**^{5}), 7.66 (J = 2.15 Hz, d, 1H, Ar**H**^{2}), 7.81 (J = 8.10 Hz, d, 1H, Ar**H**^{6}), 10.08 (s, 1H, O**H**)
$C_{14}H_{20}O_2N_2$, M_r 248.33; **Elem. analysis**: calc. %C 67.72 %H 8.12 %N 11.28, found %C 67.50 %H 8.29 %N 11.48.

[3-(*N*-methylpiperazin-1-ylmethyl)-4(-hydroxy)phenyl] ethylketone (XV)
Yield 33%, mp 80–83 °C (hexane); R_f 0.24
IR (cm^{-1}): 2900–3300 (νOH), 1684 (νC=O), 1585 (νC=C), 1268 (νC-N); **UV** (CH_3OH, ε in $m^2.mol^{-1}$): λ_1 219 log ε_1 2.51, λ_2 268 log ε_2 2.51
^{1}**H-NMR** (DMSO-d_6, δ in ppm): 1.22 (t, 3H, C**H**$_3$CH$_2$CO), 2.34 (s, 3H, NC**H**$_3$), 2.54–2.58 (m, 8H, C**H**$_2$ piperazine 2,3,5,6), 2.92 (q, 2H, COC**H**$_2$CH$_3$), 2.34 (s, 3H, NC**H**$_3$), 3.76 (s, 2H, C**H**$_2$N), 6.84 (J = 8.50 Hz, d, 2H, Ar**H**^{5}), 7.69 (J = 2.30 Hz, d, 1H, Ar**H**^{2}), 7.84 (J = 8.20 Hz, d, 1H, Ar**H**^{6}), 10.60 (s, 1H, O**H**)
$C_{15}H_{22}O_2N_2$, M_r 262.35; **Elem. analysis**: calc. %C 68.67 %H 8.45 %N 10.68, found %C 68.50 %H 8.39 %N 10.48.

Determination of antioxidant activity

DPPH assay (Brand-Williams et al., 1995)
This method determines the antioxidant capacity of the tested compounds based on their reaction with the stable radical 2,2-diphenyl-1-(2,4,6-trinitrophenyl)-hydrazyl (DPPH). The DPPH radical yields a purple-colored solution, exhibiting maximum absorption at 517 nm. During the reduction of DPPH, a change in color of the solution from purple to yellow is observed, which is accompanied by a respective shift in the UV-VIS spectrum. The measured antioxidant capacity of the compounds is negatively correlated with their measured absorption intensity. Firstly, a methanolic solution of DPPH was prepared, with a concentration of 44 μg/mL (112 μmol. dm^{-3}). Following this, solutions of the tested sample in methanol at concentrations of either 10^{-2} mol dm^{-3} or 10^{-3} mol dm^{-3} were obtained. In the spectrophotometric assay, 270 μl of the DPPH solution and 30 μl of the solution of the tested compounds or the standard were combined. The mixture was then subjected to spectrophotometric analysis using a microplate reader, with the absorption measured after 5 minutes at 517 nm. At each designated time point, the respective absorbances were corrected for the blank DPPH value. For each sample, three measurements were obtained in parallel. The Trolox standard was utilized as a reference point for the measurement of antioxidant activity in the compounds under investigation.

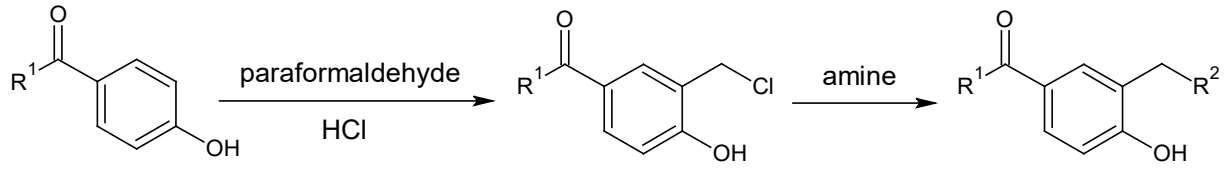
ABTS assay (Re et al., 1999)
Antiradical activity was measured as a percentage inhibition of the $ABTS^{\bullet+}$ cation-radical formation. Solutions of ABTS (7.7 μg/mL, 14 mmol.dm^{-3}) and $K_2S_2O_8$ (1.32 mg/mL, 4.9 mmol.dm^{-3}) in water were prepared. The two solutions were mixed in a 1:1 vol. ratio and left to cool for 24 hours in the refrigerator. The spectrophotometric measurement was conducted utilizing a 96-well plate reader. Each well of the microplate was filled with 60 μl of sample solution (10^{-2} or 10^{-3} mol.dm^{-3}, respectively) and 240 μl of ABTS solution. Absorbance was measured using a spectrophotometer at a wavelength of 734 nm, 5 minutes after mixing the solutions. A total of three parallel measurements were conducted for each sample. In the course of the reaction, the colorless 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid is oxidized by potassium peroxydisulfate, resulting in the formation of the stable blue-green $ABTS^{\bullet+}$ radical. Adding antioxidants reduces the $ABTS^{\bullet+}$ radical and causes discoloration.

Conformational analysis

Conformational analysis was performed using SYBIL 6.8 software on a Silicon Graphics SGI 02 computer. Spatial models of the studied compounds were modeled using standard parameters and the Tripos potential field. The conformers obtained were subjected to complete optimization using the semi-empirical AM1 method (Tripos).

DISCUSSION

The aim of this work was to prepare 3-(aminomethyl)-4-(hydroxy)phenyl]alkylketones by means of a two-step synthesis (Scheme 1), except for [4-hydroxy-3-(piperidinomethyl)phenyl]methylketone which was synthesized by Mannich reaction. The preparation of some of the compounds has been described previously, using various synthetic procedures, that is, II (Borthakur et al., 1984; Aljohani et al., 2019), III (Rastogi et al., 1992), VII (Aljohani et al., 2019), IX (Borthakur et al., 1984; Aljohani et al., 2020), XI (Borthakur et al., 1984; Aljohani et al., 2019; Reddy et al., 2008; Dai et al., 2017), and XIV (Boesen, 2003). The products contain a phenolic group and a basic group in position 2 relative to the phenolic group. The compounds under study (I-XV) (see Table 1) were prepared from [3-(chloromethyl)-4-(hydroxy)phenyl] alkylketones as starting compounds. These were obtained from 4-hydroxyphenylalkylketones by an electrophilic substitution reaction of paraformaldehyde with hydrochloric



Scheme 1. Synthesis of the target compounds (R^1/R^2 see Table 1)

acid (Čižmáriková et al., 2002). During the first stage, [3-(chloromethyl)-4-(hydroxy)phenyl]alkylketones were synthesized by electrophilic substitution reaction in a 55-62% yield. These are halogen derivatives with increased reactivity, which can result in diminished yields due to competing pathways, such as the formation of enamines, imines, tertiary amines, or quaternary ammonium salts. The reaction was carried out in a low-polarity environment (benzene or toluene) and in the presence of an excess of aliphatic amines (dimethylamine, diethylamine, isopropylamine, isobutylamine, tert-butylamine) and heterocyclic amines (pyrrolidine, morpholine, azepane, 4-methylpiperazine), achieving a yield of 30–60%. The products are white solids with melting points between 39 and 94 °C, soluble in organic solvents. The purity of the prepared compounds was checked using thin-layer chromatography with a propan-1-ol and diethylamine mobile phase in a 9:1 ratio, and the R_f values were calculated. Finally, the IR, UV, and ^{1}H-NMR spectra of the products were measured.

In the IR spectra, valence vibration bands were identified at 2500–3300 (νOH), 1665–1685 (νC=O), 1583–1607 (νC=C), and 1251–1286 (νC-N). In UV spectra, the prepared compounds exhibited two absorption bands corresponding to transitions at λ_1 218–220 nm (log ε_1 2.52 $m^2.mol^{-1}$) and λ_2 268–318 nm (log ε_2 2.53–3.12 $m^2.mol^{-1}$). In the ^{1}H-NMR spectra of the prepared compounds, proton signals of the phenolic group were identified within the range of 10.50–11.51 ppm. In addition, signals of protons of the aromatic nucleus, a singlet signal of CH_2N at 3.63–4.11 ppm, signals of protons of the amine moiety, and signals of CH_2 and CH_3 groups of the acyl and of the aliphatic side chain were also identified.

The compound 4-hydroxy-3-piperidinomethylphenylmethyl ketone (IX) was synthesized in a study by Borthakur et al. (1984). However, the authors only isolated it in the form of oil. For this reason, a Mannich reaction with a 60% yield was conducted. In addition to IR, UV, and NMR spectra, the structure was confirmed by MS spectra.

To expand knowledge of the potential biological effects of synthesized substances, primary screening of their antioxidant activity was performed on selected final compounds and intermediates of their synthesis. The DPPH method was used to screen antioxidant activity, as well as the ABTS method, which is more sensitive to this type of substance than the DPPH assay. The ABTS method is based on the decolorization of the blue-green solution of the activated radical $ABTS^{\cdot+}$ after its reaction with an antioxidant substance. The results of antioxidant activity measurements for all substances tested are shown in Table 2. The investigated compounds demonstrate significantly higher oxidation activity values than corresponding compounds with alkoxymethyl groups (Čižmáriková et al., 2020). The antioxidant activity determined by the DPPH method ranged from 2.9% to 6.2%, and that determined by the ABTS method for compounds with tertiary nitrogen ranged from 84.2% to 99.1%. The value obtained using this method for compound IV with secondary nitrogen (NH-$CH(CH_3)_2$) was 33.5%. The intermediate product [3-(chloromethyl)-4-(hydroxy)phenyl] methylketone (EACh) showed higher activity using both the DPPH method (4.3%) and the ABTS method (8.2%), whereas 4-hydroxyphenylmethylketone (4-OHaceto) showed low activity (0.94%) using only the ABTS method. Compounds with alkoxy groups have been shown to possess significantly lower antioxidant activity values, ranging from 0.55% to 12.58% by the DPPH method and from 0.92% to 28.14% by the ABTS method (Čižmáriková et al., 2020). Interestingly, the presence of nitrogen atoms also had a positive effect on increased antioxidant activity in beta-blocker-type substances (Čižmáriková et al., 2020, Čižmáriková et al., 2021). The distinguishing characteristic of these compounds is the formation of a hydrogen bond between the phenolic group and the nitrogen atom in the side chain, which was investigated using conformational analysis. The Sybyl program was employed to obtain 3D models of molecules and calculate the energy of a larger number of bonds around which rotation is possible and conformers that arose by rotation around simple bonds. The number of conformers for each compound was determined by the volume and spatial arrangement of substituents, as well as the number of bonds around which rotation is possible. Of the final compounds selected for analysis, the compound featuring an isobutyl substituent (V) yielded the highest number of conformers, a consequence of its flexible chain. The compound with a tert-butyl group (VI) gives the least conformers due to its conformational rigidity. When performing conformational analysis, the most suitable conformers were subjected to complete optimization using the semi-empirical AM1 method (Table 3). From the resulting conformers obtained in this way, the most optimal conformers were selected and their geometric parameters characterizing the hydrogen bond, distances between atoms, and hydrogen bond angle were measured. In compounds with branched carbon chains V, VI and a nitrogen atom, there was the possibility of forming

Table 2. Antioxidant activities of the compounds investigated

Substance	R^1	R^2	Inhibition DPPH[%]±SD	Inhibition ABTS[%]±SD
I	CH_2CH_3	$N(CH_3)_2$	4.0±0.9	99.1±1.0
IV	CH_2CH_3	$NHCH(CH_3)_2$	6.2±1.2	33.5±1.1
VII	CH_3	pyrrolidin-1-yl	4.1±0.9	94.1±0.8
IX	CH_3	piperidino	5.1±0.7	92.7±1.1
X	CH_2CH_3	piperidino	4.5±1.1	90.8±1.0
XI	CH_3	morpholino	3.8±0.5	85.9±3.9
XII	CH_2CH_3	morpholino	3.5±0.4	84.3±2.3
XIV	CH_3	*N*-methylpiperazin-1-yl	3.6±0.5	98.7±0.6
XV	CH_2CH_3	*N*-methylpiperazin-1-yl	2.9±1.5	99.1±0.2
X	CH_2CH_3	azepan-1-yl	3.8±0.6	98.7±0.8
	4-OHaceto	–	n	0.94±0.01
	EACh	–	4.3±2.5	8.2±0.4

Table 3. Conformational analysis of [3-aminomethyl-4-(hydroxy)phenyl)methylketones

Compound	Heat of formation ΔH_{form}(1) * [kJ.mol^{-1}]	Heat of formation ΔH_{form}(2) ** [kJ.mol^{-1}]	Length of the hydrogen bond [nm] NH...O	Length of the hydrogen bond [nm] OH...N	Angle [°]	Energy [kJ.mol^{-1}]
II	-272.33	-259.62		0.247	132.56	12.71
V	-332.48 -331.22	-312.75 -312.75	0.237	0.236	120.17 128.56	19.73 18.47
VI	-301.63 -294.44	-280.14 -280.14	0.229	0.244	123.07 134.70	21.49 14.30
VII	-249.25	-238.01		0.243	131.00	11.24
IX	-295.64	-285.08		0.255	132.35	10.82
XI	-305.64	-295.53		0.238	134.91	10.11
XIII	-203.65	-191.28		0.246	131.63	12.37
XIV	-385.94	-409.93		0.250	131.20	10.03

** Heat of formation without the contribution of hydrogen bonds*
*** Heat of formation with the contribution of hydrogen bonds*

a hydrogen bond between the hydrogen atom of the amino group and the oxygen atom of the phenol group NH···O or a hydrogen bond between OH···N. In compound (V) with an isobutyl group, given the geometric parameters and heat of formation of the given conformer, the formation of an NH···O intramolecular hydrogen bond is more likely than in the conformer with an intramolecular hydrogen bond between the hydrogen atom of the OH group and the amino nitrogen. The assumption is that the length (NH···O) is equal to 0.237 nm, the heat of formation ΔH is 332.48 kJ/mol, and the angle between the NH···O atoms is 120.17°. These findings are consistent with data in the literature (Nunes et al., 2007, Grabowski, 2007), where the formation of intramolecular hydrogen bonds NH···O is considered more likely. The energy of the hydrogen bond was approximated by the difference between the heat of formation of the conformation with the hydrogen bond and the same conformation without the hydrogen bond. When compounds with a built-in heterocycle (VII, IX, XIII, and XIV) are compared based on hydrogen bond length and bond energy, small differences in hydrogen bond energy are observed, with their energy being lower than that of compounds with an aliphatic chain (V and VI) (see Table 3).

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