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ORIGINAL ARTICLE

Antipathogenic effects of structurally-related Schiff base derivatives: Structure–activity relationship

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Salicylidenebenzylamine;
Schiff base

Abstract Eighteen structurally-related Schiff base derivatives, which belong to salicylidenebenzylamine and 2-hydroxy-1-naphthylidenebenzylamine families were prepared and characterized by spectroscopic techniques. All the synthesized compounds were screened *in vitro* for their antibacterial and antifungal activities. Human pathogenic gram-negative (*Escherichia coli*, *Proteus mirabilis*, *Pseudomonas aeruginosa* and *Serratia marcescens*), gram-positive bacteria (*Staphylococcus epidermidis*, *Staphylococcus aureus* and *Bacillus subtilis*), and fungi (*Alternaria alternata*, *Aspergillus niger*, *Penicillium roqueforti*, and *Saccharomyces cerevisiae*) were evaluated based on their toxicity to different concentrations of Schiff base compounds. For assessment of toxicity to pathogens, a disc diffusion assay was used to test the antimicrobial properties. The results revealed some antimicrobial activities of some of the synthesized compounds. Among the tested pathogens, the synthesized salicylidinaniline derivatives show highly potent action towards *Alternaria alternata*. Interestingly, a compound which contains the –Cl group is only effective against gram negative bacteria, but not gram positive bacteria. No remarkable antibacterial or antifungal activities were observed in the presence of $-CH_3$ or –Br group. Furthermore, most of the naphthalene-containing compounds show no growth retardation towards bacterial or fungal pathogens. On the other hand, the presence of –OH or –SH group at *para* or *ortho* position, respectively, on the aniline site is correlated with an increased inhibitory drug effect on all pathogens. The importance of our findings to the drug research and developments is discussed in the context of finding a correlation between the structural properties of the new drugs and their biological activities.

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1. Introduction

Schiff bases play an important role in biological systems with several applications. They act as anticancer (Desai et al., 2001; Przybylski et al., 2008; Sinha et al., 2008), antibacterial (Abdel Aziz et al., 2012; Al-Kahraman et al., 2010; Amin et al., 2010; Karthikeyan et al., 2006; Przybylski et al., 2009; Ronad et al., 2010; Vukovic et al., 2010), antifungal (Al-Kahraman et al., 2010; Panneerselvam et al., 2005; Saravanan et al., 2010; Vukovic et al., 2010), antiviral (Jarrahpour et al., 2007), antiparasitic agents (Al-Kahraman et al., 2010) in addition to other biological performances (Odabasoglu et al., 2007; Vicini et al., 2003). In particular, the interest on Schiff base derivatives, which belong to the salicylidenebenzylamine (**SA**) family has been renewed very recently by some medicinal chemists due to their known antimicrobial, antifungal and antitumor activities (Abdel Aziz et al., 2012; Al-Kahraman et al., 2010; Kumar et al., 2010; Nair et al., 2002; Unver et al., 2005). Some of these derivatives were also used as starting materials to prepare the final therapeutic products (Guo et al., 2011; Tang et al., 2011).

Of relevant studies, the applications of **SA**-based Schiff base derivatives in cellular imaging, as well as building units in constructing sensing assemblies have also been published recently (Kim et al., 2012a,b; Singh et al., 2008). Not to mention, 2-hydroxy Schiff base derivatives have been characterized in many occasions as molecular switches due to the keto-enol tautomeric equilibrium, which they exhibit in solid state and in solution (Fita et al., 2005; Ohshima et al., 2004; Salman and Saleh, 1997a,b, 1998; Sauer et al., 2006). Generally, Schiff base ligands were prepared in several forms of acyclic and macrocyclic through convenient and straightforward synthetic methods with the prospective of understanding the structural effects on the recognition behaviours of the designed molecules (Sreenivasolu, 2012).

The intermolecular recognitions form the basis for the most impressive functions of living systems and life science (Sreenivasolu, 2012). Along with this line, the prediction of the absolute biological signals for potential molecule on the basis of their specific structures appears to be important to the ongoing drug researches and developments (Bajorath, 2012; Saleh et al., 2011). Therefore, the antibacterial and antifungal tests in the present work were conducted on a series of Schiff base **SA** compounds and other 2-hydroxy Schiff base derivatives, which share common structural features in order to gain more insights on the exact relationship between their specific chemical structures and the absolute biological data.

As shown in Fig. 1, the proposed **SA** and the other 2-hydroxy Schiff base compounds differ only by the presence/absence of one phenyl/pyridine ring on the aldehyde/amine sites. Additionally, several potential substituents were introduced to the *ortho* and *para* position of the aniline or aryl site of the **SA** derivatives. The rationale behind this selection stems from the fact that by adding an aromatic ring, one expects an increase in the lipophilicity of the drug, which should enhance its penetration into the bacterial/fungal cell membrane. In addition, ligation of such aromatic ring should decrease the basicity of the examined drug, thus suppressing its binding with acidic DNA molecule. The long-term goal is to advance our understanding towards the establishment of reliable structure–activity relationship.

2. Experimental

2.1. Materials

Compounds **1**–**18** (Fig. 1) were obtained by the condensation of salicylaldehyde or 2-hydroxynaphthaldehyde with the appropriate commercial aromatic amines in refluxing ethanol (Scheme 1). The crude products were recrystallized from ethanol and characterized by spectroscopic methods. All the products are known and show characteristic infrared (IR) stretching frequency for the imine (KBr disc) between 1614 and 1620 cm^{-1} and a peak at δ = 8.9 ppm in the ^1H NMR corresponding to imine = CH proton (Abdel-Latif et al., 2007; Bennett et al., 2009; Dal et al., 2007; Ligtenbarg et al., 1999; Ghedini et al., 1991; Goetz, 1968; Guo et al., 2011; Jain and Sain, 2008; Karakas et al., 2004; Kumar et al., 2010; Makal et al., 2011; Ohshima et al., 2004; Ozha et al., 1974; Sanchez et al., 2002; Singh et al., 2008; Tisato et al., 1990).

Reagent grade chemicals and solvents were purchased from Sigma Aldrich and were used without further purification. Melting points were determined on a Stuart Scientific melting point apparatus model SMP 10 and are uncorrected. IR spectra were recorded on a KBr disc. The NMR spectra were recorded on a Varian instrument at 400 and 100 MHz for ^1H NMR and ^{13}C NMR spectra, respectively. The proton chemical shifts were reported in parts per million (δ ppm) and coupling constants (J) in Hertz (Hz) and s, d, t, m, br s refer to singlet, doublet, triplet, multiplet and broad, respectively.

2.1.1. 2-((*E*)-(Phenylimino)methyl)phenol (*1*)

A stirred mixture of salicylaldehyde (1.22 g, 10 mmol) and aniline (837 mg, 9 mmol) in bench ethanol (10 mL) was refluxed for 3 h. The mixture was cooled in an ice-bath and the resulting yellow crystals were filtered, washed with cold ethanol and dried under *vacuo* to give **1**. Yield: 650 mg (37%); mp: 44–45 °C; ^1H NMR (400 MHz, DMSO-d_6): δ = 6.92–6.97 (m, 2H), 7.25–7.30 (m, 1H), 7.36–7.45 (m, 5H), 7.61–7.64 (m, 1H), 8.91 (s, 1H), 13.15 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 117.0, 119.5, 119.7, 121.8, 127.4, 129.9, 133.1, 133.7, 148.5, 160.8, 163.9.

2.1.2. 2-((*E*)-(4-Chlorophenylimino)methyl)phenol (*2*)

Compound **2** was prepared from salicylaldehyde (1.22 g, 10 mmol) and 4-chloroaniline (1.15 g, 9 mmol); Yield: 1.38 g (66%); mp: 101–102 °C; ^1H NMR (400 MHz, DMSO-d_6): δ = 6.93–6.96 (m, 2H), 7.36–7.47 (m, 5H), 7.60–7.63 (m, 1H), 8.90 (s, 1H), 12.82 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 117.0, 119.6, 119.7, 123.6, 129.8, 131.6, 133.0, 133.9, 147.4, 160.7, 164.4.

2.1.3. 2-((*E*)-(4-Bromophenylimino)methyl)phenol (*3*)

Compound **3** was prepared from salicylaldehyde (1.22 g, 10 mmol) and 4-bromoroaniline (1.55 g, 9 mmol); Yield: 1.69 g (68%); mp: 110–112 °C; ^1H NMR (400 MHz, DMSO-d_6): δ = 6.93–6.97 (m, 2H), 7.32–7.42 (m, 3H), 7.58–7.64 (m, 3H), 8.91 (s, 1H), 12.78 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 117.1, 119.7, 120.0, 124.0, 132.7, 133.0, 134.0, 147.9, 160.7, 164.4.

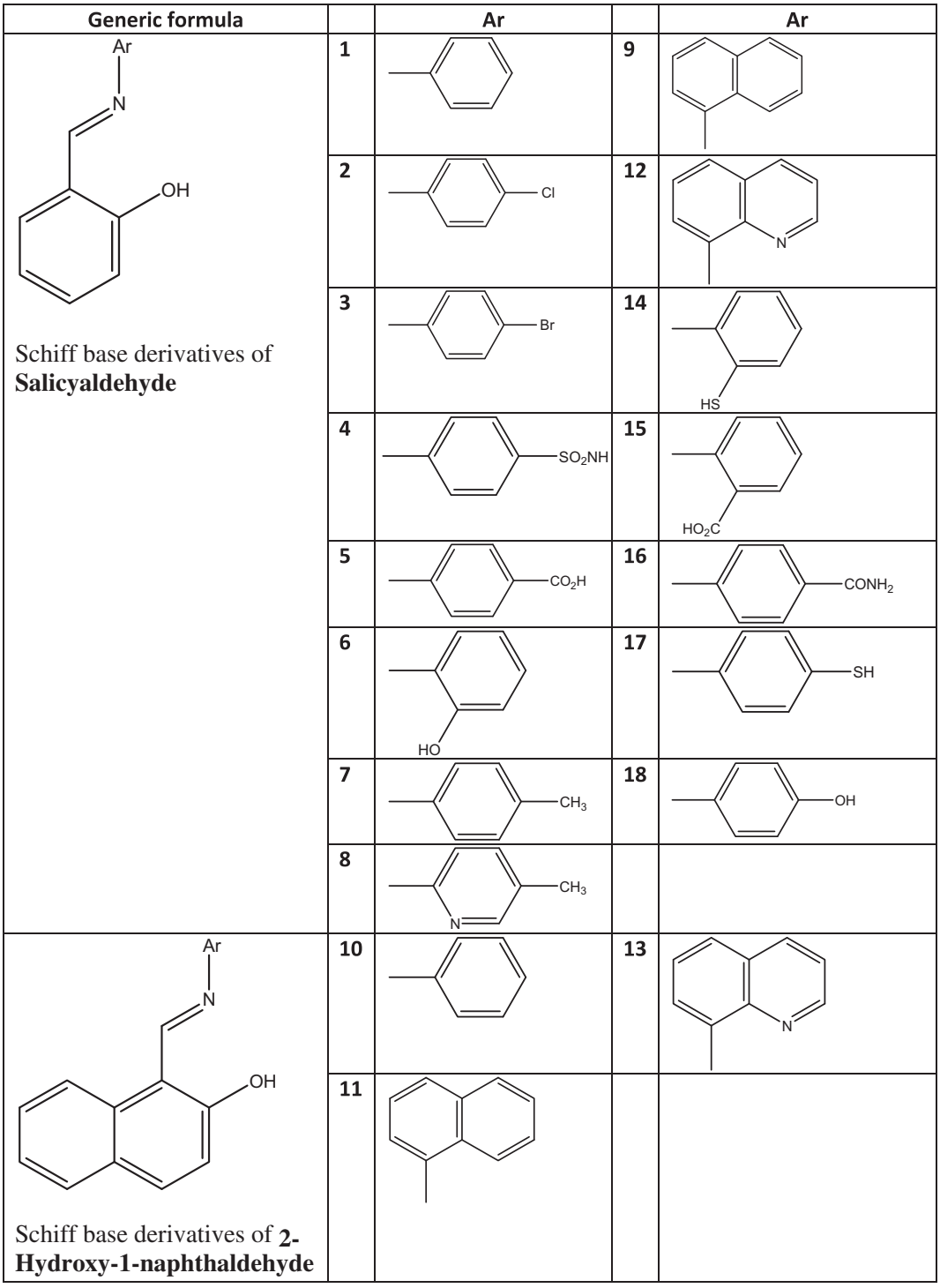


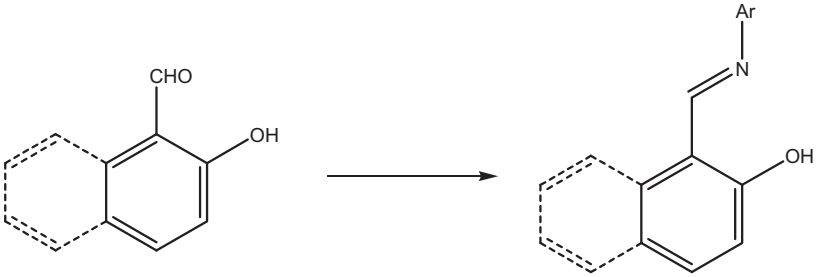
Figure 1 The chemical structures of the examined structurally-related Schiff base derivatives.

*2.1.4. (E)-4-(2-Hydroxybenzylideneamino)benzenesulfonamide (**4**)*

Compound **4** was prepared from salicylaldehyde (1.22 g, 10 mmol) and 4-aminosulfonamide (1.40 g, 9 mmol); Yield: 0.54 g (23%); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.95–7.00 (m, 2H), 7.39–7.45 (m, 2H), 7.52–7.55 (m, 2H), 7.68 (dd, J_{AB} = 7.6 Hz, J_{AX} = 2.0 Hz, 1H); 7.85–7.87 (m, 2H), 8.97 (s, 1H), 12.62 (s br, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 117.1, 119.7, 122.2, 127.5, 133.1, 134.3, 142.4, 151.6, 160.7, 165.5.

*2.1.5. 2-((E)-(2-Hydroxybenzylideneamino)methyl)benzoic acid (**5**)*

Compound **5** was prepared from salicylaldehyde (1.22 g, 10 mmol) and 4-aminobenzoic acid (1.23 g, 9 mmol); Yield: 1.62 g (74%); ^{1}H NMR (400 MHz, DMSO-d_6):



Scheme 1 Reaction conditions: $ArNH_2$, EtOH, reflux 3 h.

δ = 6.94–6.99 (m, 2H)7.39–7.47 (m, 3H), 7.65–7.68 (m, 1H), 7.97–8.00 (m, 2H), 8.96 (s, 1H), 12.65 (s br, 1H), 12.90 (s br, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 117.1, 119.8, 122.0, 129.2, 131.2, 133.1, 134.3, 152.6, 160.8, 165.2, 167.3.

*2.1.6. 2-((E)-(2-Hydroxyphenylimino)methyl)phenol (**6**)*

Compound **6** was prepared from salicylaldehyde (1.22 g, 10 mmol) and 2-aminophenol (982 mg, 9 mmol); Yield: 1.63 g (85%); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.83–6.97 (m, 4H), 7.06–7.13 (m, 1H), 7.32–7.38 (m, 2H), 7.58 (dd, J_{AB} = 8.0 Hz, J_{AX} = 1.6 Hz, 1H), 8.94 (s, 1H), 9.72 (s br, 1H), 13.80 (s br, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 117.0, 117.1, 119.1, 119.9, 120.03, 120.06, 128.5, 132.8, 133.3, 135.4, 151.6, 161.2, 162.1.

*2.1.7. 2-((E)-(p-Tolylimino)methyl)phenol (**7**)*

Compound **7** was prepared from salicylaldehyde (1.22 g, 10 mmol) and 4-methylaniline (965 mg, 9 mmol); Yield: 1.38 g (72%); mp: 95–96 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.24 (s, 3H), 6.91–6.95 (m, 2H), 7.19–7.21 (m, 2H), 7.26–7.29 (m, 2H), 7.37 (dd, J_{AB} = 15.6 Hz, J_{AX} = 2.0 Hz, 1H), 7.36–7.37 (m, 1H), 7.59 (dd, J_{AB} = 8.0 Hz, J_{AX} = 2 Hz, 1H), 8.89 (s, 1H), 13.2 (s br, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.0, 117.0, 119.5, 119.7, 121.6, 130.3, 132.9, 133.4, 136.9, 145.8, 160.8, 162.9.

*2.1.8. 2-((E)-(5-Methylpyridin-2-ylimino)methyl)phenol (**8**)*

Compound **8** was prepared from salicylaldehyde (732 mg, 6 mmol) and 5-methyl-2-aminopyridine (540 mg, 5 mmol); Yield: 730 mg (69%); mp: 104–105 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.24 (s, 3H), 6.90–6.96 (m, 2H), 7.22–7.28 (m, 1H), 7.34–7.42 (m, 1H), 7.60–7.69 (m, 2H), 8.28 (s, 1H), 9.40 (s, 1H), 13.16 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 17.9, 117.1, 119.4, 119.63, 119.68, 132.8, 133.6, 134.1, 139.5, 149.4, 155.5, 161.3, 163.9.

*2.1.9. 2-((E)-(Naphthalen-1-ylimino)methyl)phenol (**9**)*

Compound **9** was prepared from salicylaldehyde (1.22 g, 10 mmol) and 1-naphthaldehyde (1.41 g, 9 mmol); Yield: 1.29 g (53%); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.96–7.04 (m, 2H), 7.36–7.56 (m, 2H), 7.50–7.58 (m, 3H), 7.70–7.73 (m, 1H), 7.82–7.85 (m, 1H), 7.93–7.94 (m, 1H), 8.14–8.17 (m, 1H), 8.97 (s, 1H), 13.1 (s br, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 114.9, 117.1, 119.7, 120.2, 122.9, 126.7, 127.0, 127.1, 128.2, 128.4, 132.9, 133.9, 134.0, 146.0, 160.80, 160.81, 164.5.

*2.1.10. 1-((E)-(Phenylimino)methyl)naphthalen-2-ol (**10**)*

Compound **10** was prepared from 2-hydroxynaphthaldehyde (1.72 g, 10 mmol) and aniline (837 mg, 9 mmol); Yield: 1.59 g (67%); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.96 (d, J = 9.2 Hz, 1H), 7.27–7.33 (m, 2H), 7.45–7.53 (m, 3H), 7.61 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 9.2 Hz, 1H), 8.45 (d, J = 8.4 Hz, 1H), 9.62 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 108.9, 120.7, 120.8, 122.8, 123.9, 126.9, 127.0, 128.6, 129.5, 130.1, 133.7, 137.5, 144.0, 155.7, 171.6.

*2.1.11. 1-((E)-(Naphthalen-1-ylimino)methyl)naphthalen-2-ol (**11**)*

Compound **11** was prepared from 2-hydroxynaphthaldehyde (1.72 g, 10 mmol) and 1-napthylmine (1.29 g, 9 mmol); Yield: 1.68 g (63%); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.13 (d, J = 9.2 Hz, 1H), 7.34–7.38 (m, 1H), 7.53–7.68 (m, 4H), 7.81–7.84 (m, 2H), 7.88 (d, J = 8.0 Hz, 1H), 7.97–8.01 (m, 2H), 8.22 (d, J = 8.4 Hz, 1H), 8.55 (d, J = 8.8 Hz, 1H), 9.80 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 109.8, 115.5, 121.0, 121.7, 122.2, 124.1, 126.8, 127.0, 127.1, 127.3, 127.4, 127.46, 128.6, 128.8, 129.5, 133.4, 134.1, 137.1, 142.3, 158.3, 168.8.

*2.1.12. 2-(E)-(Quinolin-8-ylimino)methyl)phenol (**12**)*

Compound **12** was prepared from salicylaldehyde (0.67 g, 5.5 mmol) and 8-aminoquinoline (0.70 g, 5 mmol); Yield: 1.01 g (81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.94 (t, J = 7.9 Hz, 1H), 7.07 (d, J = 7.9 Hz, 1H), 7.39 (t, J = 7.9 Hz, 1H), 7.43 (d, J = 7.9 Hz, 1H), 7.44 (dd, J = 8.3, 4.2 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.57 (t, J = 8.1 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H), 8.18 (dd, J = 8.3, 1.7 Hz, 1H), 8.92 (s, 1H), 8.97 (dd, J = 4.2, 1.7 Hz, 1H), 12.64 (s br, 1H).

*2.1.13. (6Z)-6-((Quinolin-8-ylamino)methylene)cyclohexa-2,4-dienone (**13**)*

Compound **13** was prepared from 2-hydroxynaphthaldehyde (1.72 g, 10 mmol) and 8-aminoquinoline (1.30 g, 9 mmol); Yield: 2.23 g (83%); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.70 (d, J = 9.6 Hz, 1H), 7.24–7.27 (m, 1H), 7.46–7.50 (m, 1H), 7.63–7.85 (m, 3H), 8.41–8.47 (m, 3H), 9.01–9.03 (m, 1H), 9.59 (d, J = 11.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 108.7, 115.1, 120.4, 123.0, 123.9, 124.9, 126.7, 127.4, 128.8, 128.9, 129.6, 134.7, 136.8, 136.9, 139.2, 139.8, 147.8, 150.6, 181.7.

*2.1.14. 2-((E)-(2-Mercaptophenylimino)methyl)phenol (**14**)*

Compound **14** was prepared from salicylaldehyde (1.22 g, 10 mmol) and 2-aminothiophenol (1.13 g, 9 mmol); Yield: 1.90 g (92%); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.49 (d, J = 2.4 Hz, 1H), 6.53–6.57 (m, 1H), 6.66 (d, J = 7.6 Hz, 1H), 6.75–6.87 (m, 4H), 6.93 (d, J = 7.6 Hz, 1H), 7.06–7.11

(m, 1H), 7.39 (d, J = 6.4 Hz, 1H), 9.89 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 109.0, 115.3, 118.9, 119.2, 121.6, 125.6, 126.3, 129.0, 130.0, 148.3, 153.9.

2.1.15. (E)-2-(Hydroxybenzylideneamino)benzoic acid (15)

Compound **15** was prepared from salicylaldehyde (1.22 g, 10 mmol) and 2-aminobenzoic acid (1.23 g, 9 mmol); Yield: 1.42 g (65%); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.91–6.96 (m, 2H), 7.30–7.45 (m, 3H), 7.62–7.60 (m, 2H), 7.84 (d, J = 6.8 Hz, 1H), 8.83 (s br, 1H), 13.00 (s br, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 110.0, 115.0, 116.7, 117.6, 119.5, 119.9, 122.7, 129.7, 131.6, 134.2, 136.8, 151.9, 161.2, 170.0.

2.1.16. 2-((E)-(4-Hydroxyphenylimino)methyl)phenol (16)

Compound **16** was prepared from salicylaldehyde (1.22 g, 10 mmol) and 4-hydroxyphenol (982 mg, 9 mmol); Yield: 0.72 g (37%); mp; 135–137 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.80–6.94 (m, 4H), 7.28–7.36 (m, 3H), 7.54–7.56 (m, 1H), 8.86 (s, 1H), 9.66 (s br, 1H), 13.4 (s br, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 116.4, 116.9, 119.4, 119.9, 123.1, 132.6, 132.9, 139.6, 157.4, 160.6.

2.1.17. 2-((E)-(4-Mercaptophenylimino)methyl)phenol (17)

Compound **17** was prepared from salicylaldehyde (256 mg, 2.1 mmol) and 4-aminothiophenol (245 mg, 2 mmol); Yield: 0.21 g (46%); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.92–6.97(m, 2H), 7.36–7.43 (m, 3H), 7.57–7.62 (m, 3H), 8.92 (s, 1H), 12.85 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 117.1, 119.67, 119.71, 123.0, 129.4, 133.0, 134.0, 134.4, 148.2, 160.7, 164.3.

2.1.18. (E)-4-(2-Hydroxybenzylideneamino)benzamide (18)

Compound **18** was prepared from salicylaldehyde (1.22 g, 10 mmol) and 4-aminobenzamide (1.22 g, 9 mmol); Yield: 0.89 g (41%); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.94–6.99 (m, 2H), 7.38–7.46 (m, 4H), 7.66 (dd, J_{AB} = 7.2 Hz, J_{AX} = 1.6 Hz, 1H), 7.93–7.96 (m, 2H), 8.01 (s br, 1H), 8.98 (s, 1H), 12.85 (s br, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 113.0, 117.1, 119.7, 121.4, 121.6, 129.4, 129.6, 132.8, 133.1, 134.0, 151.0, 152.1, 160.8, 164.9, 167.9, 168.7.

2.2. Biological activity

All the compounds were screened for their *in vitro* antimicrobial activity according to the disc diffusion method (Bauer et al., 1966). The assay was determined against gram negative bacteria including *Escherichia coli* (*E. coli*), *Proteus mirabilis* (*P. mirabilis*), *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Serratia marcescens* (*S. marcescens*), gram positive bacteria including *Staphylococcus epidermidis* (*S. epidermidis*); *Staphylococcus aureus* (*S. aureus*) and *Bacillus subtilis* (*B. subtilis*), and fungi including *Alternaria alternata* (*A. alternata*), *Aspergillus niger* (*A. niger*), *Penicillium italicum* (*P. italicum*), *Penicillium roqueforti* (*P. roqueforti*), and *Saccharomyces cerevisiae* (*S. cerevisiae*). Sterile 6 mm-diameter sensitivity discs were impregnated with different concentrations (100, 200 and 400 μg/mL) of the synthesized compounds dissolved in DMSO. Each concentration was prepared in four replicates. Data in the results came only from 400 μg/mL, unless otherwise stated. Discs of each tested compound were laid onto nutrient agar for bacteria or potato dextrose agar (PDA) for fungi. The plates were then incubated for 24 h at 37 °C for bacteria and for 72 h at 28 °C for fungi. Similar discs for the positive antibacterial and antifungal controls, Ampicilin (100 μg/disc; Sigma, St. Louis, USA) and Cycloheximide (50 μg/disc; Sigma, St. Louis, USA), respectively, were prepared (Al-Omar, 2010; Elnakeeb et al., 1965). The results were recorded by measuring the zones of growth inhibition surrounding the discs. The mean value obtained of three independent replicates was used to calculate the zone of growth inhibition of each sample. The compound activities at a concentration of 100 μg/disc are presented in Tables 1 and 2.

2.3. Optical titration experiment

Binding strength of a given Schiff base with Salmon DNA was monitored by the common UV–vis spectrophotometric titration method (Saleh et al., 2011), which reflects the stability of the studied DNA-chelating complex. In the titration experiment, the total concentration of the free Schiff base (ligand) was kept constant and that of DNA was gradually increased. The absorption spectra were then recorded for a given Schiff base in ethylene glycol solvent as a function of DNA concentration under ambient temperature. The variation in the absorbance at a selected wavelength (chosen so that the changes are as large as possible) was then analysed to obtain the stability constants (K) of the complexes using a nonlinear formula in the Sigma Plot software (version 6.1, SPCC, Inc., Chicago, Illinois, USA), which we have previously reported (Saleh et al., 2011). The molar extinction coefficients of the complex were left as a floating parameter in the analysis by Levenberg–Marquardt algorithm provided by the software itself.

3. Results and discussion

The antibiotic activity within a particular class of compounds is often modulated by subtle changes within its core structure. Naphthyl rings were introduced in Schiff bases **9**, **10** and **11** to investigate the effect of steric bulk while the basicity of the imine nitrogen in **2** and **3** was controlled by electron-withdrawing halogens in the *para* position of the aromatic amine precursor. In addition, hydrogen bonding in a host–guest interaction is usually crucial in determining the biological activity of drugs. Therefore, we prepared and investigated Schiff bases possessing hydrogen donors capable of intramolecular (**6**, **14**, **15**) and intermolecular (**4, 5**, **16**, **17**, and **18**) hydrogen bonding. The effect of hydrogen bond acceptors was also examined in compounds **8**, **12**, and **13.**

To investigate the antimicrobial effect of the salicylidinaniline and naphthylidene compounds, we tested all synthesized compounds (Fig. 1) for their *in vitro* antimicrobial activity against a panel of standard strains of the Gram-positive bacteria: *S. epidermidis*, *S. aureus* and *B. subtilis*; the Gram-negative bacteria: *E. coli*, *P. mirabilis*, *P. aeruginosa* and *S. marcescens*; and the pathogenic fungi: *A. alternata*, *A. niger*, *P. italicum* and *S. cerevisiae*. The primary screening was carried out using the agar disc-diffusion method (Bauer et al., 1966). The diameter of the growth inhibition zones was measured after 24 h in bacteria and 72 h in fungi. The results of the antibacterial testing of compounds (400 μg/mL) and their corresponding antibiotic Ampicillin (100 μg/disc) are shown in Table 1; whereas the antifungal testing and the corresponding antibiotic drug

Table 1 Antibacterial activity of the synthesized Schiff base compounds **1**–**18**[a].

Zone of inhibition in mm[b]								
Compound	Substituents on the aryl amine site	Gram negative bacteria			Gram positive bacteria			
		E. coli	*P. mirabilis*	*P. aeruginosa*	*S. marcescens*	*S. epidermidis*	*S. aureus*	*B. subtilis*
1	H	–	–	–	–	12	–	–
2	Cl	7	–	9	9	–	–	–
3	Br	–	–	–	–	–	–	–
4	SO_2NH_2	–	–	–	NT	–	–	–
5	CO_2H	–	10	–	–	–	15	–
6	OH (*othro*)	7	8	–	–	–	–	16
7	CH_3	–	–	–	–	–	–	–
8	CH_3	–	–	–	–	–	–	–
9		–	–	–	–	–	–	–
10		–	–	–	–	–	–	–
11		–	–	–	–	–	–	–
12		–	–	–	–	–	–	17
13		–	–	–	–	14	–	–
14	SH (*ortho*)	–	3	9	11	8	9	11
15	CO_2H (*ortho*)	–	–	–	–	–	–	–
16	$CONH_2$	–	–	–	NT	–	–	–
17	SH	–	–	–	NT	5	–	–
18	OH	10	5	–	NT	6	–	15
Ampicilin (100 μg/disc)		16	14	15	4	19	18	18

–, not active; NT, not tested.
[a] The concentration of test compounds was (400 μg/mL). Solvent used DMSO.
[b] Mean value (SEM).

Table 2 Antifungal activity of the synthesized compounds **1**–**18**[a].

Zone of inhibition in mm[b]					
Compound	Substituents on the aryl amine site	Fungi			
		A. alternata	*A. niger*	*P. roqueforti*	*S. cerevisiae*
1	H	8	11	–	9
2	Cl	10	–	–	–
3	Br	–	–	–	–
4	SO_2NH_2	4	–	–	–
5	CO_2H	9	–	–	–
6	OH (*othro*)	9	–	–	–
7	CH_3	–	–	–	–
8	CH_3	–	–	–	–
9		9	–	9	–
10		–	–	9	–
11		–	–	–	–
12		–	–	–	11
13		–	–	–	–
14	SH (*ortho*)	8	12	8	12
15	CO_2H (*ortho*)	10	–	–	–
16	$CONH_2$	–	–	4	–
17	SH	5	–	5	–
18	OH	11	18	19	17
Cycloheximide (50 μg/disc)		17	16	14	19

–, not active; NT, not tested.
[a] The concentration of test compounds was (400 μg/mL). Solvent used DMSO.
[b] Mean value (SEM).

cycloheximide (50 μg/disc) are shown in Table 2. In case the inhibition diameter exceeds 14 mm, the compound has strong antimicrobial activity; between 8 and 13 mm it is moderate; whereas less than 7 mm inhibition zone, it is considered weak.

The results revealed that the synthesized compounds showed varying degrees of inhibition against the tested microbes. In general, the best activity was displayed by compounds **14** and **18** (Table 1), since they showed potential antimicrobial

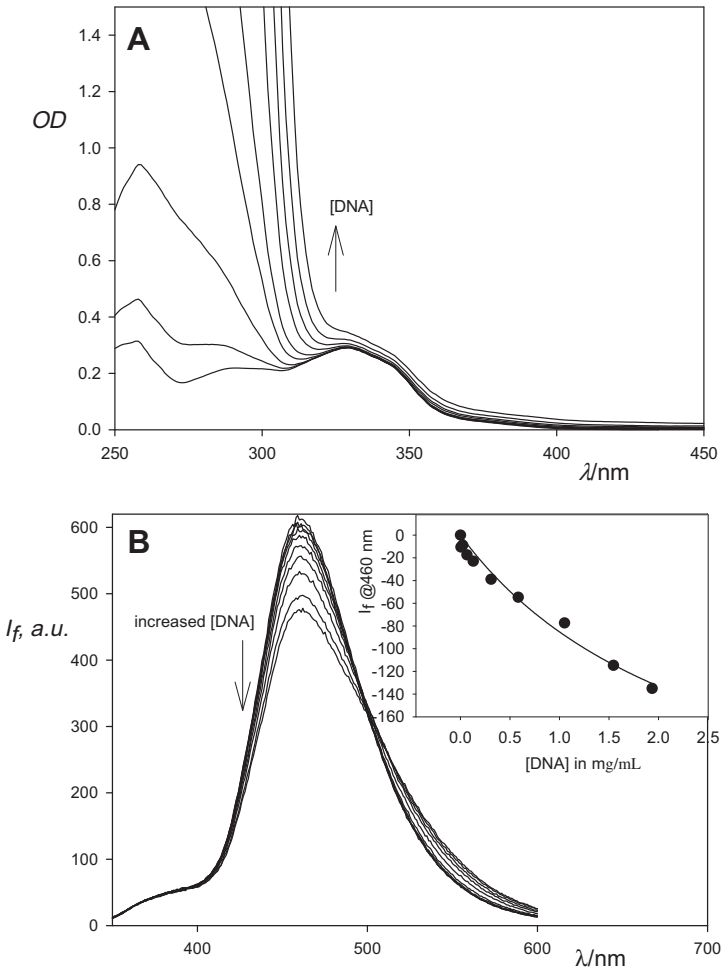


Figure 2 Binding spectrophotometric titrations of Schiff base **14** (70 μM) with DNA (Salmon tests) up to 2 mg/ml in a water–ethylene glycol (1:1, v/v) mixture at room temperature by (**A**) UV–visible and (**B**) fluorescence. No changes in the optical spectral profile. The *inset* shows the nonlinear fitting of the emission data according to a 1:1 complexation model; $K = 0.39 \pm 2.66 \times$ (Molar mass of DNA) M^{-1} ($R = 0.99$), which is very weak and contains large error!

activity against almost all bacterial pathogens tested. Previous reports supported our data of antibacterial activity of Schiff bases structured with either hydroxyl (–OH; compound **14**) or sulfhydryl (–SH; compound **18**) group. In these studies, not only the aromatic –OH group in curcumin analogues showed an inhibitory effect, but also a combination of a Schiff base with the sulphide/disulphide bond in the acyl side chain had moderate activities against some pathogenic bacteria (Alwan, 2012; Amin et al., 2010; Kim et al., 2012a,b; Ronad et al., 2010; Vukovic et al., 2010).

The Gram positive bacteria *S. epidermidis* and *B. subtilis* are considered the most sensitive among the bacteria tested on the eighteen Schiff base derivatives (Table 1). Compound **13** was selectively active (inhibition zone > 14 mm) against *S. epidermidis*, compound **5** against *S. aureus*, and compounds **6**, **12** and **18** against *B. subtilis*. Thus, none of the Gram-negative bacteria showed a strong inhibition zone towards any of the tested compounds (Table 1). Moderate or weak activity towards all Gram-negative bacteria was observed for compounds **2**, **5**, **6**, **14**, and **18**. Meanwhile, compounds **3**, **4,** **7**, **8**, **9**, **10**, **11**, **15**, and **16** were inactive against the tested bacteria. These results suggest that some of the synthesized salicylidinanilines are only active against Gram-positive pathogenic bacteria.

Schiff bases bearing the *ortho* sulfhydryl group (i.e. compounds **14**) or *para* hydroxyl group on aniline site (i.e. compound **18**) had moderate-strong inhibitory activity to all fungal strains; yet compound **18** is the most active (Table 2). Schiff bases carrying these crucial groups showed antioxidant activity (Vukovic et al., 2010), which may influence the fungal cell permeability via interference with the synthesis of cellular walls, deactivation of different cellular enzymes, denaturation of one (or more) cellular proteins, or formation of a H-bond between the these groups and the target component of the cellular structure, which may ultimately interfere with the fungal growth or cell death (Cacic et al., 2010). Interestingly, Fig. 2 demonstrated the lack of binding between derivative **14** and the DNA, which might suggest that the interaction with cellular membrane or proteins, not with DNA, is what rationalizes the trend in the corresponding biological data.

Among all tested microorganisms, the fungus, *A. alternata*, is the most sensitive (Table 2). Except compounds **1**, **14** and **18**, the rest of the synthesized compounds were practically inactive against *A. niger*. Compounds **4**, **16** and **17** produced either no

or weak activity relative to the antifungal drug cycloheximide or any other synthesized compounds (Table 2). While, the fungal pathogen, *A. alternata*, is susceptible to most of the synthesized drugs, none of the fungal pathogens grew on compound **3**, **7**, **8**, **11**, or **13**. In general, the examined Schiff base derivatives, showing an antifungal activity belong to either moderate or strong antipathogenicity, suggesting a potential use of these synthesized drugs against fungal pathogens. Overall, our data demonstrate high broad-spectrum inhibitory activity of Schiff base compounds containing hydroxyl and/or sulfhydryl groups against microorganisms (Tables 1 and 2) and cancer (personal communication, R.I.).

It is also interesting to compare our findings with previously published data by other research groups on our selected compounds, namely compounds **4** (Kumar et al., 2010), **6** (Abdel Aziz et al., 2012), and **7** (Al-Kahraman et al., 2010). Compound **4** (200 μg/ml) was tested by (Kumar et al., 2010) against *B. subtilis, S. aureus, E. coli,* and *A. niger* and the result indicated moderate inhibitory action in contrast to our findings (Table 1). Compound **6** was examined by (Abdel Aziz et al., 2012) against two bacterial strains *E. coli* and *S. aureus* (Table 1). Their results showed higher inhibitory growth effects when compared to our data (Table 1; viz. **13** versus **7** for *E. coli* and **13** versus nothing for *S. aureus*. This might be explained by the higher concentration that they had used (20 mg/ml versus 400 μg/ml). Compound **7** was tested by Yasinazi and his research group (Al-Kahraman et al., 2010) against different types of fungi to what we have tested, yet on four types of bacteria that were also studied by us in Table 1 (*E. coli, P. aeruginosa, B. subtilis,* and *S. aureus*) using relatively similar concentration (1 mg/ml for the antibacterial activity and 200 mg/ml for the antifungal activity), and their results supported lack of activity for this derivative in particular [6]. Putting together, the present work constitutes a comprehensive investigation of what appears to be of renewed interest in the medicinal fields for such type of drugs.

4. Conclusion

In summary, having a series of Schiff base derivatives that share common structural properties and by considering their antibacterial and antifungal effects, it was possible to rationalize the trend in the biological data on the basis of specific structural properties of the examined drugs. Generally speaking, drugs with –OH and –SH group tend to be mostly active than otherwise substituted, depending on their position on Schiff base backbone structures. Thus, the present findings are useful in advancing the efforts towards achieving a systematic prediction of the absolute biological effects in a rational way. Such information is currently in high demand to the biological and medicinal communities.

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