α-Enones in heterocyclic synthesis of indazole, thiazine, chromene and quinoline derivatives with their antimicrobial activities

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α-Enones **1a,b** react additively with hydrazine hydrate, thiourea, diethyl malonate, malononitrile, as well as ethyl cyanoacetate. Simultaneous cyclisation of the resulting 1:1 adducts yields indazole, thiazine, chromene and quinoline derivatives. The structures of all the synthesised compounds were confirmed by micro analytical and spectral data. The antimicrobial activity of some of the synthesised compounds were tested.

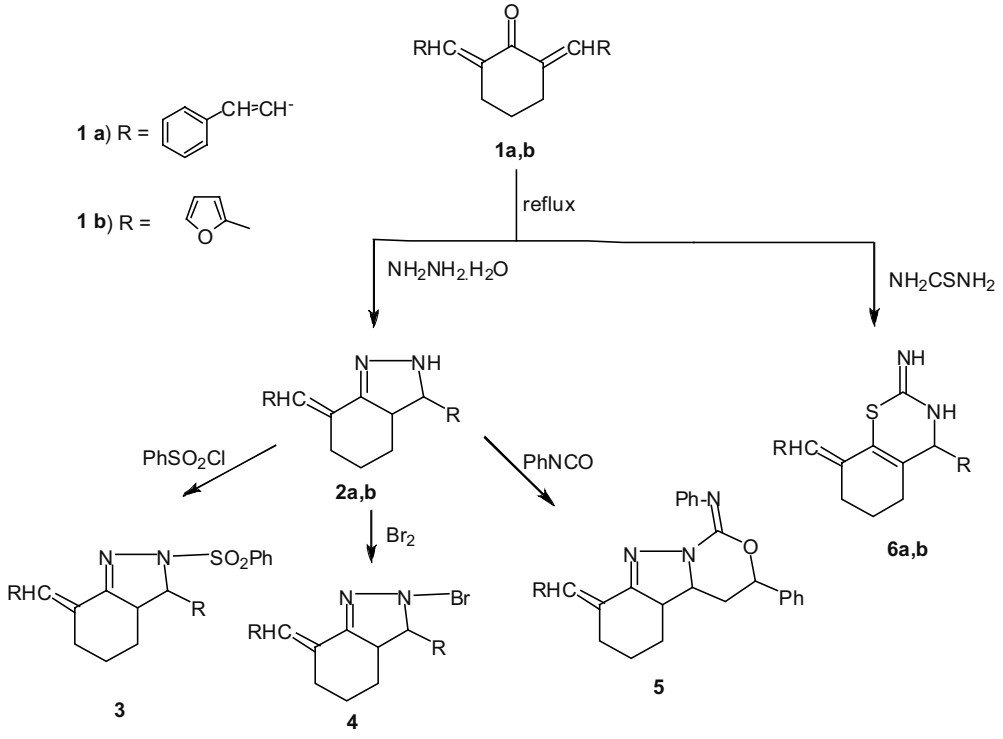
Keywords: α-enones, indazole, thiazine, chromene and quinoline derivatives

Enones are versatile reagents and their chemistry has considerable interest.[1,2] Having multiple electrophilic and nucleophilic centres, enones react with both electrophiles and nucleophiles.[1-4] Moreover, they undergo a variety of cycloaddition and self condensation reactions.[1,5-9] In the present investigation, we use enones as building block in the synthesis of fused heterocyclic ring systems. Also, we study the antibacterial and antifungal activities of the newly formed heterocycles.

Results and discussion

The new derivatives were prepared following the reaction sequences depicted in Schemes 1 and 2. Treatment of 2,6-bis-(3-phenylallylidene)cyclohexanone (**1a**) and/or 2,6-bis(furan-2-ylmethylene)cyclohexanone (**1b**) with hydrazine hydrate in absolute ethanol afforded indazole derivatives **2a,b** in a one-pot reaction. The olefinic double bond of **1a** and/or **1b** is activated by the ketone group therefore; the β-carbon atom will accept nucleophiles. The formation of indazole derivatives **2a,b** can be visualised on the basis of cyclocondensation of hydrazine with enones **1a,b**. Treatment of compound **2a** with benzenesulfonyl chloride or bromine gave derivatives **3** and **4**. However, **2a** reacted with phenyl isocyanate to produce compound **5**. Refluxing of compounds **2a,b** and thiourea in absolute ethanol with a catalytic amount of potassium hydroxide furnished thiazine derivative **6a,b** in a good yield (see Scheme 1). The structure of compounds **2–6**, was proven by their microanalytical and spectral data. Their IR spectra showed absorption bands correlated with υ(NH) except for compounds **3–5** and υ(C=N). The ^{1}H NMR spectra displayed signals corresponding with their proposed structures. The MS spectra of representative compounds revealed their molecular ions or important fragments which is in accord with their suggested assignments (see Experimental).

Enones **1a,b** react under Michael conditions with diethyl malonate, malononitrile and ethyl cyanoacetate to produce chromene derivatives **7a–c** and quinoline derivatives **7d,e** as shown in Scheme 2. The reactions proceed through attack of the β-carbon atom of α,β-unsaturated system to afford intermediate compounds (not isolated), that underwent



Scheme 1

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cyclisation to give the title compounds **7a–e**. The structure of compounds **7a–e**, was proven by their microanalytical and spectral data. Their IR spectra showed absorption bands correlated with υ(C=O) for compounds **7a,d,e**, υ(CN) and υ(NH) for compounds **7b–e**. The ^{1}H NMR spectra displayed signals corresponding with their structures. Their MS spectra revealed their molecular ions peaks or important fragments which is in accord with their structures (see Experimental).

Conclusion

In our investigation, we have synthesised fused heterocyclic ring systems in one-pot reactions to explore their bioactivity.

Experimental

General

Melting points were determined in open capillary tubes on a Gallenkemp melting point apparatus and are uncorrected. The elemental analyses were carried out at the Micro Analytical Unit, Faculty of Science, Cairo University by using Perkin-Elmer 2400 CHN elemental analyser. The IR spectra recorded on Perkin Elmer Spectrum RXIFT-IR systems as KBr discs. The ^{1}H NMR spectra were measured on Varian Gemini 200 MHz instrument with chemical shift (δ) expressed in ppm downfield from TMS as internal standard, in $CDCL_3$ or DMSO-d_6. Mass spectra were recorded on Shimadzu GC-MS, QP 1000 EX instrument operating at 70 eV. TLC was carried out the monitoring of the progress of all reactions and homogeneity of the synthesised compounds. TLC was determined using TLC aluminum sheets silica gel F_{254} (Merck).

Reaction of enones **1a,b** *with the different nucleophiles; general procedure*

To a solution of **1a** and/or **1b** (0.01 mole) in ethanol (20 mL), and equimolar amounts of hydrazine hydrate, thiourea, diethyl malonate or malononitrile was added and the reaction mixture was refluxed for 4–6 hours (TLC). A solution of KOH (2 g) in 2 mL water was added in case of reaction with thiourea and a few drops of piperidine in case of reaction with diethyl malonate and malononitrile. The crude material was filtered off and recrystallised from the suitable solvent to give compounds **2a,b**, **6a,b** and **7a–c** respectively.

*7-(3-Phenylallylidene)-3-styryl-3,3a,4,5,6,7-hexahydro-2*H*-indazole* **(2a)**: Yield, 86%; orange crystals; m.p. 162–164 °C (ethanol); IR (KBr) ν: 3281 (NH), 3028 (ArH), 2924 (CH_2), 1595 (C=N), 747, 692 ($δ_{5H}$) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.2–3.1 (m, 7H, $CH_2(CH_2)_2CH$), 3.9–4.1 (m, 1H, H–NH), 6.33 (d, 1H, *J* = 15.4 Hz, CH=), 6.37 (d, 1H, *J* = 16.2 Hz, CH=), 6.5–7.5 (m, 13H, 10ArH + 3CH=), 7.2 (br. s, 1NH exchangeable); MS (70 eV) *m/z* (%): 340 ($M^{+\cdot}$, 35), 341 ($M^{+\cdot}$ + 1, 15), 339 ($M^{+\cdot}$-1, 15), 263 (100), 262 (7),130 (39), 116 (11), 90 (5). Anal. Calcd for $C_{24}H_{24}N_2$ (340.46); C, 84.67; H, 7.11; N, 8.23. Found: C, 84.33; H, 6.78; N, 7.88%.

*3-(Furan-2-yl)-7-(furan-2-ylmethylene)-3,3a,4,5,6,7-hexahydro-2*H*-indazole* **(2b)**: Yield, 93%; yellowish brown crystals; m.p. 155–157°C (ethanol); IR (KBr) ν: 3150 (NH), 2924 (CH_2), 1558 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 1.2–2.2 (m, 7H, $CH_2(CH_2)_2CH$), 4.6–4.7 (m, 1H, CH–NH), 6.2–7.8 (m, 7 H, 6ArH + 1CH=), 7.2 (br. s, 1NH exchangeable); MS (70 eV) *m/z* (%): 268 ($M^{+\cdot}$, 10), 267 (M^{+}–1, 12), 266 (20), 237 (12), 187 (16), 81 (65), 55 (100). Anal. Calcd for $C_{16}H_{16}N_2O_2$ (268.31); C, 71.62; H, 6.01; N, 10.44. Found: 71.39; H, 5.91; N, 10.21%.

*8-(3-Phenylallylidene)-4-styryl-3,4,5,6,7,8-hexahydro-2*H*-1,3-benzothiazin-2-imine* **(6a)**: Yield, 86%; orange crystals; m.p. 160–162 °C (ethanol); IR (KBr) ν: 3381 (NH), 3276, 3174 (NH), 3026 (ArH), 2930 (CH_2), 1653 (C=N), 1610 (C=C), 750, 697 ($δ_{5H}$) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.25–3.13 (m, 6H, $(CH_2)_3$), 4.2 (d, 1H, *J* = 8.2 Hz, CH-S), 6.4 (d, 1H, *J* = 15.2 Hz, CH=), 6.80–7.58 (m, 14, 10ArH + 4CH=), 8.2, 9.5 (br. s, 2, NH exchangeable). MS (70 eV) *m/z* (%): 384 ($M^{+\cdot}$, 2), 382 (5), 327 (23), 326 (21), 212 (21), 211 (15), 91 (100). Anal. Calcd for $C_{25}H_{24}N_2S$ (384.54); C, 78.09; H, 6.29; N, 7.28. Found: C, 78.16; H, 5.89; N, 7.11%.

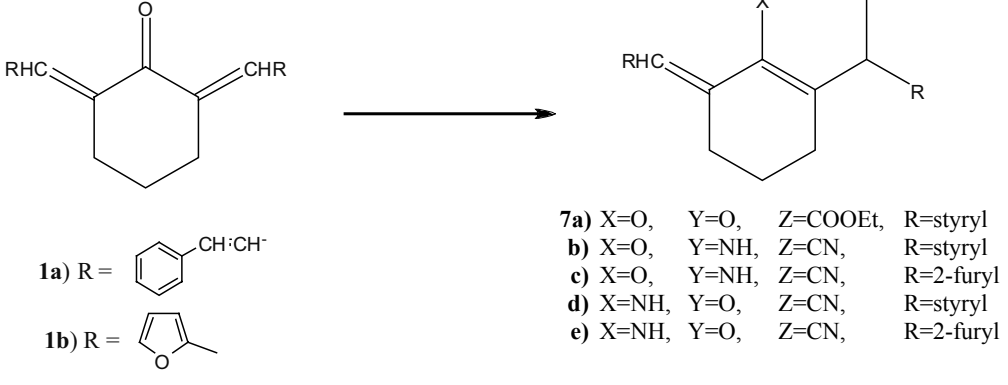
*4-(Furan-2-yl)-8-(furan-2-ylmethylene)-3,4,5,6,7,8-hexahydro-2*H*-1,3-benzothiazin-2-imine* **(6b)**: Yield, 91%; yellowish brown crystals; m.p. 155–157 °C (ethanol); IR (KBr) ν: 3220, 3100 (NH), 3055 (ArH), 2928 (CH_2), 1532 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 1.2–3.2 (m, 6H, $(CH_2)_3$), 5.8–5.9 (m, 1H, CH–NH), 6.2–7.8 (m, 7H, 6ArH + 1CH=), 2.4, 13.4 (br. s, 2NH exchangeable); MS (70 eV) *m/z* (%): 312 ($M^{+\cdot}$, 71), 310 (42), 270 (25), 269 (100), 267 (25), 253 (56), 167 (62), 119 (27). Anal. Calcd for $C_{17}H_{16}N_2O_2S$ (312.39); C, 65.36; H, 5.16; N, 8.97. Found: C, 65.08; H, 5.00; N, 8.71%.

*Ethyl 2-oxo-8-(3-phenylallylidene)-4-styryl-3,4,5,6,7,8-hexahydro-2*H*-chromene-3-carboxylate* **(7a)**: Yield, 86%; yellow crystals; m.p. 150–152 °C; (butanol); IR (KBr) ν: 3057 (ArH), 2928 (CH_2), 1719, 1656 (C=O), 1610 (C=C), 750, 696 ($δ_{5H}$) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.12–4.12 (m, 13H, aliphatic H), 6.6–7.8 (m, 15H, 10ArH + 5CH=); MS (70 eV) *m/z* (%): 440 ($M^{+\cdot}$, 0), 329 (25), 328 (30), 327 (50), 326 (100), 235 (80), 179 (50), 131 (10), 115 (95). Anal. Calcd for $C_{29}H_{28}O_4$ (440.53); C, 79.07; H, 6.41. Found: C, 78.83; H, 6.23%.

*2-Imino-8-(-3-phenylallylidene)-4-styryl-3,4,5,6,7,8-hexahydro-2*H*-chromene-3-carbonitrile* **(7b)**: Yield, 83%; brown crystals; m.p. 130–132 °C (ethanol); IR (KBr) ν: 3332 (NH), 3162 (NH), 3028 (ArH), 2935 (CH_2), 2192 (CN), 1622 (C=N), 752, 696 ($δ_{5H}$) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 1.4–3.1 (m, 8H, aliphatic -H), 6.8–7-8 (m, 15 H, 10ArH + 5CH=), 7.2 (br. s 1NH, exchangeable); MS (70 eV) *m/z* (%): 393 ($M^{+\cdot}$, 0), 199 (17), 198 (26), 129 (39), 91 (91), 77 (96), 76 (35), 65 (52), 52 (100). Anal. Calcd for $C_{27}H_{24}N_2O$ (392.49); C, 82.62; H, 6.16; N, 7.14. Found: C, 82.31; H, 5.89; N, 6.88%.

4-*(Furan-2-yl)-8-(furan-2-ylmethylene)-2-imino-3,4,5,6,7,8-hexahydro-2*H*-chromene-3-carbonitrile* **(7c)**: Yield, 86%; dark brown crystals; m.p. 95–96 °C (petroleum ether 60–80); IR (KBr) ν: 3140 (NH), 3050 (ArH), 2944 (CH_2), 2198 (CN), 1592 (C=N), cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.2–4.01 (m, 8H, aliphatic – H), 6.2–7.6 (m, 7H, 6ArH + 1CH=), 9.04 (br. s, 1NH, exchangeable). Anal. Calcd for $C_{19}H_{16}N_2O_3$ (320.34); C, 71.24; H, 5.03; N, 8.74. Found: C, 70.87; H, 4.90; N, 8.56%.

*7-(-3-Phenylallylidene)-2-(phenylsulfonyl)-3-styryl-3,3a,4,5,6,7-hexahydro-2*H*-indazole* **(3)**: A solution of **2a** (0.01 mole) in pyridine (10 mL), and benzenesulfonyl chloride (0.01 mole) was heated on water path for 3 hours, Then, the reaction mixture was poured into ice/HCl mixture. The crude material was filtered off and recrystallised



7a) X=O, Y=O, Z=COOEt, R=styryl
b) X=O, Y=NH, Z=CN, R=styryl
c) X=O, Y=NH, Z=CN, R=2-furyl
d) X=NH, Y=O, Z=CN, R=styryl
e) X=NH, Y=O, Z=CN, R=2-furyl

Scheme 2

from ethanol. (86% yield); brown crystals; m.p. 60–62 °C; IR (KBr) ν: 3060 (ArH), 2943 (CH_2), 1625 (C=N), 752, 688 (δ_{5H}) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.6–2.9 (m, 7H, $CH_2(CH_2)_2CH$), 3.6–3.8 (m, 1H, CH–N), 6.43, (d, 2H, *J* = 15.6 Hz, CH=), 6.76 (d, 2H, *J* = 13.8 Hz, CH=), 7.0–8.9 (m, 16H, 15ArH + 1 CH=); MS (70 eV) *m/z* (%): 480 ($M^{+\cdot}$, 0), 339 (7), 338 ($M^+ - PhSO_2$, 20), 261 (16), 141 (7), 116 (19), 91 (59), 77 (100). Anal. Calcd for $C_{30}H_{28}N_2O_2S$ (480.62); C, 74.97; H, 5.87; N, 5.83. Found: C, 74.62; H, 5.65; N, 5.73%.

2-Bromo-7-(3-phenylallylidene)-3-styryl-3,3a,4,5,6,7-hexahydro-2H-indazole **(4)**: A solution of **2a** (0.01 mole), in chloroform (30 mL), and bromine (0.01 mole) was stirred at room temperature for 3 hours. Evaporating the solvent, gave an oily product, triturated with light petroleum, the solid product obtained was recrystallised from ethanol (77% yield); reddish brown crystals; m.p. 142–144 °C; IR (KBr) ν: 3063 (ArH), 2937 (CH_2), 1615 (C=N), 750, 689 (δ_{5H}) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.2–3.8 (m, 8H, aliphatic- H), 5.8–6.2 (m, 4H, CH=), 7.1–7.8 (m, 11H, 10ArH + 1CH=); MS (70 eV) *m/z* (%): 419 ($M^{+\cdot}$, 0), 413 (36), 412 (24), 121 (15), 103 (14), 102 (8), 91 (16), 80 (100), 79 (53). Anal. Calcd for $C_{24}H_{23}BrN_2$ (419.36); C, 68.74; H, 5.53; N, 6.68. Found: C, 68.45; H, 5.17; N, 6.41%.

N-*(3-Phenyl-8-(3-phenylallylidene)-3,4,4a,4b,5,6,7,8-octahydro-1H-[1,3]oxazino[3,4-b]indazol-1-ylidene)aniline* **(5)**: A solution of **2a** (0.01 mole) and phenyl isocyanate (0.01 mole) in dry diethyl ether (30 mL) was stirred at room temperature for 10 hours. The crude solid was filtered off and recrystallised from butanol. (81% yield); yellow crystals; m.p. 194–196 °C; IR (KBr) ν: 3026 (ArH), 2932 (CH_2), 1593, 1519 (C=N), 750, 694 (δ_{5H}) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.2–3.2 (m, 10H, aliphatic-H), 4.9–5.0 (m, 1H, CH-O), 5.8–7.7 (m, 17H, 15ArH + 2CH=), 6.53 (d, 1H, *J* = 12.8 Hz, 1CH=); MS (70 eV) *m/z* (%): 457 ($M^{+\cdot}$, 0), 442 (4), 340 (20), 338 (13), 236 (40), 135 (85), 117 (12), 77(100). Anal. Calcd for $C_{31}H_{29}N_3O$ (459.58); C, 81.02; H, 6.36; N, 9.14. Found: C, 80.87; H, 6.15; N, 8.87%.

Reaction of enone **1a,b** *with ethyl cyanoacetate; general procedure*

A mixture of **1a** and/or **1b** (0.01 mole), ethyl cyanoacetate (0.01 mole), and ammonium acetate (2 g) was fused at 150–160 °C for 8 hours. The obtained solid was washed with water, sucked, and crystallised from *n*-butanol to give the corresponding compounds **7d** and **7e** respectively.

2-Oxo-8-(3-phenylallylidene)-4-styryl-1,2,3,4,5,6,7,8-octahydroquinoline-3-carbonitrile **(7d)**: Yield, 85%; brown crystals; m.p. 170–162 °C; IR (KBr) ν: 3183 (NH), 3055 (ArH), 2931 (CH_2), 2214 (CN), 1624 (CO), 749, 695(δ_{5H}) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.4–3.7 (m, 8H, aliphatic- H), 6.2–7.6 (m, 15H, 10ArH + 5CH=), 7.8 (br. s, 1NH, exchangeable); MS (70 eV) *m/z* (%): 392 ($M^{+\cdot}$, 31), 393 ($M^{+\cdot}$ + 1, 13), 391 (17), 366 (4), 299 (42), 211 (14), 152 (10), 115 (20), 91(100). Anal. Calcd for $C_{27}H_{24}N_2O$ (392.49); C, 82.62; H, 6.16; N, 7.14. Found: C, 82.37; H, 5.94; N, 6.90%.

4-(Furan-2-yl)-8-(furan-2-ylmethylene)-2-oxo-1,2,3,4,5,6,7,8-octahydroquinoline-3-carbonitrile **(7e)**: Yield, 86%; brown crystals; m.p. 290–292 °C; IR (KBr) ν: 3200 (NH), 2938 (CH_2), 2214 (CN), 1636 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.4–4.05 (m, 8H, aliphatic-H), 6.2–7.6 (m, 7H, 6ArH + 1CH=); 7.8 (br. s, 1NH, exchangeable); MS (70 eV) *m/z* (%): 320 ($M^{+\cdot}$, 12), 321 ($M^{+\cdot}$ + 1, 4), 319 (2), 239 (5), 211 (3), 141 ((3), 132 (2), 81 (100). Anal. Calcd for $C_{19}H_{16}N_2O_3$ (320.34); C, 71.24; H, 5.03; N, 8.74. Found: C, 70.89; H, 4.87; N, 8.53%.

Biological activity

The antimicrobial screening of some of the synthesised compounds was done using the agar plate diffusion method.[10] The possible antimicrobial activities of compounds **2a, 3, 5, 6a, 7b** were investigated to four standard organisms including the Gram positive bacteria: *Staphylococcus aureus* (S), and *Bacillus subtilis* (B); fungi: *Candida albicans* (C), and *Penicillium italicum* (P). The obtained results are presented in Table 1.

Antibacterial activity

The antibacterial activity was tested against Gram positive bacteria: *Staphylococcus aureus* (S), and *Bacillus subtilis* (B). Various concentrations of the synthesised compounds (1, 2.5, 5 mg mL^{-1}) dissolved in dimethylsulfoxide (DMSO) were added to each filter paper disc and DMSO was used as control. Plates were incubated at 37 °C and examined for zone of inhibition around each disc after 24 h (Table 1). The antibacterial activity was evaluated by measuring the zone of inhibition against the test organisms. The results were compared with commercial standard antibiotic chloramphenicol (St).

Antifungal activity

The antifungal bioassay was tested against *Candida albicans* (C), and *Penicillium italicum* (P) by the disc method in potato–dextrose-agar (PDA) medium with various concentrations (1, 2.5, 5 mg mL^{-1}). The fungi test plate was incubated for 72 h at 28 °C. The antifungal activity was evaluated by measuring the zone of inhibition against organisms. Terbinafin was used as commercial standard (St).

Data in Table 1 emphasised the fact that the chemical agents symbolised **2a, 3, 5, 6a, 7b** exhibit various degree of activities against gram positive bacteria and fungi. Against *Staphylococcus aureus* (S) compounds **3, 5**, **6a**, **7b** show strong activity at low concentrations (1, 2.5 mg mL^{-1}) and moderate activity at high concentrations (5 mg mL^{-1}) except compound **3** that shows comparable activity with chloramphenicol. Against *Candida albicans* (C), compound **7b** shows a stronger activity than terbinafin at low concentration.

Table 1 Mean diameters of inhibition zones (mm) caused by 100 µL of antibacterial and antifungal activities in the agar plate diffusion method

No.	Conc./ mg mL^{-1}	Gram positive bacteria		Fungi	
		S	B	C	P
2a	1	0	3	0	0
2a	2.5	3	8	6	0
2a	5	9	14	12	0
3	1	5	7	3	4
3	2.5	8	10	7	6
3	5	15	16	10	17
5	1	5	4	0	0
5	2.5	8	7	4	0
5	5	14	16	9	8
6a	1	5	4	2	0
6a	2.5	8	6	6	0
6a	5	12	16	14	0
7b	1	5	7	7	0
7b	2.5	9	10	11	0
7b	5	12	17	15	5
St	1	4	11	6	4
St	2.5	6	18	10	9
St	5	15	22	19	19

Well diameter 6 mm (100 uL of each concentration was tested). 0 = zone of (mm) inhibition reflecting no inhibition of growth.

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