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CHEMISTRY
Research article

n-PROPYL GALLATE AS SUBSTRATE IN THE MANNICH REACTION

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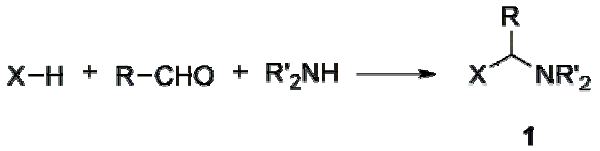
Accepted November 16, 2016

The Mannich reaction represents the only known synthetic method for the replacement in a single step of a hydrogen atom in an organic substrate with an aminoalkyl group. Suitable organic substrates in the Mannich reaction should either be electron-rich molecules or have an activating group in their structure. Phenols are a classical example of such electron-rich substrates in the Mannich reaction, and while monohydroxylic phenols have been widely used as substrates in this transformation, only scarce information on the aminoalkylation of polyhydroxylic phenols is available in the literature. The current paper investigates the Mannich reaction of such a polyhydroxylic substrate, namely the well-known antioxidant *n*-propyl gallate, with formaldehyde as the aldehyde component and two equivalents of cyclic secondary amines (piperidine, morpholine, 4-benzylpiperazine, 4-phenyl-piperazine and 1,2,3,4-tetrahydroisoquinoline) as amine reagents. The structure of the resulting novel bis-aminomethyl derivatives of *n*-propyl gallate, designed as potential inhibitors of radical formation, has been confirmed by NMR analysis.

Key words: Mannich reaction, aminomethylated phenols, *n*-propyl gallate, antioxidant.

INTRODUCTION

In the classical Mannich reaction, a substrate X–H containing at least one active hydrogen atom undergoes condensation with an aldehyde component (R–CHO, which is usually formaldehyde, R = H) and an amine reagent (R'_2NH) to afford an aminomethyl (or an aminoalkyl) derivative of the initial substrate, generally referred to as a Mannich base **1** (Scheme 1).



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Scheme 1. The Mannich reaction.

Phenols, naphthols and phenols fused to cycloalkanes, cycloalkenes or heteroaromatic rings are commonly used as substrates in the Mannich reaction,[1,2] and the resulting amino-methylated phenols have found various uses and applications.[3] To mention only a few, aminomethylated phenols have been reported as catalysts for the crosslinking of epoxy resins,[4] precursors of polyols for polyurethanes,[5] complexing agents for radioactive technetium,[6] corrosion inhibitors,[7] detergents[8] or antioxidants for lubricating oils.[9] Nonetheless, as the most significant contributions of the Mannich reaction belong to medicinal chemistry, it is not unexpected to find aminomethylated phenols amongst drug candidates, and even in-use drugs. Thus, a series of studies report the cytotoxicity of phenolic single and double Mannich bases of chalcone analogues,[10–12] naphthols,[13] 8-hydroxy-quinoline derivatives,[14] flavones,[15] or hydroxyl-carbazoles.[16] In addition, phenolic Mannich bases derived from 3-hydroxy-4*H*-pyran-4-one derivatives have been thoroughly investigated as anti-bacterials[17–19] and antifungals.[20,21] Several established antimalarials, such as bialamicol, amodiaquine or pyronaridine are examples of validated drugs featuring a phenolic Mannich base structure. Finally, a large number of phenolic Mannich bases have been evaluated as antioxidants. Aminomethylated thymol derivatives were more efficient than parent thymol in both xanthine

*This communication is Part 26 of the series "Synthesis and reactivity of Mannich bases".

oxidase inhibition test and inhibition of lipid peroxidation using rat liver homogenate,[22] whereas aminomethylated hydroxybenzophenones had moderate to high ability in scavenging DPPH radicals.[23] 8-Hydroxyquinoline–tacrine hybrids exhibited potent peroxyl radical absorbance capacities in a test employing ORAC-FL (oxygen radical absorbance capacity) method,[24] while aminomethylation of natural flavones was shown to improve the antioxidant efficiency, bioavailabilty and water solubility of the parent flavones.[25,26]

While the Mannich reaction of monohydroxylic phenols with various structures has been explored extensively, there is only scarce information on the aminomethylation of polyhydroxylic phenols. The Mannich reaction using catechol,[27] resorcinol derivatives,[28] hydroquinone[29] or pyrogallol and hydroxylhydroquinone[30] as substrates has been briefly investigated. Several Mannich bases of pyrrogallol exhibited antioxidant and antiradiation activity,[31] as well as antibacterial and antifungal activity.[32] Aminomethylation was successful for a series of pyrogallol derivatives such as gallacetophenone[33] or gallic acid and its esters,[34] which were claimed to be useful as antioxidants in food and plastics.

n-Propyl gallate is an effective antioxidant used in cosmetics, foods, fats, oils, emulsions or waxes,[35] which is only slightly toxic when ingested and practically non-toxic when applied to skin.[36] As the literature shows that phenolic Mannich bases may also act as antioxidants, aminomethylated *n*-propyl gallate derivatives are expected to behave as antioxidants as well. The present study deals with the synthesis and characterization of several Mannich bases with potential radical inhibiting properties, which are derived from *n*-propyl gallate as a substrate in the aminomethylation reaction.

EXPERIMENTAL PART

n-Propyl gallate (Fluka), formaldehyde 37% (Aldrich), the amines employed in the Mannich reaction and the solvents were reagent grade and were used as received. Melting points were taken on a MEL-TEMP capillary melting point apparatus and are uncorrected. HPLC was run on a Waters analytical system, using a Symmetry Shield RP_{18} 3.5 μm (4.6 × 50 mm) column. The mobile phase consisted from water and acetonitrile, both solvents containing 0.1% trifluoroacetic acid. The flow rate of the mobile phase through the column was 1.5 mL/min, and the acetonitrile gradient was 0–80%. The acetonitrile gradient was applied for 10 min, starting 0.5 min after the sample had been injected. NMR analysis was conducted on a Brucker Avance instrument in $CDCl_3$. The signals owing to residual protons in the deuterated solvents were used as internal standards for the ^{1}H NMR spectra. The chemical shifts for the carbon atoms are given relative to deuteriochloroform (δ = 77.16 ppm).

Direct aminomethylation of *n*-propyl gallate – general procedure

Secondary amine (10 mmoles) was added to a solution of formaldehyde 37% (10 mmoles, 0.9 mL) in ethanol (5 mL), and then the mixture was stirred at room temperature for 15 min. *n*-Propyl gallate **2** (1.06 g, 5 mmoles) was then added to the stirred solution at room temperature. Mannich bases **5** and **6** separated a few minutes after *n*-propyl gallate had dissolved, while in the case of compounds **3** and **4**, the initially homogeneous reaction mixture was kept at room temperature overnight until a crystalline precipitate formed. The solid was filtered, washed with a small amount of cold ethanol, air-dried and recrystallized from ethanol. In the case of Mannich base **7**, the supernantant was removed with a pipette after 10 h to give a heavy oil, which was triturated with *n*-hexane (3 × 10 mL) and subsequently recrystallized from ethanol.

n-Propyl 2,6-bis(piperidin-1-ylmethyl)-3,4,5-trihydroxybenzoate ***3***. This compound was obtained as off-white crystals using piperidine as amine reagent in the Mannich reaction; yield 57%; mp 141–142 °C; t_R = 5.05 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (t, J = 7.2 Hz, 3H, $-CH_2CH_2C\underline{H}_3$), 1.46 (br s, 4H, $-CH_2N(CH_2CH_2)_2C\underline{H}_2$), 1.61 (t, J = 4.8 Hz, 8H, $-CH_2N(CH_2C\underline{H}_2)_2CH_2$), 1.68–1.81 (m, 2H, $-CH_2C\underline{H}_2CH_3$), 2.48 (br s, 8H, $-CH_2N(C\underline{H}_2CH_2)_2CH_2$), 3.57 (s, 4H, $-C\underline{H}_2N(CH_2CH_2)_2CH_2$), 4.20 (t, J = 6.8 Hz, 2H, $-C\underline{H}_2CH_2CH_3$), 9.69 (br s, 3H, -OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.8, 22.2, 24.0, 25.9, 53.8, 59.1, 66.8, 109.8, 123.6, 133.9, 145.6, 169.2.

n-Propyl 2,6-bis(morpholin-4-ylmethyl)-3,4,5-trihydroxybenzoate ***4***. This compound was obtained as off-white crystals using morpholine as amine reagent in the Mannich reaction; yield 72%; mp 174–175 °C; t_R = 4.2 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (t, J = 7.2 Hz, 3H, $-CH_2CH_2C\underline{H}_3$), 1.69–1.81 (m, 2H, $-CH_2C\underline{H}_2CH_3$), 2.55 (s, 8H, $-CH_2N(C\underline{H}_2CH_2)_2O$), 3.61 (s, 4H, $-C\underline{H}_2N(CH_2CH_2)_2O$), 3.72 (s, 4H, $-CH_2N(CH_2C\underline{H}_2)_2O$), 4.23 (t, J = 6.8 Hz, 2H, $-C\underline{H}_2CH_2CH_3$), 9.03 (br s, 3H, -OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.7, 22.2, 52.8, 58.6, 66.8, 67.1, 109.6, 124.3, 134.0, 145.2, 168.8.

n-Propyl 2,6-bis(4-benzylpiperazin-1-ylmethyl)-3,4,5-trihydroxybenzoate ***5***. This compound was obtained as off-white crystals using 4-benzylpiperazine as amine reagent in the Mannich reaction; yield 55%; mp 93–95 °C; t_R = 5.65 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (t, J = 7.2 Hz, 3H, $-CH_2CH_2C\underline{H}_3$), 1.68–1.81 (m, 2H, $-CH_2C\underline{H}_2CH_3$), 2.55 (br s, 16H, $PhCH_2N(C\underline{H}_2C\underline{H}_2)_2NCH_2$-), 3.51 (s, 4H, $PhC\underline{H}_2N(CH_2CH_2)_2NCH_2$-), 3.62 (s, 4H, $PhCH_2N(CH_2CH_2)_2NC\underline{H}_2$-), 4.20 (t, J = 6.8 Hz, 2H, $-C\underline{H}_2CH_2CH_3$), 6.42 (br s, 3H, -OH), 7.21–7.35 (m, 10H, aromatic protons); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.7, 22.2, 52.4, 52.8, 58.3, 62.9, 67.0, 109.8, 123.9, 127.3, 128.4, 129.3, 133.9, 137.8, 145.4, 169.0.

n-Propyl 2,6-bis(4-phenylpiperazin-1-ylmethyl)-3,4,5-trihydroxybenzoate ***6***. This compound was obtained as off-white crystals using 4-phenylpiperazine as amine reagent in the Mannich reaction; yield 79%; mp 204–205 °C (dec.); t_R = 7.15 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (t, J = 7.2 Hz, 3H, $-CH_2CH_2C\underline{H}_3$), 1.71–1.84 (m, 2H, $-CH_2C\underline{H}_2CH_3$), 2.74 (br s, 8H, $PhN(CH_2C\underline{H}_2)_2NCH_2$-), 3.25 (br s, 8H,

PhN($C\underline{H}_2CH_2)_2NCH_2$-), 3.71 (s, 4H, PhN($CH_2C\underline{H}_2)_2NC\underline{H}_2$-), 4.26 (t, J = 6.8 Hz, 2H, -$C\underline{H}_2CH_2CH_3$), 6.86–6.97 (6H, m, aromatic protons), 7.23–7.33 (4H, m, aromatic protons), 8.70 (br s, 3H, -OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.8, 22.2, 49.3, 52.5, 58.3, 67.1, 109.8, 116.5, 120.4, 124.2, 129.3, 134.0, 145.3, 150.9, 169.0.

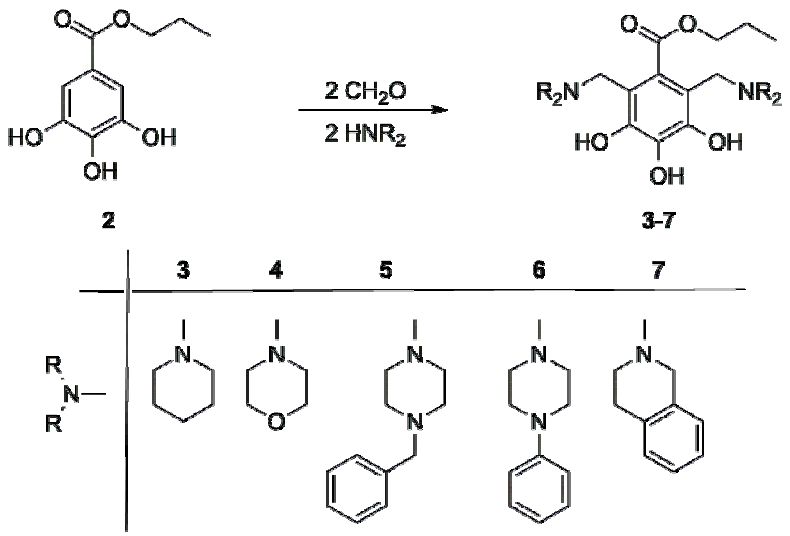
n-Propyl 2,6-bis(1,2,3,4-tetrahy-droisoquinolin-2-ylmethyl)-3,4,5-trihydroxy-benzoate 7. This compound was obtained as off-white crystals using 1,2,3,4-tetrahydroisoquinoline as amine reagent in the Mannich reaction; yield 42%; mp 132–133 °C; t_R = 6.55 min; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.99 (t, J = 7.2 Hz, 3H, -$CH_2CH_2C\underline{H}_3$), 1.67–1.80 (m, 2H, -$CH_2C\underline{H}_2CH_3$), 2.78–2.92 (m, 4H, -$CH_2N(CH_2$-$)CH_2C\underline{H}_2$-), 2.92–3.05 (m, 4H, -$CH_2N(CH_2$-$)C\underline{H}_2CH_2$-), 3.77 and 3.84 (br s, 4H and 4H, -$C\underline{H}_2N(C\underline{H}_2$-$)CH_2CH_2$-), 4.21 (t, J = 6.8 Hz, 2H, -$C\underline{H}_2CH_2CH_3$), 7.03 (d, J = 6.4 Hz, 2H, aromatic protons), 7.08–7.22 (6H, m, aromatic protons), 8.67 (br s, 3H, -OH); ^{13}C NMR (300 MHz, $CDCl_3$): δ 10.8, 22.2, 28.7, 50.0, 55.2, 58.0, 67.0, 109.9, 124, 126.1, 126.7, 126.8, 128.8, 133.2, 133.5, 134.1, 145.6, 169.2.

RESULTS AND DISCUSSION

Generally, the Mannich reaction of phenolic substrates affords a derivative of the initial substrate having an aminomethyl moiety preferably *ortho* to the phenolic hydroxyl; however, aminomethylation may occur *para* to the phenolic hydroxyl if no free *ortho* positions are available. As a substrate in the Mannich reaction, *n*-propyl gallate has a highly substituted aromatic ring, which presents only two potential sites for aminomethylation, each of them being situated *ortho* to one phenolic hydroxyl and *para* to another phenolic hydroxyl. Because of the symmetry presented by the molecule of *n*-propyl gallate, monoaminomethylation of this substrate at any of these two sites would lead to the same Mannich base. Despite the presence in the structure of *n*-propyl gallate of a deactivating substituent (*i.e.*, the ester function), the strong activation exerted by two phenolic hydroxyls on both potential amino-methylation sites is expected to straightforwardly generate a bis-Mannich base, provided the appropriate twofold excess of aldehyde component and amine reagent are employed. With a view to simplify the course of the reaction and limit the formation of a mixture of aminomethylation products, the Mannich reaction of *n*-propyl gallate reported in this study was conducted using a 1:2:2 ratio between substrate, formaldehyde, and various cyclic secondary amines, respectively. Amino-methylation of phenols is generally conducted at the reflux temperature of the solvent (usually lower alcohols) employed to dissolve the reactants.[1] However, highly reactive phenolic substrates, such as naphthols,[37] are known to undergo amino-methylation even at room temperature. The order in which the reactants are added to the solvent does not seem to be relevant to the outcome of the Mannich reaction: both addition of formaldehyde to a solution comprising the substrate and the amine, and addition of the substrate to the preformed aminomethylating agent obtained by mixing formaldehyde and the amine reagent have been equally employed in aminomethylation experimental procedures. When *n*-propyl gallate (1 equivalent) was added to the mixture of formaldehyde (2-equivalents) and either 4-benzyl-piperazine or 4-phenylpiperazine, (2 equivalents), aminomethylation proceeded swiftly to yield crystalline solids that started to separate from the reaction mixture after a few minutes at room temperature. In these two cases, the resulting solid residue was filtered after three hours, recrystallized from ethanol, and the proton spectra was recorded to confirm their identity as bis-Mannich bases **5** and **6**, respectively (Scheme 2). Under identical reaction conditions, bis-Mannich bases **3** and **4** were also obtained as crystalline solids using piperidine and morpholine, respectively, as amine reagents in the Mannich reaction of *n*-propyl gallate (Scheme 2), but, in these two cases, the separation of solids from the reaction mixture was clearly much slower; therefore, with a view to maximize the amount of isolated reaction product, the reaction was allowed to proceed overnight. However, seeding the reaction mixture with a crystal from a previous run five minutes after the substrate had been added was shown to induce a rapid and substantial separation of Mannich base **3** quite similar with the separation observed in the case of piperazine-derived Mannich bases **5** and **6**. In contrast, aminomethylation of *n*-propyl gallate using 1,2,3,4-tetrahydroisoquino-line as amine reagent yielded a heavy oil, which, after the supernatant had been removed with a pipette, was triturated three times with *n*-hexane. The sticky mass that was obtained was then recrystallized two times from ethanol prior to NMR analysis, which confirmed the identity of bis-Mannich base **7** (Scheme 2).

The purity of the synthesized bis-Mannich bases was checked by HPLC. No trace of *n*-propyl gallate (t_R = 6.35 min), or any by-products or impurities could be detected in the samples purified by recrystallization. The crude crystalline solid that was isolated from the aminomethylation of *n*-propyl gallate using piperidine as amine reagent was also analyzed by HPLC, and no evidence of a by-product (such as the corresponding mono-Mannich base) could be found. However, the formation of the mono-Mannich base as a by-product in this reaction could not be entirely

dismissed, as no investigation by HPLC has been undertaken for the mother liquor from which this crude crystalline solid was isolated. According to the retention times determined for Mannich bases **3**–**7**, aminomethylation generally increases the NMR analysis of Mannich bases **3**–**7** confirmed that, under these experimental conditions, *n*-propyl gallate **2** underwent aminomethylation at positions 2 and 6 of the aromatic ring to afford bis-Mannich bases. No signal could be noticed in the aromatic region of the ^{1}H NMR spectra of bis-Mannich bases **3** and **4**, whereas only aromatic protons associated with the aromatic moieties introduced through aminomethylation were observed in the aromatic region of the proton spectra of bis-Mannich bases **5**–**7**. Bis-aminomethylation of *n*-propyl gallate **2** to bis-Mannich bases **3**–**7** under these experimental conditions has been further supported by the relative ratio of 2 to 1 between the values obtained for the integration of each type of magnetically equivalent protons in the aminomethyl moieties and the values of the integrals for each type of magnetically equivalent protons in the *n*-propyl moiety. The peaks in the ^{1}H NMR spectra of bis-Mannich bases **3**–**7** have been tentatively assigned to various magnetically distinct hydrogens in the structure of these compounds (as reported in the Experimental Part), and the hydrogens in the methylene group bridging the aromatic ring with the different amine residues in these compounds have been found to resonate at 3.6–3.7 ppm. A broad singlet integrating for three protons was noticeable at chemical shift values in the range of 6.4–9.7 ppm in all proton spectra of bis-Mannich bases **3**–**7**.



Scheme 2. Synthesis of bis-Mannich bases **3–7** of *n*-propyl gallate through direct aminomethylation.polarity of Mannich bases 3–7 compared to that of the starting material 2. While Mannich bases 3 and 4 derived from aliphatic secondary amines piperidine and morpholine, respectively, are clearly more polar than *n*-propyl gallate 2, the use of secondary amines having aromatic motifs in their structure as amine reagents in aminomethylation leads to Mannich bases whose polarity ranges from slightly less polar than the starting material (in the case of compound 5 derived from 4-benzylpiperazine) to slightly more polar (in the case of compound 6 derived from 4-phenylpiperazine).

Bis-aminomethylation of *n*-propyl gallate **2** to bis-Mannich bases **3** and **4** was further supported by the examination of these compounds' ^{13}C NMR spectra. Only four peaks were identified in the aromatic region of these spectra, namely the signals at approximately 110 ppm (corresponding to C^2 and C^6), 124 ppm (corresponding to C^1), 134 ppm (corresponding to C^4), and 145 ppm (corresponding to C^3 and C^5). If mono-aminomethylation had occurred instead, the inspection of the ^{13}C NMR spectra of compounds **3** and **4** would have revealed six distinct signals. In addition, no signals in the aromatic region could be seen of the DEPT spectrum of compound **3**, which confirms that all of the aromatic carbon atoms in the structure of this Mannich base are quaternary (data not shown). The carbon atom in the methylene group originating from formaldehyde and linking the aromatic ring

with the different amine residues in bis-Mannich bases **3**–**7** has been associated with the peak at approximately 67 ppm.

CONCLUSIONS

Investigation of the behavior of *n*-propyl gallate as substrate in direct Mannich reaction showed that aminomethylation occurred in positions 2 and 6 of the aromatic ring (*ortho* and *para* to the phenolic hydroxyls, respectively) to afford hitherto unknown bis-aminomethyl derivatives **3**–**7** in reasonable yields, when the reaction was carried out using various secondary amines as amines reagents in ethanol at room temperature. Introduction of aminomethyl functions containing aliphatic secondary amines such as piperidine or morpholine onto this substrate slightly increases the polarity of bis-Mannich bases **3** and **4** compared to the polarity of *n*-propyl gallate in HPLC experiments, whereas the use of amines containing aromatic rings in their structure as amine reagents for the amino-methylation of *n*-propyl gallate affords bis-Mannich bases that are at least as polar as the substrate subjected to aminomethylation, if not less polar. The structure of the obtained highly hindered bis-Mannich bases, which could potentially act as effective antioxidants through the inhibition of radical chain reactions or protection against the action of metal ions by chelation, has been investigated using NMR spectroscopy.

REFERENCES

1. Tramontini M., Advances in the chemistry of Mannich bases, *Synthesis*, **1973**, 703.
2. Tramontini M.; Angiolini L., Further advances in the chemistry of Mannich bases, *Tetrahedron*, **1990**, *46*, 1791.
3. Tramontini M.; Angiolini L., "Mannich Bases: Chemistry and Uses", CRC Press, Inc., Boca Raton, FL, 1994, pp. 217–270.
4. Gotlib E.M.; Voskresenskaya O.M.; Khamitov I.K.; Verizhnikov L.V.; Liakumovich A.G., Effect of inhibitors of radical processes on curing epoxy oligomers with dimethylaminomethylphenols (in Russian), *Plast. Massy*, **1989**, (*6*), 58; cf. *Chem. Abstr.*, **1990**, *112*, 21690w.
5. Moore, S.E.; Williams, S.J., Significantly reduced catalyst consumption in rigid foams, *J. Cell. Plast.*, **2000**, *36*, 57.
6. Wilson J.G.; Katsifis A.G., Phenolic analogues of amino carboxylic acid ligands for ^{99m}Tc. Part V. *N*-Benzyl-2-(2-hydroxyphenyl)glycines (bhpg) and *N*-benzyl-2-(4-hydroxyphenyl)glycines (isobhpg), *Aust. J. Chem.*, **2000**, *53*, 583.
7. Ravichandran K.; Kumar N.M.; Subash K.; Narayanan T.S.N.S., Mannich base derivatives – a novel class of corrosion inhibitors for cooling water systems, *Corros. Rev.*, **2001**, *19*, 29.
8. Kulieva Kh.N.; Namazova I.I.; Ismailova N.D.; Dorokhina I.V., Detergent-dispersing additives based on high-molecular-weight alkylphenols (in Russian), *Khim. Tekhnol. Topl. Masel*, **1988**, (*1*), 3; cf. *Chem. Abstr.*, **1988**, *108*, 97491.
9. Ahmed M.H.; Ghuiba F.M.; Habib O.M.O.; Gharieb H.K., Synthesis and evaluation of some lube oil additives from local coal tar phenols, *Hung. J. Ind. Chem.*, **1989**, *17*, 311.
10. Gul H.I.; Yerdelen K.O.; Gul M.; Das U.; Pandit B.; Li P.-K.; Secen H.; Sahin F., Synthesis of 4′-hydroxy-3′-piperidinomethylchalcone derivatives and their cytotoxicity against PC-3 cell lines, *Arch. Pharm. (Weinheim)*, **2007**, *340*, 195.
11. Vijaya Bhaskar Reddy M.; Su C.-R.; Chiou W.-F.; Liu Y.-N.; Chen R.Y.-H.; Bastow K.F.; Lee K.-H.; Wu T.-S., Design, synthesis, and biological evaluation of Mannich bases of heterocyclic chalcone analogs as cytotoxic agents, *Bioorg. Med. Chem.*, **2008**, *16*, 7358.
12. Bilginer S.; Gul H.I.; Mete E.; Das U.; Sakagami H.; Umemura N.; Dimmock J.R., 1-(3-Aminomethyl-4-hydroxyphenyl)-3-pyridinyl-2-propen-1-ones: A novel group of tumour-selective cytotoxins, *J. Enzyme Inhib. Med. Chem.*, **2013**, *28*, 974.
13. Yadav Y.; MacLean E.D.; Bhattacharyya A.; Parmar V.S.; Balzarini J.; Barden C.J.; Too C.K.L.; Jha, A., Design, synthesis and bioevaluation of novel candidate selective estrogen receptor modulators, *Eur. J. Med. Chem.*, **2011**, *46*, 3858.
14. Shaw A.Y.; Chang C.-Y.; Hsu M.-Y.; Lu P.-J.; Yang C.-N.; Chen H.-L.; Lo C.-W.; Shiau C.-W.; Chern M.-K., Synthesis and structure-activity relationship study of 8-hydroxyquinoline-derived Mannich bases as anticancer agents, *Eur. J. Med. Chem.*, **2010**, *45*, 2860.
15. Liu R.; Zhao B.; Wang D.-E.; Yao T.; Pang L.; Tu Q.; Ahmed S.M.; Liu J.-J.; Wang J., Nitrogen-containing apigenin analogs: preparation and biological activity, *Molecules*, **2012**, *17*, 14748.
16. Issa S.; Walchshofer N.; Kassab I.; Termoss H.; Chamat, S.; Geahchan A.; Bouaziz Z., Synthesis and antiproliferative activity of oxazinocarbazole and *N*,*N*-bis(carbazolylmethyl)amine derivatives, *Eur. J. Med. Chem.*, **2010**, *45*, 2567.
17. Us D.; Berk B.; Gürdal E.; Aytekin N.; Kocagöz T.; Çağlayan B.; Aksan Kurnaz I.; Demir Erol D., Mannich base derivatives of 3-hydroxy-6-methyl-4*H*-pyran-4-one with antimicrobial activity, *Turk. J. Chem.*, **2010**, *34*, 447.
18. Karakaya G.; Aytemir M.D.; Özçelik B.; Çaliş Ü., Design, synthesis and in vivo/in vitro screening of novel chlorokojic acid derivatives, *J. Enzyme Inhib. Med. Chem.*, **2013**, *28*, 627.

19. Emami S.; Ghafouri E.; Faramarzi M.A.; Samadi N.; Irannejad H.; Foroumadi A., Mannich bases of 7-piperazinylquinolones and kojic acid derivatives: Synthesis, *in vitro* antibacterial activity and *in silico* study, *Eur. J. Med. Chem.*, **2013**, *68*, 185.
20. Aytemir M.D.; Özçelik B., A study of cytotoxicity of novel chlorokojic acid derivatives with their antimicrobial and antiviral activities, *Eur. J. Med. Chem.*, **2010**, *45*, 4089.
21. Aytemir M.D.; Çaliş Ü.; Özalp M., Synthesis and evaluation of anticonvulsant and antimicrobial activities of 3-hydroxy-6-methyl-2-substituted 4*H*-pyran-4-one derivatives, *Arch. Pharm. (Weinheim)*, **2004**, *337*, 281.
22. Shen A.-Y.; Huang M.-H.; Liao L.-F.; Wang T.-S., Thymol analogues with antioxidant and L-type calcium current inhibitory activity, *Drug Dev. Res.*, **2005**, *64*, 195.
23. Bandgar B.P.; Patil S.A.; Totre J.V.; Korbad B.L.; Gacche R.N.; Hote B.S.; Jalde S.S.; Chavan H.V., Synthesis and biological evaluation of nitrogen-containing benzophenone analogues as TNF-α and IL-6 inhibitors with antioxidant activity, *Bioorg. Med. Chem. Lett.*, **2010**, *20*, 2292.
24. Fernández-Bachiller M.I.; Pérez C.; González-Muñoz G.C.; Cond, S.; López M.G.; Villarroya M.; García A.G.; Rodríguez-Franco M.I., Novel tacrine−8-hydroxyquinoline hybrids as multifunctional agents for the treatment of Alzheimer's disease, with neuroprotective, cholinergic, antioxidant, and copper-complexing properties, J. Med. Chem., 2010, 53, 4927.
25. Li N.-G.; Song S.-L.; Shen M.-Z.; Tang Y.-P.; Shi Z.-H.; Tang H.; Shi Q.-P.; Fu Y.-F.; Duan J.-A., Mannich bases of scutellarein as thrombin-inhibitors: Design, synthesis, biological activity and solubility, *Bioorg. Med. Chem.*, **2012**, *20*, 6919.
26. Joshi D.; Field J.; Murphy J.; Abdelrahim M.; Schonherr H.; Sparrow J.R.; Ellestad G.; Nakanishi K.; Zask A., Synthesis of antioxidants for prevention of age-related macular degeneration, *J. Nat. Prod.*, **2013**, *76*, 450.
27. Caulfield M.J.; Russo T.; Solomon D.H., Controlled synthesis of novel dibenzene-1,2-diol Mannich bases, *Aust. J. Chem.*, **2000**, *53*, 545.
28. Chi K.-W.; Ahn Y.S.; Park T.H.; Ahn J.S.; Kim H.A.; Park J.Y., Synthesis of Mannich bases using substituted aromatic alcohols with secondary amines: Relative reactivity and regioselectivity depending on substrates, *J. Korean Chem. Soc.*, **2001**, *45*, 51.
29. Kim J.Y.; Kim G.; Lee S.J.; Shon O.J.; Kim S.K.; Suh I.H.; Kim J.S., Proton-diionizable bis-calix[4]azacrown ether through Mannich reaction, *Bull. Korean Chem. Soc.*, **2002**, *23*, 137.
30. Novikova A.P.; Lipunova G.N.; Postovskii I.Ya., Mannich reaction of pyrogallol and hydroxyhydroquinone (in Russian), *Zh. Org. Khim.*, **1973**, *9*, 588; cf. *Chem. Abstr.*, **1973**, *78*, 136231u.
31. Postovskii I.Ya.; Novikova A.P.; Chechulina L.A.; Lyubomudrova L.N., Antioxidant and antiradiation activity of Mannich bases in a series of pyrogallols and hydroxyhydroquinone (in Russian), *Tr. Instit. Khim., Ural. Nauchn. Tsentr., Akad. Nauk SSSR*, **1978**, *37*, 24; cf. *Chem. Abstr.*, **1980**, *92*, 128829.
32. Avramova P.; Dryanovska-Noninska L., Mannich bases of pyrogallol (in Bulgarian), *Probl. Farm.*, **1981**, *9*, 51; cf. *Chem. Abstr.*, **1981**, *95*, 97732.
33. Baicu T.; Leonte M.; Jilăveanu A.; Georgescu M.; Leonte A., (Intreprinderea Chimică "Sinteza" Oradea), *Rom. Pat.* 68352 February 27, 1980; cf. *Chem. Abstr.*, **1981**, *95*, 7088.
34. Leonte M.; Georgescu M.; Toma G.; Sinchievici E.; Roncea C., (Combinatul Petrochimic Piteşti), *Rom. Pat.* 61894 April 15, 1977; cf. *Chem. Abstr.*, **1979**, *91*, 211070.
35. Augustin M.A.; Berry S.K., Effectiveness of antioxidants in refined, bleached and deodorized palm olein, *J. Am. Oil Chem. Soc.*, **1983**, *60*, 105.
36. Cosmetic, Toiletry and Fragrance Association (Washington, DC, USA), Final report on the safety assessment of propyl gallate, *J. Am. Coll. Toxicol.*, **1985**, *4*, 23.
37. Shriner R.L.; Grillot G.F.; Teeters W.O., *p*-Aminobenzoates of piperidino- and morpholino-methylnaphthols, *J. Am. Chem. Soc.*, **1946**, *68*, 946.