

In vitro Investigation of the Antimicrobial Activity of a Series of Lipophilic Phenols and Naphthols

Thavendran Govender,^a Usha Govinden,^a Chunderika Mocktar,^a Hendrik G. Kruger,^a Jelena Veljković,^b Nikola Cindro,^b Damir Bobinac,^b Ivana Žabčić,^b Kata Mlinarić-Majerski^b and Nikola Basarić^{b*}

^aCatalysis and Peptide Research Unit, School of Health Sciences, University of KwaZulu-Natal, Durban, South Africa.

^bDepartment of Organic Chemistry and Biochemistry, Ruđer Bošković Institute, Bijenička cesta 54, 10 000 Zagreb, Croatia.

Received 11 August 2015, revised 20 January 2016, accepted 5 February 2016.

ABSTRACT

Five groups of phenols/naphthols (42 compounds in total) were synthesized and screened against Gram-positive *Staphylococcus aureus* and *Bacillus subtilis*, Gram-negative *Escherichia coli* and *Klebsiella pneumoniae*, and the fungus *Candida albicans*. Whereas compounds were found inactive against Gram-negative bacteria, potent activities against Gram-positive bacteria were observed. The activities correlate with the ability of molecules to form quinone methides, suggesting potential new modes of action.

KEYWORDS

Antimicrobial activity, phenols, naphthols, quinone methides.

1. Introduction

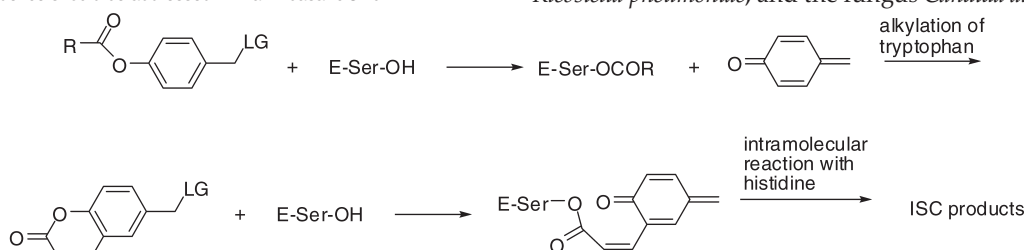
Bacterial infections are responsible for a vast number of human diseases. Moreover, development of bacterial resistance to common antibiotics is stimulating intensive research devoted to discovery of new targets in combating the bacteria. In search for new and improved antibiotics with new mechanism of action, it is important to screen many new libraries of compounds.

Antimicrobial activity of simple phenols,¹ and their carboxylic acid derivatives has been investigated.² It is generally accepted that phenols and benzyl alcohols exert antimicrobial action^{3–6} on the non-specific ability to alter membranes in Gram-negative bacteria.^{7–10} On the other hand, a more specific mode of action of phenolic compounds has been suggested, especially against Gram-positive bacteria, since the bactericidal concentrations are not dependent on the type of cell wall.¹¹ It was suggested that phenolic compounds inhibit DNA synthesis, due to an effect associated with the inhibition of RNA and protein synthesis.¹¹ Furthermore, antibacterial properties are ascribed to a large number of food products due to the presence of phenolic natural compounds.¹² Examples include berries,¹³ vine,¹⁴ tropical vegetables,¹⁵ and mushrooms.¹⁶ Recently, an investigation of antimicrobial activities have been conducted on a series of naphthol derivatives of Mannich bases.¹⁷ The latter series of compounds can in principle be transformed to quinone methides (QM) intermediates during metabolic processes. QMs are interesting substrates in

the development of antimicrobial agents since it was demonstrated that they act as alkylating agents and inhibitors of serine proteases and β -lactamases.¹⁸ Depending on their structure, they are mechanism-based enzyme inhibitors, or suicide substrates. When QMs are formed from cyclic compounds such as coumarins, they usually induce cross-linking of the enzyme in the reaction with a histidine. On the contrary, free QM formed in the active site of the enzyme usually reacts with neighbouring tryptophan residues (Scheme 1).¹⁸

We became interested in the photochemical generation of QMs with sterically congested lipophilic substituents^{19,20} and their antiproliferative activities.^{21–24} A series of simple phenols,¹⁹ biphenyls,^{20–22} naphthols,²³ and anthrols²⁴ were synthesized and their antiproliferative activities were investigated. Since compounds that generate QMs are known β -lactamase inhibitors,¹⁸ we were also prompted to investigate their antimicrobial activities. Potentially, they can be used in combination with β -lactam derivatives as antibiotics. Herein we report an investigation of the antimicrobial activity of five series of lipophilic derivatives of phenols and naphthols and/or benzyl alcohols (Figs. 1–5) with the aim of developing a SAR relationship. Moreover, many of our derivatives bear an adamantyl substituent, and the antibacterial activity of a number of adamantane derivatives has been reported.^{25–29} The *in vitro* antimicrobial testing was performed on five strains of microorganisms, Gram-positive *Staphylococcus aureus* and *Bacillus subtilis*, Gram-negative *Escherichia coli* and *Klebsiella pneumoniae*, and the fungus *Candida albicans*.

* To whom correspondence should be addressed. E-mail: nbasari@irb.hr



Scheme 1



2. Materials and Methods

2.1. Compounds

The structures of the investigated compounds comprise phenols (Fig. 1), 2-hydroxybiphenyls (Fig. 2), 3-hydroxybiphenyls (Fig. 3), 4-hydroxybiphenyls (Fig. 4), naphthols (Fig. 5) or their corresponding methoxy or QM derivatives. All compounds were prepared according to previously published procedures.^{19–23} Chiral compounds 7–9 were synthesized as racemic mixtures.

2.1.1. Synthesis of Phenol Derivatives 1–9

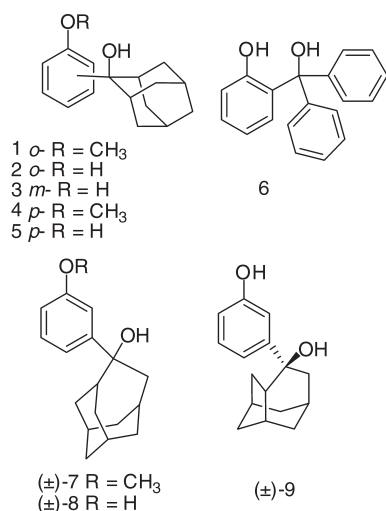


Figure 1 Phenol derivatives.

2-Hydroxy-2-(2-methoxyphenyl)adamantane (1) was prepared in a Grignard reaction from 2-adamantanone and 2-bromanisole in 50 % yield according to the published procedure.¹⁹ Characterization of product 1 compares well with literature (mp = 87–88 °C).¹⁹ ¹H NMR (CDCl₃, 300 MHz) δ /ppm: 7.44 (dd, 1H, *J* = 1.5 Hz, *J* = 7.7 Hz), 7.21 (dt, 1H, *J* = 1.5 Hz, *J* = 8.1 Hz), 6.93 (dt, 1H, *J* = 1.5 Hz, *J* = 7.7 Hz), 6.90 (d, 1H, *J* = 8.1 Hz), 3.85 (s, 3H), 3.42 (s, 1H, OH), 2.66 (br s, 2H), 2.54 (br s, 1H), 2.50 (br s, 1H), 1.65–1.90 (m, 8H), 1.61 (d, *J* = 12.5 Hz, 2H).

2-Hydroxy-2-(2-hydroxyphenyl)adamantane (2) was prepared from 1 by treatment with BBr₃ in 45 % yield according to the published procedure.¹⁹ Characterization of product 2 compares well with literature (mp = 170–171 °C).¹⁹ ¹H NMR (DMSO-*d*₆, 300 MHz) δ /ppm: 9.28 (s, 1H, OH), 7.32 (dd, 1H, *J* = 1.2 Hz, *J* = 7.7 Hz), 7.05 (dt, 1H, *J* = 1.5 Hz, *J* = 8.5 Hz), 6.73–6.82 (m, 2H), 4.93 (s, 1H, OH), 2.61 (br s, 2H), 2.44 (br s, 1H), 2.40 (br s, 1H), 1.60–1.50 (m, 8H), 1.51 (d, 2H, *J* = 12 Hz).

2-Hydroxy-2-(3-hydroxyphenyl)adamantane (3) was prepared from 2-hydroxy-2-(3-methoxyphenyl)adamantane by treatment with BBr₃ in 85 % yield according to the published procedure.¹⁹ Characterization of product 3 compares well with literature (mp = 160–161 °C).¹⁹ ¹H NMR (DMSO-*d*₆, 600 MHz) δ /ppm: 9.17 (s, 1H, OH), 7.11 (t, 1H, *J* = 7.7 Hz), 6.87–6.90 (m, 2H), 6.60 (ddd, 1H, *J* = 0.9 Hz, *J* = 2.3 Hz, *J* = 7.7 Hz), 4.48 (s, 1H, OH), 2.37 (br s, 3H), 2.35 (br s, 1H), 1.79 (br s, 1H), 1.52–1.68 (m, 9H).

2-Hydroxy-2-(4-methoxyphenyl)adamantane (4) was prepared in a Grignard reaction from 2-adamantanone and 4-bromanisole in 65 % yield according to the published procedure.¹⁹ Characterization of product 4 compares well with literature (mp = 104–105 °C).¹⁹ ¹H NMR (CDCl₃, 300 MHz) δ /ppm: 7.46 (d, 2H,

J = 8.8 Hz), 6.89 (d, 2H, *J* = 8.8 Hz), 3.80 (s, 3H, OCH₃), 2.52 (br s, 2H), 2.42 (br s, 1H), 2.38 (br s, 1H), 1.89 (br s, 1H), 1.65–1.75 (m, 9H), 1.49 (br s, 1H, OH).

2-Hydroxy-2-(4-hydroxyphenyl)adamantane (5) was prepared from 4 by treatment with BBr₃ in 90 % yield according to the published procedure.¹⁹ Characterization of product 5 compares well with literature (mp = 301–302 °C).¹⁹ ¹H NMR (DMSO-*d*₆, 300 MHz) δ /ppm: 9.20 (s, 1H, OH), 7.24 (d, 2H, *J* = 8.6 Hz), 6.71 (d, 2H, *J* = 8.6 Hz), 4.30 (s, 1H, OH), 2.37 (br s, 3H), 2.31 (br s, 1H), 1.78 (br s, 1H), 1.50–1.68 (m, 9H).

Diphenyl-(2-hydroxyphenyl)methanol (6) was prepared from diphenyl-(2-methoxyphenyl)methanol by treatment with BBr₃ in 90 % yield according to the published procedure.³⁰ Characterization of product 6 compares well with literature (mp = 148–150 °C).³⁰ ¹H NMR (CDCl₃, 300 MHz) δ /ppm: 8.10 (s, 1H, OH), 6.40–7.40 (m, 14H), 3.70 (s, 1H, OH).

4-(3-Methoxyphenyl)homoadamantan-4-ol (7) was prepared in a Grignard reaction from homoadamantan-4-one and 3-bromanisole in 67 % yield according to the published procedure.³¹ Characterization of product 7 compares well with literature (mp = 130–132 °C).³¹ ¹H NMR (CDCl₃, 300 MHz) δ /ppm: 7.25 (t, 1H, *J* = 8.0 Hz), 7.19–7.12 (m, 2H), 6.78 (d, 1H, *J* = 8.0 Hz), 3.81 (s, 3H), 2.81 (dd, 1H, *J* = 3.8, 15.0 Hz), 2.48 (d, 1H, *J* = 14.0 Hz), 2.22–2.03 (m, 3H), 2.01–1.89 (m, 4H), 1.89–1.68 (m, 4H), 1.60–1.47 (m, 4H).

4-(3-Hydroxyphenyl)homoadamantan-4-ol (8) was prepared from 7 by treatment with sodium thiolate in 90 % yield according to the published procedure.^{19,31} Characterization of product 8 compares well with literature (mp = 162–164 °C).³¹ ¹H NMR (DMSO-*d*₆, 300 MHz) δ /ppm: 9.14 (s, 1H), 7.07 (dd (t), 1H, *J* = 7.8 Hz), 7.00 (dd (t), 1H, *J* = 2.0 Hz), 6.96 (d, 1H, *J* = 7.8 Hz), 6.56 (dd, 1H, *J* = 2.0, 7.8 Hz), 4.81 (s, 1H), 2.61–2.50 (m, 2H), 2.13–1.95 (m, 2H), 1.91–1.65 (m, 7H), 1.59–1.33 (m, 5H).

exo-4-(3-Hydroxyphenyl)protoadamantan-4-ol (9) was prepared from *exo*-4-(3-methoxyphenyl)protoadamantan-4-ol by treatment with sodium thiolate in 46 % yield according to the published procedure (mp = 176–178 °C).^{19,31} Characterization of product 9 compares well with literature.³¹ ¹H NMR (DMSO-*d*₆, 300 MHz) δ /ppm: 9.13 (s, 1H), 7.07 (dd (t), 1H, *J* = 7.8 Hz), 6.91–6.86 (m, 2H), 6.57 (dd, 1H, *J* = 1.6, 7.6 Hz), 4.56 (s, 1H), 2.58 (dd (t), 1H, *J* = 8.2 Hz), 2.46–2.36 (m, 1H), 2.33–2.24 (m, 1H), 2.07 (bs, 4H), 1.74 (d, 1H, *J* = 13.0 Hz), 1.67–1.40 (m, 3H), 1.29 (dd (t), 2H, *J* = 13.0 Hz), 1.19 (d, 1H, *J* = 12.0 Hz).

2.1.2. Synthesis of 2-Hydroxybiphenyl Derivatives 10–15

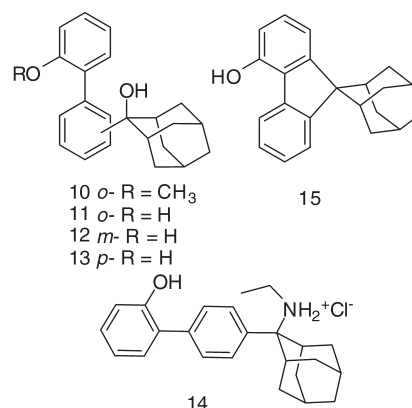


Figure 2 2-Hydroxybiphenyl derivatives.

2-(2-Hydroxyadamantan-2-yl)-2'-methoxybiphenyl (10) was prepared in a Grignard reaction from adamantan-2-one and 2-bromo-2'-methoxybiphenyl in 76 % yield according to the published procedure.²⁰ Characterization of product **10** compares well with literature (mp = 114–115 °C).²⁰ ¹H NMR (CDCl₃, 600 MHz) δ/ppm: 7.68 (d, 1H, J = 8.1 Hz), 7.38 (dt, 1H, J = 1.6 Hz, J = 8.1 Hz), 7.34 (dt, 1H, J = 1.7 Hz, J = 8.1 Hz), 7.27 (dt, 1H, J = 1.1 Hz, J = 7.4 Hz), 7.18 (dd, 1H, J = 1.6 Hz, J = 7.4 Hz), 7.00–7.04 (m, 2H), 6.93 (d, 1H, J = 8.3 Hz), 3.86 (br s, 1H, OH), 3.74 (s, 3H, OCH₃), 2.59 (br s, 1H), 2.34 (dt, 1H, J = 2.2 Hz, J = 12.4 Hz), 2.11 (dt, 1H, J = 2.2 Hz, J = 12.4 Hz), 1.80–1.90 (m, 2H), 1.60–1.72 (m, 5H), 1.54 (dt, 1H, J = 2.2 Hz, J = 12.4 Hz), 1.40 (dt, 1H, J = 2.2 Hz, J = 12.4 Hz), 1.32 (dq, 1H, J = 3.2 Hz, J = 12.4 Hz), 1.23 (dq, 1H, J = 3.2 Hz, J = 12.4 Hz).

2-(2-Hydroxyadamantan-2-yl)-2'-hydroxybiphenyl (11) was prepared from **10** by treatment with sodium thiolate in 60 % yield according to the published procedure.²⁰ Characterization of product **11** compares well with literature (mp = 194–196 °C).²⁰ ¹H NMR (DMSO-*d*₆, 300 MHz), δ/ppm: 9.83 (s, 1H, OH), 7.60 (d, 1H, J = 7.4 Hz), 7.36 (dt, 1H, J = 1.5 Hz, J = 7.3 Hz), 7.26 (dt, 1H, J = 0.9 Hz, J = 7.3 Hz), 7.17 (dt, 1H, J = 1.5 Hz, J = 7.5 Hz), 7.09 (dd, 1H, J = 1.5 Hz, J = 7.5 Hz), 6.95 (dd, 1H, J = 1.5 Hz, J = 7.5 Hz), 6.83–6.90 (m, 2H), 5.30 (s, 1H, OH), 2.50 (br s, 1H), 2.24 (d, 1H, J = 12.1 Hz), 2.08 (br s, 2H), 1.75 (d, 1H, J = 11.6 Hz), 1.44–1.69 (m, 6H), 1.36 (d, 1H, J = 12.1 Hz), 1.29 (d, 1H, J = 12.1 Hz), 1.21 (d, 1H, J = 11.6 Hz).

3-(2-Hydroxyadamantan-2-yl)-2'-hydroxybiphenyl (12) was prepared from 3-(2-hydroxyadamantan-2-yl)-2'-methoxybiphenyl by treatment with BBr₃ in 69 % yield according to the published procedure.²⁰ Characterization of product **12** compares well with literature (mp = 179–181 °C).²⁰ ¹H NMR (DMSO-*d*₆, 300 MHz) δ/ppm: 9.45 (s, 1H, OH), 7.62 (br s, 1H), 7.32–7.44 (m, 3H), 7.23 (dd, 1H, J = 1.6 Hz, J = 7.5 Hz), 7.14 (dt, 1H, J = 1.6 Hz, J = 8.0 Hz), 6.92 (dd, 1H, J = 0.8 Hz, J = 8.0 Hz), 6.87 (dt, 1H, J = 1.0 Hz, J = 7.4 Hz), 4.60 (br s, 1H, OH), 2.50 (br s, 2H), 2.41 (br s, 1H), 2.38 (br s, 1H), 1.55–1.85 (m, 10H).

4-(2-Hydroxyadamantan-2-yl)-2'-hydroxybiphenyl (13) was prepared from 4-(2-hydroxyadamantan-2-yl)-2'-methoxybiphenyl by treatment with BBr₃ in 40 % yield according to the published procedure.²⁰ Characterization of product **13** compares well with literature (mp = 215–217 °C).²⁰ ¹H NMR (DMSO-*d*₆, 300 MHz), δ/ppm: 9.48 (s, 1H, OH), 7.52 (d, 2H, J = 8.6 Hz), 7.48 (d, 2H, J = 8.6 Hz), 7.25 (dd, 1H, J = 1.5 Hz, J = 7.4 Hz), 7.13 (dt, 1H, J = 1.5 Hz, J = 8.1 Hz), 6.93 (dd, 1H, J = 1.0 Hz, J = 8.1 Hz), 6.86 (dt, 1H, J = 1.0 Hz, J = 7.4 Hz), 4.57 (s, 1H, OH), 2.50 (br s, 1H), 2.42 (br s, 1H), 2.38 (br s, 1H), 1.82 (br s, 1H), 1.55–1.75 (m, 10H).

4-[2-(N-ethylaminoadamantan-2-yl)]-2'-hydroxybiphenyl hydrochloride (14) was prepared from 4-(2-hydroxyadamantan-2-yl)-2'-hydroxybiphenyl by reduction with Raney Ni in 27 % yield according to the published procedure (mp = 242–245 °C).²⁰ Characterization of product **14** compares well with literature.²⁰ ¹H NMR (DMSO-*d*₆, 300 MHz) δ/ppm: 9.69 (s, 1H, OH), 8.43 (br s, 2H, NH₂), 7.69 (d, 2H, J = 7.6 Hz), 7.65 (d, 2H, J = 7.6 Hz), 7.31 (dd, 1H, J = 7.3 Hz, J = 1.3 Hz), 7.18 (dt, 1H, J = 8.0 Hz, J = 1.5 Hz), 6.99 (d, 1H, J = 8.0 Hz), 6.89 (dd, 1H, J = 7.3 Hz, J = 8.0 Hz), 3.35 (q, 2H, J = 7.4 Hz), 2.90 (br s, 2H), 2.61 (br s, 1H), 2.47 (br s, 1H), 2.42 (br s, 1H), 1.94 (br s, 1H), 1.62–1.86 (m, 8H), 1.05 (t, 3H, J = 7.4 Hz).

Spiro[adamantane-2,9'-(4'-hydroxy)fluorene] (15) was prepared from **10** by treatment with BBr₃ in 99 % yield according to the published procedure.²⁰ Characterization of product **15** compares well with literature (mp = 158–160 °C).²⁰ ¹H NMR (CDCl₃, 600

MHz) δ/ppm: 8.31 (dd, 1H, J = 1.0 Hz, J = 7.7 Hz), 8.11 (d, 1H, J = 8.1 Hz), 7.71 (d, 1H, J = 7.9 Hz), 7.37 (dt, 1H, J = 0.8 Hz, J = 7.6 Hz), 7.26 (dt, 1H, J = 1.5 Hz, J = 7.5 Hz), 7.12 (t, 1H, J = 7.9 Hz), 6.72 (d, 1H, J = 7.9 Hz), 5.08 (s, 1H, OH), 2.85–3.00 (m, 4H), 2.18 (br s, 2H), 1.98 (br s, 2H), 1.70–1.80 (m, 4H), 1.55–1.60 (m, 2H).

2.1.3. Synthesis of 3-Hydroxybiphenyl Derivatives 16–21

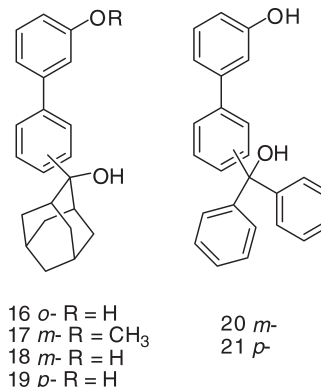


Figure 3 3-Hydroxybiphenyl derivatives.

2-(2-Hydroxyadamantan-2-yl)-3'-hydroxybiphenyl (16) was prepared from 2-(2-hydroxyadamantan-2-yl)-3'-methoxybiphenyl by treatment with sodium thiolate in 20 % yield according to the published procedure.²² Characterization of product **16** compares well with literature (mp = 119–120 °C).²² ¹H NMR (DMSO-*d*₆, 600 MHz) δ/ppm: 9.26 (s, 1H, OH), 7.56 (d, 1H, J = 7.9 Hz), 7.32 (dt, 1H, J = 1.4 Hz, J = 8.1 Hz), 7.22 (t, 1H, J = 7.3 Hz), 7.08 (t, 1H, J = 7.8 Hz), 6.98 (dd, 1H, J = 1.4 Hz, J = 7.5 Hz), 6.80–6.86 (m, 2H), 6.67 (dd, 1H, J = 2.2 Hz, J = 8.1 Hz), 4.68 (s, 1H, OH), 2.24 (br s, 2H), 2.19 (br s, 1H), 2.17 (br s, 1H), 1.63 (br s, 1H), 1.59 (br s, 1H), 1.40–1.55 (m, 6H), 1.28–1.36 (m, 2H).

3-(2-Hydroxyadamantan-2-yl)-3'-methoxybiphenyl (17) was prepared in a Grignard reaction from 3-bromo-3'-methoxybiphenyl and 2-adamantanone in 86 % yield according to the published procedure.²² Characterization of product **17** compares well with literature.²² ¹H NMR (CDCl₃, 300 MHz) δ/ppm: 7.74 (s, 1H), 7.46–7.56 (m, 2H), 7.43 (t, 1H, J = 7.5 Hz), 7.35 (t, 1H, J = 7.9 Hz), 7.17 (d, 1H, J = 7.7 Hz), 7.11 (t, 1H, J = 2.0 Hz), 6.89 (dd, 1H, J = 2.3 Hz, J = 8.1 Hz), 3.86 (s, 3H, OCH₃), 2.62 (br s, 1H), 2.45 (br s, 1H), 2.41 (br s, 1H), 1.92 (br s, 1H), 1.68–1.82 (m, 10H).

3-(2-Hydroxyadamantan-2-yl)-3'-hydroxybiphenyl (18) was prepared from **17** by treatment with BBr₃ in 83 % yield according to the published procedure.²² Characterization of product **18** compares well with literature (mp = 181–183 °C).²² ¹H NMR (DMSO-*d*₆, 300 MHz) δ/ppm: 9.49 (br s, 1H, OH), 7.65 (s, 1H), 7.36–7.50 (m, 3H), 7.25 (t, 1H, J = 7.8 Hz), 7.00–7.08 (m, 2H), 6.76 (dd, 1H, J = 1.2 Hz, J = 7.8 Hz), 2.50 (br s, 2H), 2.42 (br s, 1H), 2.38 (br s, 1H), 1.82 (br s, 1H), 1.52–1.76 (m, 10H).

4-(2-Hydroxyadamantan-2-yl)-3'-hydroxybiphenyl (19) was prepared from 4-(2-hydroxyadamantan-2-yl)-3'-methoxybiphenyl by treatment with BBr₃ in 34 % yield according to the published procedure.²² Characterization of product **19** compares well with literature (mp = 201–203 °C).²² ¹H NMR (DMSO-*d*₆, 300 MHz) δ/ppm: 9.50 (br s, 1H, OH), 7.56 (d, 2H, J = 8.6 Hz), 7.53 (d, 2H, J = 8.6 Hz), 7.24 (t, 1H, J = 7.6 Hz), 7.06 (d, 1H, J = 7.6 Hz), 7.02 (s, 1H), 6.75 (dd, 1H, J = 1.2 Hz, J = 7.9 Hz), 2.50 (br s, 2H), 2.41 (br s, 1H), 2.38 (br s, 1H), 1.82 (br s, 1H), 1.54–1.72 (m, 10H).

(3'-Hydroxybiphenyl-3-yl)diphenylmethanol (20) was prepared from (3'-methoxybiphenyl-3-yl)diphenylmethanol by

treatment with BBr_3 in 96 % yield according to the published procedure.²² Characterization of product **20** compares well with literature (mp = 141–142 °C).²² ^1H NMR ($\text{DMSO}-d_6$, 600 MHz) δ/ppm : 9.47 (s, 1H, OH), 7.50 (t, 1H, $J = 1.4$ Hz), 7.48 (dd, 1H, $J = 1.7$ Hz, $J = 7.7$ Hz), 7.36 (t, 1H, $J = 7.7$ Hz), 7.32 (dd, 4H, $J = 7.2$ Hz, $J = 7.6$ Hz), 7.23–7.28 (m, 6H), 7.21 (t, 1H, $J = 7.8$ Hz), 7.13 (dd, 1H, $J = 1.5$ Hz, $J = 7.7$ Hz), 6.95 (dd, 1H, $J = 1.3$ Hz, $J = 7.7$ Hz), 6.92 (t, 1H, $J = 2.0$ Hz), 6.73 (dd, 1H, $J = 8.0$ Hz, $J = 2.3$ Hz), 6.51 (s, 1H, OH).

(3'-Hydroxybiphenyl-4-yl)diphenylmethanol (**21**) was prepared from (3'-methoxybiphenyl-4-yl)diphenylmethanol by treatment with BBr_3 in 98 % yield according to the published procedure.²² Characterization of product **21** compares well with literature (mp = 168–170 °C).²² ^1H NMR ($\text{DMSO}-d_6$, 600 MHz) δ/ppm : 9.49 (s, 1H, OH), 7.54 (d, 2H, $J = 8.4$ Hz), 7.32 (dd, 4H, $J = 7.2$ Hz, $J = 7.7$ Hz), 7.22–7.30 (m, 9H), 7.06 (d, 1H, $J = 7.6$ Hz), 7.02 (t, 1H, $J = 2.0$ Hz), 6.75 (dd, 1H, $J = 1.6$ Hz, $J = 8.0$ Hz), 6.46 (s, 1H, OH).

2.1.4. Synthesis of 4-Hydroxybiphenyl Derivatives 22–31

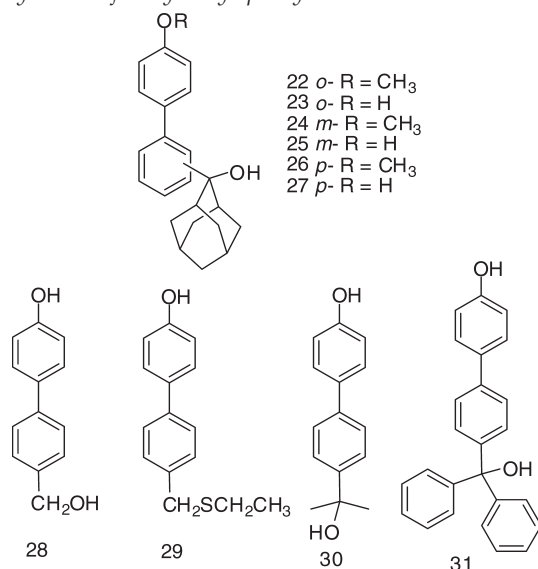


Figure 4 4-Hydroxybiphenyl derivatives.

2-(2-Hydroxyadamantan-2-yl)-4'-methoxybiphenyl (22) was prepared in a Grignard reaction from 2-bromo-4'-methoxybiphenyl and 2-adamantanone in 80 % yield according to the published procedure.²¹ Characterization of product **22** compares well with literature (mp = 125–130 °C).²¹ ^1H NMR (CDCl_3 , 300 MHz) δ/ppm : 7.61 (d, 1H, $J = 8.0$ Hz), 7.32 (t, 1H, $J = 8.0$ Hz), 7.28 (d, 2H, $J = 8.5$ Hz), 7.25 (t, 2H, $J = 8.0$ Hz), 7.10 (d, 1H, $J = 8.0$ Hz), 3.84 (s, 3H), 2.27 (s, 2H), 2.17 (br s, 1H), 2.15 (br s, 1H), 1.81 (s, 1H), 1.73 (br s, 1H), 1.62–1.69 (m, 3H), 1.60 (br s, 2H), 1.52–1.57 (m, 2H), 1.49 (d, 2H, $J = 12.4$ Hz).

2-(2-Hydroxyadamantan-2-yl)-4'-hydroxybiphenyl (23) was prepared from **22** by treatment with sodium thiolate in 69 % yield according to the published procedure.²¹ Characterization of product **23** compares well with literature (mp = 160–163 °C).²¹ ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ/ppm : 9.29 (s, 1H, OH), 7.55 (d, 1H, $J = 7.7$ Hz), 7.29 (t, 1H, $J = 7.7$ Hz), 7.16–7.26 (m, 3H), 6.98 (dd, 1H, $J = 1.0$ Hz, $J = 7.2$ Hz), 6.70 (d, 2H, $J = 8.4$ Hz), 4.73 (s, 1H, OH), 2.10–2.30 (m, 4H), 1.20–1.70 (m, 10H).

3-(2-Hydroxyadamantan-2-yl)-4'-methoxybiphenyl (24) was prepared in a Grignard reaction from 3-bromo-4'-methoxybiphenyl and 2-adamantanone in 78 % yield according to the

published procedure.²¹ Characterization of product **24** compares well with literature (mp = 103–105 °C).²¹ ^1H NMR (CDCl_3 , 300 MHz) δ/ppm : 7.71 (br s, 1H), 7.51 (d, 2H, $J = 8.8$ Hz), 7.27–7.49 (m, 3H), 6.97 (d, 2H, $J = 8.8$ Hz), 3.84 (s, 3H), 2.62 (br s, 2H), 2.45 (br s, 1H), 2.41 (br s, 1H), 1.91 (br s, 1H), 1.68–1.80 (m, 10H).

3-(2-Hydroxyadamantan-2-yl)-4'-hydroxybiphenyl (25) was prepared from **24** by treatment with BBr_3 in 79 % yield according to the published procedure.²¹ Characterization of product **25** compares well with literature (mp = 155–157 °C).²¹ ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ/ppm : 9.50 (br s, OH), 7.63 (br s, 1H), 7.46 (d, 2H, $J = 8.6$ Hz), 7.35–7.44 (m, 3H), 6.85 (d, 2H, $J = 8.0$ Hz), 2.52 (br s, 2H), 2.42 (br s, 1H), 2.38 (br s, 1H), 1.81 (br s, 1H), 1.55–1.70 (m, 10H).

4-(2-Hydroxyadamantan-2-yl)-4'-methoxybiphenyl (26) was prepared in a Grignard reaction from 4-bromo-4'-methoxybiphenyl and 2-adamantanone in 65 % yield according to the published procedure.²¹ Characterization of product **26** compares well with literature (mp = 186–187 °C).²¹ ^1H NMR (CDCl_3 , 300 MHz) δ/ppm : 7.58 (d, 2H, $J = 8.8$ Hz), 7.54 (d, 2H, $J = 8.8$ Hz), 7.53 (d, 2H, $J = 8.8$ Hz), 6.97 (d, 2H, $J = 8.8$ Hz), 3.84 (s, 3H), 2.59 (br s, 2H), 2.45 (br s, 1H), 2.40 (br s, 1H), 1.91 (br s, 1H), 1.70–1.80 (m, 10H).

4-(2-Hydroxyadamantan-2-yl)-4'-hydroxybiphenyl (27) was prepared from **26** by treatment with BBr_3 in 67 % yield according to the published procedure.²¹ Characterization of product **27** compares well with literature (mp = 225–228 °C).²¹ ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ/ppm : 9.48 (br s, OH), 7.42–7.61 (m, 6H), 6.84 (d, 2H, $J = 8.5$ Hz), 2.47 (br s, 2H), 2.41 (br s, 1H), 2.38 (br s, 1H), 1.81 (br s, 1H), 1.53–1.73 (m, 10H).

4-Hydroxymethyl-4'-hydroxybiphenyl (28) was obtained from 4-methoxy-4'-hydroxybiphenyl with sodium thiolate in 23 % yield according to the published procedure.²¹ Characterization of product **28** compares well with literature (mp = 195–196 °C).²¹ ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ/ppm : 9.50 (s, 1H, OH), 7.51 (d, 2H, $J = 8.5$ Hz), 7.46 (d, 2H, $J = 8.5$ Hz), 7.33 (d, 2H, $J = 8.5$ Hz), 6.83 (d, 2H, $J = 8.6$ Hz), 5.15 (br s, 1H, OH), 4.50 (s, 2H).

4-Thioethylmethyl-4'-hydroxybiphenyl (29) was obtained from 4-methoxy-4'-hydroxybiphenyl with sodium thiolate in 75 % yield according to the published procedure.²¹ Characterization of product **29** compares well with literature.²¹ ^1H NMR (CDCl_3 , 300 MHz) δ/ppm : 7.48 (d, 2H, $J = 8.3$ Hz), 7.47 (d, 2H, $J = 8.3$ Hz), 7.36 (d, 2H, $J = 8.3$ Hz), 6.89 (d, 2H, $J = 8.6$ Hz), 4.84 (s, 1H, OH), 3.75 (s, 2H), 2.47 (q, 2H, $J = 7.4$ Hz), 1.25 (t, 3H, $J = 7.4$ Hz). ^{13}C NMR (CDCl_3 , 75 MHz) δ/ppm : 155.0 (s), 139.2 (s), 136.9 (s), 133.5 (s), 129.0 (d), 128.1 (d), 126.6 (d), 115.6 (d), 35.5 (t), 25.2 (t), 14.2 (q).

4-Hydroxy-4'-(2-hydroxypropan-2-yl)biphenyl (30) was obtained from 4-methoxy-4'-(2-hydroxypropan-2-yl)biphenyl with sodium thiolate in 80 % yield according to the published procedure.²¹ Characterization of product **30** compares well with literature (mp = 178–180 °C).²¹ ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ/ppm : 9.48 (s, 1H, OH), 7.48 (s, 4H), 7.45 (d, 2H, $J = 8.6$ Hz), 6.83 (d, 2H, $J = 8.6$ Hz), 4.98 (br s, 1H, OH), 1.44 (s, 6H).

4'-(Hydroxydiphenylmethyl)biphenyl-4-ol (31) was obtained from (4'-methoxybiphenyl-4-yl)diphenylmethanol with BBr_3 in 83 % yield according to the published procedure.²¹ Characterization of product **31** compares well with literature (mp = 274–276 °C).²¹ ^1H NMR (CDCl_3 , 300 MHz) δ/ppm : 9.50 (br s, 1H, OH), 7.49 (t, 4H, $J = 8.7$ Hz), 7.18–7.34 (m, 12H), 6.83 (d, 2H, $J = 8.6$ Hz), 6.41 (br s, 1H, OH).

2.1.5. Synthesis of Naphthols 32–40 and the Corresponding QM Derivatives 41 and 42

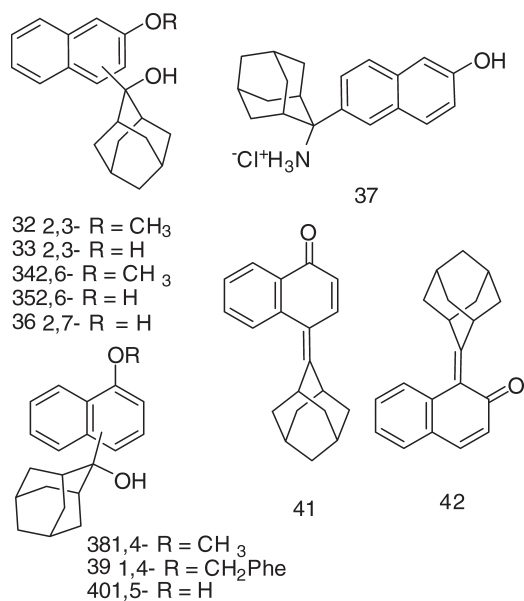


Figure 5 Naphthols and the corresponding QMs.

2-(2-Hydroxy-2-adamantyl)-3-methoxynaphthalene (32) was prepared in a Grignard reaction from 2-bromo-3-methoxynaphthalene and 2-adamantanone in 87 % yield according to the published procedure.²³ Characterization of product **32** compares well with literature (mp = 208–210 °C).²³ ¹H NMR (CDCl₃, 300 MHz) δ/ppm: 7.86 (s, 1H), 7.76 (d, 1H, J = 8.0 Hz), 7.69 (d, 1H, J = 8.0 Hz), 7.42 (dt, 1H, J = 1.2 Hz, J = 8.0 Hz), 7.34 (dt, 1H, J = 1.2 Hz, J = 8.0 Hz), 7.17 (s, 1H), 3.97 (s, 3H, OCH₃), 3.56 (s, 1H, OH), 2.78 (br s, 2H), 2.55 (br s, 2H), 1.60–2.08 (m, 10H).

2-(2-Hydroxy-2-adamantyl)-3-hydroxynaphthalene (33) was obtained from **32** with BBr₃ in 64 % yield according to the published procedure.²³ Characterization of product **33** compares well with literature (mp = 226–228 °C).²³ ¹H NMR (DMSO-*d*₆, 600 MHz) δ/ppm: 9.69 (s, 1H, OH), 7.85 (s, 1H), 7.80 (d, 1H, J = 8.1 Hz), 7.63 (d, 1H, J = 8.1 Hz), 7.36 (t, 1H, J = 8.1 Hz), 7.25 (t, 1H, J = 8.1 Hz), 7.16 (s, 1H), 5.07 (s, 1H, OH), 2.76 (br s, 2H), 2.50 (br s, 1H, covered by DMSO), 2.47 (br s, 1H), 1.80–1.85 (m, 3H), 1.72–1.80 (m, 3H), 1.67 (br s, 2H), 1.57 (d, 2H, J = 11.6 Hz).

2-(2-Hydroxy-2-adamantyl)-6-methoxynaphthalene (34) was prepared in a Grignard reaction from 2-bromo-6-methoxynaphthalene and 2-adamantanone in 81 % yield according to the published procedure.²³ Characterization of product **34** compares well with literature (mp = 162–163 °C).²³ ¹H NMR (CDCl₃, 300 MHz) δ/ppm: 7.86 (d, 1H, J = 1.1 Hz), 7.68–7.76 (m, 2H), 7.63 (dd, 1H, J = 1.8 Hz, J = 8.8 Hz), 7.09–7.16 (m, 2H), 3.90 (s, 3H, OCH₃), 2.66 (br s, 2H), 2.47 (br s, 1H), 2.43 (br s, 1H), 1.92 (br s, 1H), 1.68–1.80 (m, 10H).

2-(2-Hydroxy-2-adamantyl)-6-hydroxynaphthalene (35) was obtained from **34** with BBr₃ in 62 % yield according to the published procedure.²³ Characterization of product **35** compares well with literature (mp = 196–198 °C).²³ ¹H NMR (DMSO-*d*₆, 300 MHz) δ/ppm: 9.63 (s, 1H, OH), 7.80 (br s, 1H), 7.74 (d, 1H, J = 8.6 Hz), 7.63 (d, 1H, J = 8.8 Hz), 7.53 (dd, 1H, J = 1.2 Hz, J = 8.8 Hz), 7.01–7.08 (m, 2H), 4.57 (s, 1H, OH), 2.57 (br s, 2H), 2.44 (br s, 1H), 2.40 (br s, 1H), 1.82 (br s, 1H), 1.45–1.65 (m, 9H).

2-(2-Hydroxy-2-adamantyl)-7-hydroxynaphthalene (36) was obtained from 2-(2-hydroxy-2-adamantyl)-7-methoxynaphthalene

with BBr₃ in 63 % yield according to the published procedure.²³ Characterization of product **36** compares well with literature (mp = 250–252 °C).²³ ¹H NMR (DMSO-*d*₆, 300 MHz) δ/ppm: 7.66–7.74 (m, 3H), 7.40 (d, 1H, J = 8.8 Hz), 7.11 (d, 1H, J = 2.2 Hz), 7.03 (dd, 1H, J = 2.2 Hz, J = 8.7 Hz), 2.58 (br s, 2H), 2.44 (br s, 1H), 2.40 (br s, 1H), 1.82 (br s, 1H), 1.56–1.72 (m, 9H).

2-(2-Amino-2-adamantyl)-6-hydroxynaphthalene hydrochloride (37) was obtained from 2-(2-azido-2-adamantyl)-6-hydroxynaphthalene by reduction with Raney Ni in 19 % yield according to the published procedure.²³ Characterization of product **37** compares well with literature (mp = 256–258 °C).²³ ¹H NMR (DMSO-*d*₆, 300 MHz) δ/ppm: 9.92 (s, 1H), 8.12 (br s, 3H), 7.98 (br s, 1H), 7.75–7.85 (m, 2H), 7.56–7.62 (m, 1H), 7.11–7.16 (m, 2H), 2.86 (br s, 2H), 2.34 (br s, 1H), 2.29 (br s, 1H), 1.63–1.97 (m, 10H).

1-(2-Hydroxy-2-adamantyl)-4-methoxynaphthalene (38) was prepared in a Grignard reaction from 1-bromo-4-methoxynaphthalene and 2-adamantanone in 68 % yield according to the published procedure.³² Characterization of product **38** compares well with literature (mp = 211–212 °C).³² ¹H NMR (CDCl₃, 300 MHz, 20 °C) δ/ppm: 8.78 (d, 1H, J = 7.8 Hz), 8.31 (d, 1H, J = 7.8 Hz), 7.55 (d, 1H, J = 8.2 Hz), 7.40–7.48 (m, 2H), 6.70 (d, 1H, J = 8.2 Hz), 3.99 (s, 3H), 2.64 (d, 2H, J = 12.0 Hz), 1.93 (br s, 1H), 1.84 (br s, 1H), 1.68–1.80 (m, 6H).

1-Benzyloxy-4-(2-hydroxy-2-adamantyl)naphthalene (39) was prepared in a Grignard reaction from 1-benzyloxy-4-bromonaphthalene and 2-adamantanone in 58 % yield according to the published procedure.²³ Characterization of product **39** compares well with literature (mp = 152–153 °C).²³ ¹H NMR (CDCl₃, 600 MHz) δ/ppm: 8.78–8.81 (m, 1H), 8.39–8.48 (m, 1H), 7.52–7.57 (m, 3H, with a discernible doublet at 7.55, J = 8.3 Hz), 7.41–7.49 (m, 4H), 7.35–7.38 (m, 1H), 6.79 (d, 1H, J = 8.3 Hz), 5.26 (s, 2H), 2.67 (br s, 1H), 2.65 (br s, 1H), 1.95 (br s, 1H), 1.85 (s, 1H), 1.70–1.82 (m, 6H).

1-Hydroxy-5-(2-hydroxy-2-adamantyl)naphthalene (40) was prepared by catalytic hydrogenation of 1-benzyloxy-5-(2-hydroxy-2-adamantyl)naphthalene in 82 % yield according to the published procedure.²³ Characterization of product **40** compares well with literature (mp = 218–220 °C).²³ ¹H NMR (CD₃OD) δ/ppm: 8.26 (d, 1H, J = 8.8 Hz), 8.17 (d, 1H, J = 8.5 Hz), 7.65 (d, 1H, J = 7.4 Hz), 7.32 (dd, 1H, J = 8.2, J = 7.5 Hz), 7.16 (dd, 1H, J = 8.8, J = 7.5 Hz), 6.75 (d, 1H, J = 7.5 Hz), 2.70 (s, 1H), 2.69 (s, 1H), 1.87 (br s, 1H), 1.62–1.81 (m, 6H).

1-(2-Adamantylidene)naphthalene-2(1H)-one (41) was obtained in a reaction of 1-bromo-2-hydroxynaphthalene with BuLi and 2-adamantanone in 48 % yield according to the published procedure.²³ Characterization of product **41** compares well with literature (mp = 152–153 °C).²³ ¹H NMR (DMSO-*d*₆, 600 MHz) δ/ppm: 7.48–7.52 (m, 2H), 7.30–7.37 (m, 3H), 6.22 (d, 1H, J = 9.8 Hz), 4.10 (br s, 1H), 3.43 (br s, 1H), 1.94–2.02 (m, 6H), 1.84–1.90 (m, 4H), 1.77 (d, 2H, J = 12.2 Hz).

4-(2-Adamantylidene)naphthalene-1(4H)-one (42) was obtained by hydrogenation of **39** in 83 % yield according to the published procedure.²³ Characterization of product **42** compares well with literature (mp = 158–160 °C).²³ ¹H NMR (DMSO-*d*₆, 600 MHz) δ/ppm: 8.14 (d, 1H, J = 10.3 Hz), 8.04 (dd, 1H, J = 7.8 Hz, J = 1.4 Hz), 7.71 (d, 1H, J = 7.8 Hz), 7.64 (dt, 1H, J = 1.3 Hz, J = 8.0 Hz), 7.51 (dt, 1H, J = 0.9 Hz, J = 7.4 Hz), 6.3 (d, 1H, J = 10.3 Hz), 3.73 (s, 1H), 3.61 (s, 1H), 1.85–2.17 (m, 12H).

2.2. Antimicrobial Testing

Preliminary antimicrobial screening of the compounds was

determined in duplicate using a modification of the Kirby-Bauer disc diffusion method. All compounds were dissolved in dimethyl sulfoxide (DMSO) and tested against *Staphylococcus aureus* ATCC 25923 (Gram-positive), *Bacillus subtilis* ATCC 6633 (Gram-positive), *Candida albicans* ATCC 10231 (fungus) *Escherichia coli* ATCC 25922 (Gram-negative) and *Klebsiella pneumoniae* ATCC 31488 (Gram-negative). The microbial cultures were grown overnight at 37 °C on Nutrient Agar plates (Biolab, South Africa), adjusted to 0.5 McFarlands standard using distilled water and lawn inoculated onto Mueller-Hinton agar (MHA) plates (Biolab, South Africa). 30 µL of each sample was inoculated onto antibiotic assay discs (6 mm diameter) and placed on the MHA plates which were incubated overnight at 37 °C and zones of inhibition were measured. DMSO was used as a control. Thereafter, minimum inhibitory concentrations (MIC) were determined in triplicate with compounds displaying antimicrobial activity using the broth dilution method. Serial dilutions (10000–19.56 µg/mL) of the compounds (with the exception of compounds **16** [4200–8.20 µg/mL] and **37** [4700–9.18 µg/mL]) were prepared from the stock solutions and tested against the cultures used in the preliminary antimicrobial activity studies.

3. Results and Discussion

MICs as determined by the broth dilution method are presented in Table 1. Generally, the compounds are not active against Gram-negative bacteria. The only exception was compound **37** that exhibited very weak activity against *E. coli*. Similarly, only compounds **3** and **41** exhibited antifungal activity, but only at higher concentrations. On the contrary, compounds were found to be more potent against Gram-positive bacteria. This finding suggests that the antimicrobial activity is not due to the non-specific ability to alter membranes, but rather an unknown mechanism of action. The activity against Gram-positive bacteria has been reported also for the adamantyl derivatives of oxadiazoles, thioureas and thiadiazoles.^{25,26,29} However, the activity data are not comparable since different activity tests were employed.³³ Adamantyl derivative of Platensimycin was found also as extremely potent against Gram-positive methicillin-resistant *Staphylococcus aureus* (MRSA) exhibiting activity in the range 1–2 µg/mL.^{27,28}

With respect to the SAR it is difficult to make a straightforward conclusion, since compounds from each library were found to be active. However, the findings of this study suggest that only compounds with two aromatic rings exert activity against

Gram-positive bacteria. Both 2-hydroxy-2-adamantyl and diphenylmethanol derivatives were found to be active against the tested strains, suggesting that incorporation of the adamantyl group does not enhance the activity. With respect to the substitution on the biphenyl skeleton, better activities were observed for derivatives of 3- and 4-, than for 2-hydroxy-biphenyl. From the naphthalene derivatives only compound **37** was found to be active. The data suggest that the ammonium functional group at the benzylic position (compounds **14** and **37**) instead of the hydroxyl (compounds **13** and **35**) probably contributes to the enhancement of the antimicrobial effect. Since the ammonium is a better leaving group, this finding suggests that the activity could be correlated with the ability of these compounds to be metabolically transformed to QMs. The most active compound is QM **41**. However, the structure of QM is also important since the other QM derivative **42** exerts no activity. To verify the proposed action mechanism of the investigated compounds it would be of significant importance to detect QMs formed in a metabolic process inside the living cells. However, such a detection is not warranted since all QMs except **41** and **42** are transient species, reactive intermediates with submillisecond lifetimes.^{19–24}

4. Conclusion

Five groups of compounds containing in total 42 phenol and naphthol derivatives were synthesized and screened for antimicrobial activity. Generally, compounds were found to be more active against Gram-positive bacteria suggesting some new mechanism of action. From the SAR studies it can be concluded that the mode of action can be correlated with the ability of compounds to form QMs. This hypothesis is to be further tested, and if shown to be true, will have an impact in the further design of antimicrobial agents.

Acknowledgements

These materials are based on work financed by the Croatian Foundation for Science (HRZZ grant no. 02.05/25 and IP-2014-09-6312), the Ministry of Science Education and Sports of the Republic of Croatia (grant No. 098-0982933-2911), The National Research Foundation (South Africa), Aspen Pharmacare and the University of KwaZulu-Natal.

Supplementary Material

The online supplement contains a table with zones of inhibition (in mm) of the compounds ($n = 3$).

Table 1 MIC (µg/mL) of the compounds^a ($n = 3$).

Compound	<i>Staphylococcus aureus</i> ATCC 25923	SD	<i>Bacillus subtilis</i> ATCC 6633	SD	<i>Candida albicans</i> ATCC 10231	SD	<i>Escherichia coli</i> ATCC 25922	SD
3	–		–		5000	2	–	
14	2500	2	625	1	–	–	–	
16	525	1	131.2	0.1	–	–	–	
20	625	0	625	0.1	–	–	–	
21	5000	2	413.67	1.8	–	–	–	
23	312.5	1	625	0.1	–	–	–	
25	5000	2	–	–	–	–	–	
31	520.83	180.42	416.67	1.82	–	–	–	
37	1175	1	587.5	1	–	–	2350	1
41	76.1	0.1	76.1	0.1	2500	1	–	

^a The MIC is defined as the minimum drug concentration that inhibits growth of the organism and is represented as an average. The MICs were determined in triplicate, using the broth dilution method. The compounds were dissolved in DMSO and DMSO was used as a control.

(–) indicates no compound activity.

SD– standard deviation.

References

- 1 J.J. Lucchini, J. Corre and A. Cremieux, Antibacterial activity of phenolic compounds and aromatic alcohols. *Res. Microb.*, 1990, **141**, 499–510.
- 2 C. Cueva, M.V. Moreno-Arribas, P. Martín-Álvarez, G. Bills, M.F. Vicente, A. Basilio, C. López Rivas, T. Requena, J. M. Rodríguez and B. Bartolomé, Antimicrobial activity of phenolic acids against commensal, probiotic and pathogenic bacteria. *Res. Microb.*, 2010, **161**, 372–382.
- 3 W.B. Hugo, Phenols: a review of their history and development as antimicrobial agents. *Microbios.*, 1978, **23**, 83–85.
- 4 M. Lang and R.M. Rye, The uptake by *E. coli* and growth inhibitory properties of benzyl alcohol and phenethyl alcohol. *J. Pharm. Pharmacol.*, 1972, **24**, 219–226.
- 5 O'Neal and T.M. Buttle, Effects of alcohols on micro-organisms. *Adv. Microb. Physiol.*, 1984, **25**, 253–300.
- 6 J. Corre, J.J. Lucchini, G.M. Mercier and A. Cremieux, Antibacterial activity of phenethyl alcohol and resulting membrane alterations. *Res. Microb.*, 1990, **141**, 483–497.
- 7 S. Silver and L. Wendt, Mechanism of action of phenethyl alcohol: breakdown of cellular permeability barrier. *J. Bact.* 1967, **93**, 560–566.
- 8 M.T. Silva, J.C.F. Sousa, M.A.E. Macedo, J. Polonia and A.M. Parente, Effects of phenethyl alcohol on *Bacillus* and *Streptococcus*. *J. Bact.*, 1976, **127**, 1359–1369.
- 9 P. Gilbert, E.G. Beveridge and P.B. Corne, Effect of phenoxyethanol on the permeability of *E. coli* NCTC 5933 to inorganic ions. *Microbios.*, 1977, **19**, 17–26.
- 10 R.G. Kroll and G.D. Anagnostopoulos, Potassium fluxes on hyperosmotic shock and the effect of phenol and bronopol (2-bromo-3-nitropropan-1,3-diol) on deplasmolysis of *P. aeruginosa*. *J. Appl. Bact.*, 1981, **51**, 313–323.
- 11 M.L. Higgins, T.J. Shaw, M.C. Tillman and F.R. Leach, Effect of phenethyl alcohol on cell culture growth. *Exp. Cell Res.*, 1969, **56**, 24–28.
- 12 L. Jurd, A.D. King Jr, K. Mihara and W.L. Stanley, Antimicrobial properties of natural phenols and related compounds. *Appl Microb.*, 1971, **21**, 507–510.
- 13 L.J. Nohynek, H.-L. Alakomi, M.P. Kähkönen, M. Heinonen, I.M. Helander, K.-M. Oksman-Caldentey and R.H. Puupponen-Pimiä, Berry phenolics: antimicrobial properties and mechanisms of action against severe human pathogens. *Nutrition Cancer*, 2006, **54**, 18–32.
- 14 C. Papadopoulou, K. Soulti and I.G. Roussis, Potential antimicrobial activity of red and white wine phenolic extracts against strains of *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans*. *Food Technol. Biotechnol.*, 2005, **43**, 41–46.
- 15 S.O. Salawu, A.O. Ogundare, B.B. Ola-Salawu and A.A. Akindah, Antimicrobial activities of phenolic containing extracts of some tropical vegetables. *African J. Pharm. Pharmacol.*, 2011, **5**, 486–492.
- 16 M.J. Alves, I.C.F.R. Ferreira, H.J.C. Froufe, R.M.V. Abreu, A. Martins and M. Pintado, Antimicrobial activity of phenolic compounds identified in wild mushrooms, SAR analysis and docking studies. *J. Appl. Microb.*, 2013, **115**, 346–357.
- 17 Y. Shen, M.H. Hwang, S. Roffler and C.F. Chen, Cytotoxicity and antimicrobial activity of some naphthol derivatives. *Arch. Pharm.*, 1995, **328**, 197–201.
- 18 M. Reboud-Ravaux and M. Wakselman, Quinone methides and aza-quinone methides as latent alkylating species in the design of mechanism-based inhibitors of serine protease and β -lactamase, in S. Rokita, *Quinone Methides*, John Wiley and Sons, Hoboken, USA, 2009, p 357–383.
- 19 N. Basarić, I. Žabčić, K. Mlinarić-Majerski and P. Wan, Photochemical formation and chemistry of long-lived adamantylidene quinone methides and 2-adamantyl cations. *J. Org. Chem.*, 2010, **75**, 102–116.
- 20 N. Basarić, N. Cindro, Y. Hou, I. Žabčić, K. Mlinarić-Majerski and P. Wan, Competing photodehydration and excited state intramolecular proton transfer (ESIPT) in adamantyl derivatives of 2-phenylphenols. *Can. J. Chem.*, 2011, **89**, 221–234.
- 21 N. Basarić, N. Cindro, D. Bobinac, Mlinarić-Majerski, L. Uzelac, M. Kralj and P. Wan, Sterically congested quinone methides in photodehydration reactions of 4-hydroxybiphenyl derivatives and investigation of their antiproliferative activity. *Photochem. Photobiol. Sci.*, 2011, **10**, 1910–1925.
- 22 N. Basarić, N. Cindro, D. Bobinac, L. Uzelac, K. Mlinarić-Majerski, M. Kralj and P. Wan, Zwitterionic biphenyl quinone methides in photodehydration reactions of 3-hydroxybiphenyl derivatives: laser flash photolysis and antiproliferation study. *Photochem. Photobiol. Sci.*, 2012, **11**, 381–396.
- 23 J. Veljković, L. Uzelac, K. Molčanov, K. Mlinarić-Majerski, M. Kralj, P. Wan and N. Basarić, Sterically congested adamantyl-naphthalene quinone methides. *J. Org. Chem.*, 2012, **77**, 4596–4610.
- 24 Đ. Škalamera, K. Mlinarić-Majerski, I. Martin-Kleiner, M. Kralj and P. Wan, Near-visible light generation of a quinone methide from 3-hydroxymethyl-2-anthrol. *J. Org. Chem.*, 2014, **79**, 4390–4397.
- 25 R.E. Lee, M. Protopopova, E. Crooks, R.A. Slayden, M. Terrot and C.E. Barry, Combinatorial lead optimization of [1,2]-diamines based on ethambutol as potential antituberculosis preclinical candidates. *J. Comb. Chem.*, 2003, **5**, 172–187.
- 26 M. Protopopova, C. Hanrahan, B. Nikonenko, R. Samala, P. Chen, J. Gearhart, L. Einck and C.A. Nancy, Identification of a new antitubercular drug candidate, SQ109, from a combinatorial library of 1,2-ethylenediamines. *J. Antimicrob. Chemother.*, 2005, **56**, 968–974.
- 27 K.C. Nicolaou, T. Lister, R.M. Denton, A. Montero and D.J. Edmons, Adamantaplatensimycin: a bioactive analogue of platensimycin. *Angew. Chem. Int. Ed.*, 2007, **46**, 4712–4714.
- 28 K.C. Nicolaou, A.F. Stepan, T. Lister, A. Li, A. Montero, G. Scott Tria, C.I. Turner, Y. Tang, J. Wang, R.M. Denton and D.J. Edmons, Design, synthesis, and biological evaluation of platensimycin analogues with varying degrees of molecular complexity. *J. Am. Chem. Soc.*, 2008, **130**, 13110–13119.
- 29 L. Wanka, K. Iqbal and P.R. Schreiner, The lipophilic bullet hits the targets: medicinal chemistry of adamantane derivatives. *Chem Rev.*, 2013, **113**, 3516–3604.
- 30 L. Diao and P. Wan, Chemistry of photogenerated α -phenyl-substituted *o*-, *m*-, and *p*-quinone methides from phenol derivatives in aqueous solution. *Can. J. Chem.*, 2008, **86**, 105–118.
- 31 N. Cindro, I. Antol, K. Mlinarić-Majerski, I. Halasz, P. Wan and N. Basarić, Reactivity of cations and zwitterions formed in photochemical and acid-catalyzed reactions from *m*-hydroxycycloalkyl-substituted phenol derivatives. *J. Org. Chem.*, 2015, **80**, 12420–12430.
- 32 J. Veljković, I. Antol, N. Basarić, V. Smrečki, K. Molčanov, N. Müller and K. Mlinarić-Majerski, Atropisomerism in 1-(2-adamantyl)naphthalene derivatives. *J. Mol. Struct.* 2013, **1046**, 101–109.
- 33 A.A. Kadi, N.R. El-Brollosy, O.A. Al-Deeb, E.E. Habib, T.M. Ibrahim and A.A. El-Amam, Synthesis, antimicrobial, and anti-inflammatory activities of novel 2-(1-adamantyl)-5-substituted-1,3,4-oxadiazoles and 2-(1-adamantylamino)-5-substituted-1,3,4-thiadiazoles. *Eur. J. Med. Chem.*, 2007, **42**, 235–242

Supplementary Information, *S. Afr. J. Chem.*

***In vitro* investigation of the antimicrobial activity of a series of lipophilic phenols and naphthols**

Thavendran Govender,^a Usha Govinden,^a Chunderika Mocktar,^a Hendrik G. Kruger,^a Jelena Veljković,^b Nikola Cindro,^b Damir Bobinac,^b Ivana Žabčić,^b Kata Mlinarić-Majerski,^b Nikola Basarić^{b*}

^a Catalysis and Peptide Research Unit, School of Health Sciences, University of KwaZulu-Natal, Durban, South Africa. Fax: +27 31 2603091;

^b Department of Organic Chemistry and Biochemistry, Ruđer Bošković Institute, Bijenička cesta 54, 10 000 Zagreb, Croatia. Fax: +385 1 4680 195; E-mail: nbasari@irb.hr

TABLE OF CONTENTS

1. Zones of inhibition of compounds (Table S1)	S2
--	----

Table S1: Zones of inhibition (in mm) of the compounds (n=3)

Compound	<i>Staphylococcus aureus</i> ATCC 25923	SD	<i>Bacillus subtilis</i> ATCC 6633	SD	<i>Candida albicans</i> ATCC 10231	SD	<i>Escherichia coli</i> ATCC 25922	SD
3	-		-		8.83	0.29	-	
14	14.33	0.6	24.33	0.6	-		-	
16	13.33	0.5	17.67	0.6	-		-	
20	14.67	0.6	15.33	0.5	-		-	
21	10.33	0.6	13.33	0.6	-		-	
23	17.33	0.6	16.33	0.6	-		-	
25	9	0.1	-		-		-	
31	13.67	0.6	13.67	0.5	-		-	
37	13.67	0.5	18.33	0.6	-		10.33	0.6
41	20.33	0.6	19.67	0.6	11.67	0.6	-	

Compounds were dissolved in DMSO and DMSO was used as a control.

(-) indicates no compound activity

Supplementary Information, *S. Afr. J. Chem.*

***In vitro* investigation of the antimicrobial activity of a series of lipophilic phenols and naphthols**

Thavendran Govender,^a Usha Govinden,^a Chunderika Mocktar,^a Hendrik G. Kruger,^a Jelena Veljković,^b Nikola Cindro,^b Damir Bobinac,^b Ivana Žabčić,^b Kata Mlinarić-Majerski,^b Nikola Basarić^{b*}

^a Catalysis and Peptide Research Unit, School of Health Sciences, University of KwaZulu-Natal, Durban, South Africa. Fax: +27 31 2603091;

^b Department of Organic Chemistry and Biochemistry, Ruđer Bošković Institute, Bijenička cesta 54, 10 000 Zagreb, Croatia. Fax: +385 1 4680 195; E-mail: nbasari@irb.hr

TABLE OF CONTENTS

1. Zones of inhibition of compounds (Table S1)	S2
--	----

Table S1: Zones of inhibition (in mm) of the compounds (n=3)

Compound	<i>Staphylococcus aureus</i> ATCC 25923	SD	<i>Bacillus subtilis</i> ATCC 6633	SD	<i>Candida albicans</i> ATCC 10231	SD	<i>Escherichia coli</i> ATCC 25922	SD
3	-		-		8.83	0.29	-	
14	14.33	0.6	24.33	0.6	-		-	
16	13.33	0.5	17.67	0.6	-		-	
20	14.67	0.6	15.33	0.5	-		-	
21	10.33	0.6	13.33	0.6	-		-	
23	17.33	0.6	16.33	0.6	-		-	
25	9	0.1	-		-		-	
31	13.67	0.6	13.67	0.5	-		-	
37	13.67	0.5	18.33	0.6	-		10.33	0.6
41	20.33	0.6	19.67	0.6	11.67	0.6	-	

Compounds were dissolved in DMSO and DMSO was used as a control.

(-) indicates no compound activity

Supplementary Information, *S. Afr. J. Chem.*

***In vitro* investigation of the antimicrobial activity of a series of lipophilic phenols and naphthols**

Thavendran Govender,^a Usha Govinden,^a Chunderika Mocktar,^a Hendrik G. Kruger,^a Jelena Veljković,^b Nikola Cindro,^b Damir Bobinac,^b Ivana Žabčić,^b Kata Mlinarić-Majerski,^b Nikola Basarić^{b*}

^a Catalysis and Peptide Research Unit, School of Health Sciences, University of KwaZulu-Natal, Durban, South Africa. Fax: +27 31 2603091;

^b Department of Organic Chemistry and Biochemistry, Ruđer Bošković Institute, Bijenička cesta 54, 10 000 Zagreb, Croatia. Fax: +385 1 4680 195; E-mail: nbasari@irb.hr

TABLE OF CONTENTS

1. Zones of inhibition of compounds (Table S1)	S2
--	----

Table S1: Zones of inhibition (in mm) of the compounds (n=3)

Compound	<i>Staphylococcus aureus</i> ATCC 25923	SD	<i>Bacillus subtilis</i> ATCC 6633	SD	<i>Candida albicans</i> ATCC 10231	SD	<i>Escherichia coli</i> ATCC 25922	SD
3	-		-		8.83	0.29	-	
14	14.33	0.6	24.33	0.6	-		-	
16	13.33	0.5	17.67	0.6	-		-	
20	14.67	0.6	15.33	0.5	-		-	
21	10.33	0.6	13.33	0.6	-		-	
23	17.33	0.6	16.33	0.6	-		-	
25	9	0.1	-		-		-	
31	13.67	0.6	13.67	0.5	-		-	
37	13.67	0.5	18.33	0.6	-		10.33	0.6
41	20.33	0.6	19.67	0.6	11.67	0.6	-	

Compounds were dissolved in DMSO and DMSO was used as a control.

(-) indicates no compound activity